HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dinutuximab beta for treating high-risk neuroblastoma [ID910]

Appraisal Committee Meeting – 11 April 2018
2nd Committee meeting

The scope and final matrix are available on the NICE website

The following documents are made available to the Committee:

1. **Pre-Meeting Briefing (PMB)**

2. **Company submission** from EUSA Pharma

3. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification

4. **Patient group, professional group and NHS organisation submission** from:
   - NHS England

5. **Expert personal perspectives** from:
   - Dr Martin Elliott, Consultant Paediatric Oncologist, clinical expert, nominated by NIHR
   - Dr Juliet Gray, Associate Professor and Consultant in Paediatric Oncology, clinical expert, nominated by NIHR
   - Nicholas Bird, patient expert, nominated by Solving Kids' Cancer Europe
   - Tony Heddon, patient expert, nominated by Neuroblastoma UK
   - Professor Peter Clark, NHS England National Chemotherapy Lead and Clinical Lead for the Cancer Drugs Fund, NHS England

6. **Evidence Review Group report** prepared by BMJ-TAG

7. **Evidence Review Group report factual accuracy check**

8. **Evidence Review Group erratum**

9. **Additional Analyses and Clarification for the Second Appraisal Committee** from EUSA Pharma

10. Decision Support Unit clarification questions

- Request to the company for clarification on their additional analyses
- Company response to request for clarification

11. Decision Support Unit review of the additional analyses

Pre-meeting briefing

Dinutuximab beta EUSA (dinutuximab beta) for high-risk neuroblastoma [ID910]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues: Clinical effectiveness

Overarching issues:

- Do the results of APN311-302 and the naive comparison provide robust estimates of treatment effectiveness in the high risk population to inform decision making?
- Are the estimates robust in the longer-term?
- Would a match adjusted indirect comparison (MAIC) provide more certainty regarding the treatment effectiveness of dinutuximab beta in the high risk population?
- Do the results of APN311-303 and APN311-202 and the naïve comparison provide a robust estimates of the treatment effect in the relapsed and refractory (R&R) population to inform decision making?

Other issues:

- Are the results of APN311-303 and APN311-202 for the R&R population generalisable to the NHS in England?
- Does the dosing schedule in APN311-302 (five daily infusions) reflect what is expected in NHS clinical practice?
- More than half of the people experienced a Grade 3 or Grade 4 level infections. Is the level of infection acceptable?

Disease background

- Neuroblastoma is a cancer of embryonic nerve cells called neural crest cells and has a diverse clinical presentation and prognosis depending on the tumour biology and cytogenetics
- Commonly occurs in adrenal glands (located above kidneys) or any nerve tissue of the sympathetic nervous system which runs alongside the spinal cord (neck, chest, abdomen and pelvis)
- Neuroblastoma usually affects children 5 years of age and under
- 90% of neuroblastoma cases are diagnosed by 5 years of age

What is ‘high risk’ and relapsed/refractory neuroblastoma?

- Definition is debated
- Based on clinical stage of tumour and other prognostic factors, a person is designated as being at very low, low, intermediate or high risk of relapse
- High-risk neuroblastoma: Consensus definition (International Neuroblastoma Risk Group):
    - age 1 year old or older
    - disease spread
    - the number of copies (amplification) of the MYCN oncogene
    - the amount of DNA (ploidy) in the neuroblastoma cells before autologous stem cell transplant, and
    - unfavourable tumour histopathology (tumour tissues which look abnormal)

- Relapsed or refractory neurobastoma: patients do not necessarily need to be diagnosed as high-risk neuroblastoma patients initially
- Very-low, low, and intermediate risk patients without MYCN amplification can experience relapse or suffer from refractory disease
- In 50% of high-risk cases, the patients relapse (survival from relapsed, high-risk neuroblastoma is currently <10%

Dinutuximab beta EUSA

Marketing authorisation (MA) granted May 2017	• Treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplant, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease • In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, Dinutuximab beta EUSA should be combined with interleukin-2 (IL-2). • MA granted under exceptional circumstances (when applicant can't provide comprehensive data on the efficacy and safety, approval on the basis that more data be obtained and submitted for regular review)
Mechanism of action	Immunotherapy - a monoclonal, chimeric antibody that targets GD2, a glycolipid in neuroblastoma cells
Administration	Intravenous infusion
Dosing frequency	• Continuous infusion over the first 10 days of each course at the daily dose of 10 mg/m2 ***[used in the company's modelling]*** • Five daily infusions of 20 mg/m2 administered over 8 hours, on the first 5 days of each course ***[used in the main study APN311-302]***
List price (excluding VAT)	• Acquisition cost: £7,610 per vial • Average cost of a course of treatment: body surface area of 0.63m2 and an age of 3 years, £152,200 • No patient access scheme

Relevant NICE Technology Appraisals

ID799 – Dinutuximab alpha

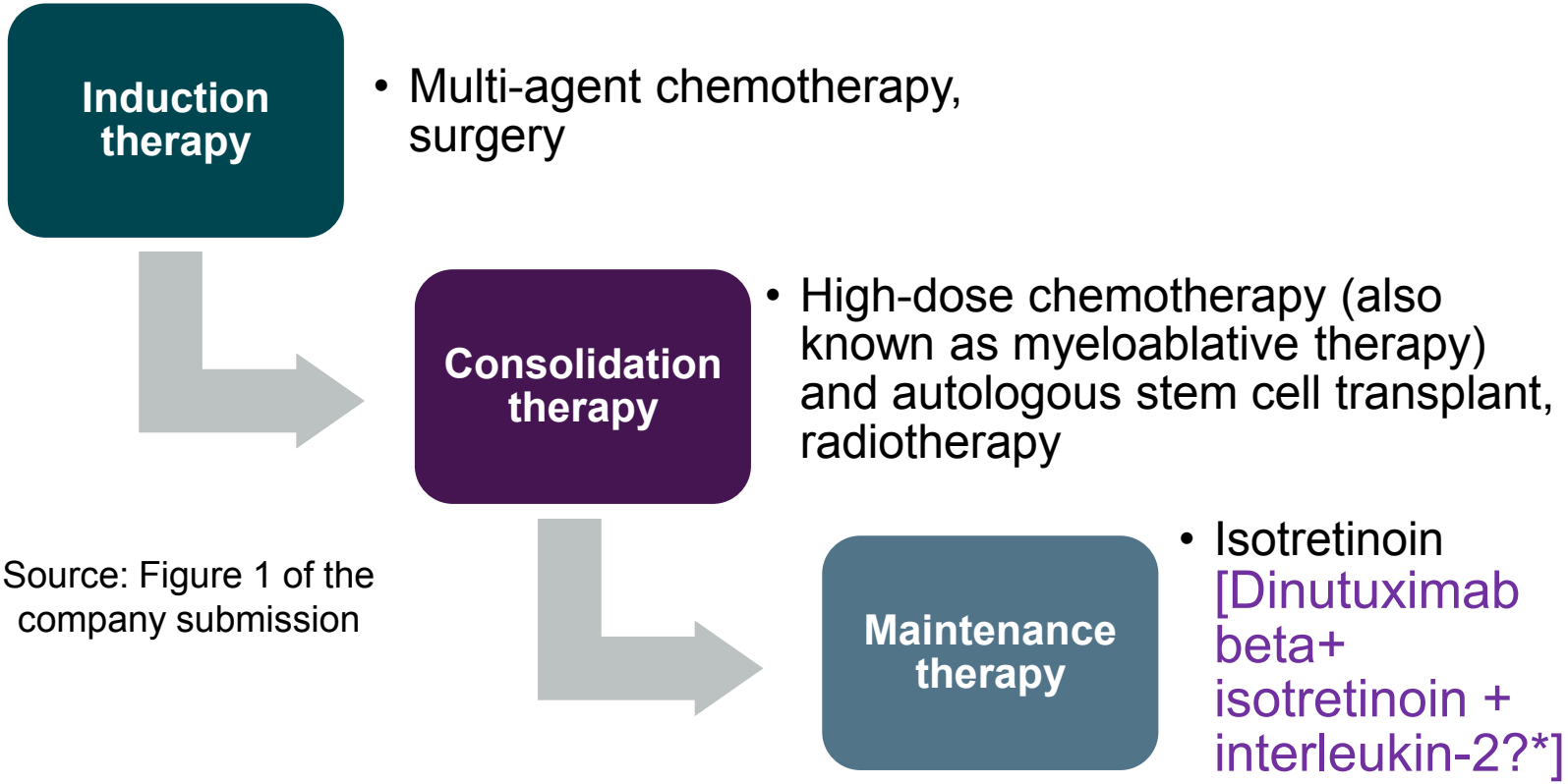
- Dinutuximab alpha (Unituxin - United Therapeutics Corporation) was being assessed in the NICE STA process (GID-TAG507) for treating high-risk neuroblastoma following myeloablative therapy and autologous stem cell transplant
- Appealed by Solving Kids Cancer
- Appeal ground 1(b): In making the assessment that preceded the recommendation, NICE has exceeded its powers
  - There has been a breach of Section 11 of the Children Act 2004, Article 3 of the UN Convention on the Rights of the Child and human rights legislation
- Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE
  - It was unreasonable for the Institute to use a 10-year cure point, given the evidence before it

→Appeal Panel upheld both appeal points

- Appraisal was suspended in February 2017 when the European marketing authorisation for the monoclonal antibody was withdrawn at the request of the holder, who cited production issues and a decision to supply only the US market as reasons for the request

Potential place of dinutuximab beta in current treatment pathway

High-risk neuroblastoma: 3 distinct phases of treatment



Source: Figure 1 of the company submission

*IL-2 be given to only those not achieving complete response to induction therapy

Relapsed/Refractory (R/R) neuroblastoma:

No defined NHS pathway for treating relapsed neuroblastoma, treatment usually comprises of chemotherapy, radiotherapy and surgery. All patients would be treated through a clinical trial. [Dinutuximab beta+ isotretinoin + interleukin-2?]

Decision problem (final scope)

	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
Population	People with high-risk neuroblastoma who have had myeloablative therapy (MAT) and autologous stem cell transplant (ASCT)	Patients with high-risk neuroblastoma, who have previously received induction chemotherapy and achieved at least a partial response, followed by MAT and ASCT, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease	APN311-302 enrolled patients who achieved at least a partial response to induction therapy and represents a narrower population than scope and marketing authorisation
Intervention	Dinutuximab beta Apeiron	As per scope	-
Comparators	Isotretinoin Dinutuximab (subject to NICE guidance)	Isotretinoin alone Dinutuximab not relevant because of withdrawal of marketing authorisation (MA)	ERG agrees with company
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Adverse effects of treatment • Health-related quality of life	• Overall survival (OS) • Event-free survival (EFS) • Adverse effects of treatment • Tumour response rate • Health-related quality of life	-
Subgroups	• People with relapsed disease • People with refractory disease ➢ ID799 (Dinutuximab alpha, Unituxin) considered only high-risk population	Company suggested simplifying the technology evaluation and focus on high-risk neuroblastoma patients who have not previously received Dinutuximab beta EUSA	ERG questions the relevance of the (R/R) population with regard to the comparability of patients in clinical trials and patients seen in UK

Patient and professional feedback

Patient feedback

- Being a parent of a child with neuroblastoma affects the everyday life significantly (constant fear of child's death)
- Clear unmet need in a very vulnerable patient population of children most whom are under the age of 5

Professional feedback

- Outcome for children with high risk neuroblastoma has lagged behind, and it accounts for a disproportionately high number of childhood cancer deaths
- There is a significant unmet need for more effective treatments in patients with high risk and relapsed neuroblastoma
- None of the existing interventions have independently resulted in a statistically significant improvement in EFS or OS
- Dinutuximab beta is an innovative treatment modality to complement other modalities used in this condition
  - Improve event free and overall survival of patients with high-risk neuroblastoma
  - Tolerable toxicity
- All patients in the UK since 2010 have received dinutuximab beta, this has become a standard of care

Clinical evidence

- **One randomised controlled trial (RCT) in high-risk population:**
  APN311-302 (one phase of the HR-NBL-1 trial) - phase III, open label, multinational trial designed to assess the efficacy and safety of adding interleukin 2 to a maintenance treatment regimen of dinutuximab beta and isotretinoin (13-cis-RA)
  - Everyone in the study received dinutuximab beta, there is **no direct evidence on dinutuximab beta versus isotretinoin alone**. Such a study was considered unethical, based on the results of the study assessing dinutuximab alpha
  - Company carried out a naïve comparison using historical controls from an earlier phase of APN311-302
  - ID799: ANBL0032 Phase 3, multicentre, prospective, partially randomised, active-controlled trial (n=226) only in high-risk neuroblastoma

- **Two observational studies in relapsed or refractory population:**
  APN311-202 (prospective design) and APN11-303 (retrospective design):
  Aim of both studies was to identify a tolerable treatment schedule of dinutuximab beta that reduced the pain-toxicity profile yet maintained the immunomodulatory effect
  - [redacted] in APN311-202 or APN311-303 had previously received dinutuximab beta – evidence on retreatment not available
  - Company does not support re-treatment with dinutuximab beta in R/R population. No ongoing studies and none planned.

Clinical trial evidence

APN311-302 High risk population

Trial	Population	Intervention	Outcomes
Randomised, phase III, open-label, multicentre study (intention-to-treat (ITT)=406; actual patients involved in analyses=370) [redacted]/370 people recruited from UK	- Established diagnosis of neuroblastoma according to the INSS - Age < 21 years - High-risk neuroblastoma - Have achieved at least a partial response to induction therapy - No previous chemotherapy except for 1 cycle of etoposide and carboplatin - Tumour cell material available for determination of biological prognostic factors	- Dinutuximab beta + isotretinoin (N=180) - Dinutuximab beta + isotretinoin + IL-2 (N=190) Dinutuximab beta admin: five 28-day cycles of dinutuximab beta (20 mg/m²/day over 5 days) Isotretinoin admin: six 28-day cycles of oral isotretinoin (160 mg/m²/day over 14 days)	1° • 3-year EFS 2° • Overall survival • Incidence of relapse/refractory • Incidence of death, infection • Overall response • Toxicity • Relationship of survival, EFS, response rates

Source: Table 11 of the company submission

- ID799: administered at a daily dose of 17.5 mg/m2 on days 4–7 during courses 1, 3 and 5 (each course lasting ~ 24 days) and on days 8–11 during courses 2 and 4 (each course lasting ~ 28 days). Course 6 includes treatment with isotretinoin alone

ERG critique of trial design & conduct: APN311-302 High risk population

- Open-label design introduces bias
- Lack of a pre-specified time point for assessment of disease status during or after treatment. Hence for EFS, it is unclear whether the exact point of disease progression is captured
- Data presented do not adhere to the ITT principle. Appears to be a complete case analysis based on 370 people for whom and electronic case report form (eCRF) was available, instead of 406 randomised
  - Unclear why an eCRF was not available for all randomised patients, or why some people did not receive any treatment
- Dosing schedule was short-term (over 5 days) → not likely to be in line with UK clinical practice (suggested that this would be continuous over 10 days). No evidence on whether rate of infusions affects clinical outcomes
- Data from 302 is immature and length of follow up insufficient to determine clinical effectiveness, particularly whether any benefit is maintained in the longer term

Clinical trial evidence

APN311-202 & 303: Relapsed and refractory populations

Trial name	Population	Intervention	Co-treatment	Primary outcomes
APN311-202 n= 44	Primary refractory or relapsed neuroblastoma Aged 1-21 years With neuroblastoma diagnosed according to INSS Received at least 1 previous high-dose treatment	100mg/m2 treatment course of dinutuximab beta, administered as one continuous 10-day infusion at 10mg/m2/day, in cycles of 35 to 49 days	IL-2, isotretinoin	Determine tolerable treatment schedule that reduces pain-toxicity profile of dinutuximab beta
APN311-303 n= 54	Patients with high-risk, relapsed or refractory neuroblastoma; Aged 1-45; who have estimated life expectancy of at least 12 weeks and who could not get adequate treatment through routine medical treatment/clinical trials	Dinutuximab beta given in combination with fixed doses of IL-2 and oral isotretinoin	IL-2, isotretinoin	Retrospectively evaluate safety and assess the pain-toxicity profile of a prolonged continuous infusion of dinutuximab beta

Source: Table 11 of the company submission

ERG critique of trial design and conduct: APN311-202 & 303 in relapsed/refractory population

- Both single-arm observational studies (202 perspective, 303 retrospective), small sample sizes, design not appropriate to capture time-to-event outcomes such as EFS and OS
- No formal statistical hypotheses, analyses methods or power calculation specified *a priori*, and in 202 no clinical outcome was pre-specified
- Likely that a proportion of those enrolled in APN311-202 and APN311-303 and classified as refractory to treatment are people originally participating in APN311-302
- In the UK since 2009 most patients with relapsed disease will have received dinutuximab first line through participation in the HR-NBL-1 / APN311-302 study
- [redacted] in 202 and 303 previously received dinutuximab beta
- There is considerable uncertainty in the extent to which the populations in the two studies are generalisable to those in England with R/R neuroblastoma

KM curve for EFS

APN311-302 - High-risk population

Concomitant administration of IL-2 does not improve EFS

EFS at 3 years for subgroup not receiving IL-2: 55.5%

EFS at 3 years for subgroup receiving IL-2: 61.2%

Source: Figure 4 of the company submission

EFS for APN311-302 - High-risk population

No difference in EFS at any time point between dinutuximab beta plus isotretinoin with and without IL-2

	Dinutuximab beta plus isotretinoin (N=180)	Dinutuximab beta plus isotretinoin plus IL-2 (N=190)
KM estimate		
1 year	72.3%	72.3%
2 years	63.2%	66.3%
3 years	55.4%	61.2%
Log-rank test	p = 0.3202*	
Cumulated number of events, n (%)		
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
3 years	79 (44.1)	69 (36.5)
4 years	[redacted]	[redacted]
Last cut off (August 2017)	[redacted]	[redacted]

Source: Table 17 of the ERG report

*p-value refers to the analysis based on 3 years' follow-up (not latest data-cut)

KM curve for OS of APN311-302 - High-risk population

Concomitant administration of IL-2 does not improve OS

OS at 3 years for subgroup not receiving IL-2: 64.1%

OS at 3 years for subgroup receiving IL-2: 69.1%

Source: Figure 5 of the company submission

OS for APN311-302 - High-risk population

No difference in OS at any time point between dinutuximab beta plus isotretinoin with and without IL-2

	Dinutuximab beta plus isotretinoin (N=180)	Dinutuximab beta plus isotretinoin plus IL-2 (N=190)
KM estimate		
1 year (%)	86.3%	87.9%
2 years (%)	76.0%	75.4%
3 years (%)	64.1%	69.1%
Log-rank test	p = 0.6114*	
Cumulated number of events, n (%)		
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
3 years	60 (33.5)	56 (29.8)
4 years	[redacted]	[redacted]
Last cut off August 2017	[redacted]	[redacted]

Source: Table 20 of the ERG report

*p-value refers to the analysis based on 3 years' follow-up (not latest data-cut)

Adjusted KM curves for EFS

APN311-202 and APN311-303 – R/R population

Source: Figure 5 of the ERG report

KM estimates of EFS

APN311-202 and APN311-303 – R/R population

Time	Relapsed neuroblastoma				Refractory neuroblastoma			
	APN311-202 (N=19)		**APN311-303** (N=29)		**APN311-202** (N=25)		**APN311-303** (N=15)	
	EPAR	CS	EPAR	CS	EPAR	CS	EPAR	CS
Number of events, n (%)	NR	[redacted]	NR	[redacted]	NR	[redacted]	NR	[redacted]
Censored	NR	[redacted]	NR	[redacted]	NR	[redacted]	NR	[redacted]
1 year	42.1%	[redacted]	44.8%	[redacted]	60.0%	[redacted]	58.2%	[redacted]
2 years	36.8%	[redacted]	31.0%	[redacted]	55.7%	[redacted]	29.1%	[redacted]
3 years	36.8%	[redacted]	24.1%	[redacted]	44.6%	[redacted]	29.1%	[redacted]

Source: Table 19 of the ERG report

Key: EPAR: European public assessment report; CS: company submission, NR: not rated; NE: not estimable

Adjusted KM curves for OS

APN311-202 and APN311-303 – R/R population

Source: Figure 8 of the ERG report

KM estimates of OS

APN311-202 and APN311-303 – R/R population

Time	Relapsed neuroblastoma				Refractory neuroblastoma			
	APN311-202 (N=19)		APN311-303 (N=29)		APN311-202 (N=25)		APN311-303 (N=15)	
	EPAR	CS	EPAR	CS	EPAR	CS	EPAR	CS
Number of events, n (%)	NR	[redacted]	NR	[redacted]	NR	[redacted]	NR	[redacted]
Censored	NR	[redacted]	NR	[redacted]	NR	[redacted]	NR	[redacted]
1 year	73.7%	[redacted]	89.7%	[redacted]	100.0 %	[redacted]	92.9%	[redacted]
2 years	42.1%	[redacted]	69.0%	[redacted]	78.3%	[redacted]	69.8%	[redacted]
3 years	42.1%	[redacted]	54.7%	[redacted]	62.5%	[redacted]	69.8%	[redacted]

Source: Table 22 of the ERG report

Key: EPAR: European public assessment report; CS: company submission, NR: not rated; NE: not estimable

ERG critique on EFS and OS trial results

APN311-302 (high risk population):

- Clinical data on the comparative clinical effectiveness of dinutuximab beta versus no dinutuximab beta are not available from a head-to-head study → APN311-302 represents the best available evidence, but the study does not inform the decision problem
  - Lack of long-term follow-up of events (i.e., limited to 5 years) potentially affects the applicability of the results for EFS and OS to the decision problem

APN311-202 and 303 (relapsed and refractory population):

- Single-arm studies, not appropriate for capturing time-to-event data, such as EFS and OS

ERG additional work:

- Using the adjusted time-to-event data supplied by the company, the ERG carried out a Cox proportional hazard analysis to generate an effect estimate of IL-2 versus no IL-2 added to dinutuximab beta and differentiation therapy with isotretinoin for the high-risk population

ERG additional work: Adjusted KM curve for EFS for APN311-302

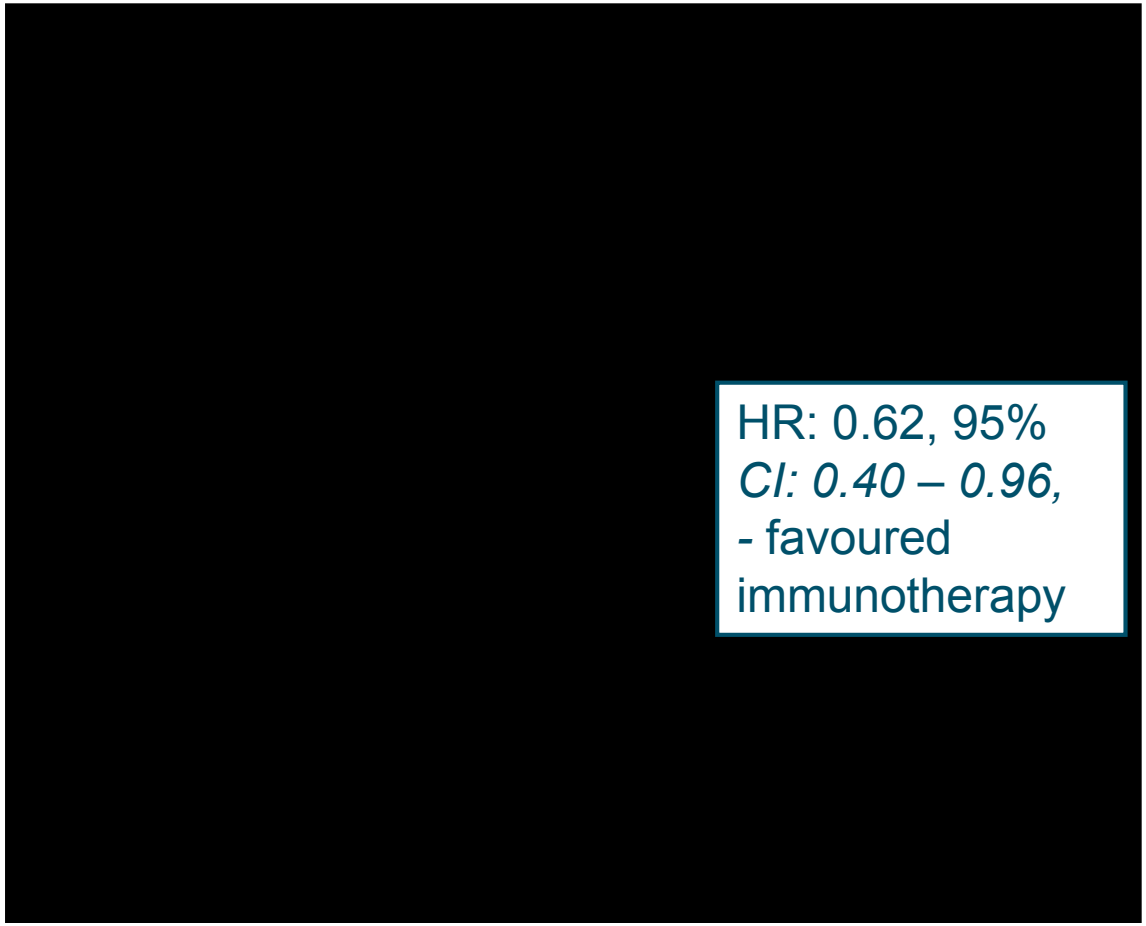
Administration of IL-2 does not provide additional benefit in EFS

ERG:
Addition of

Source: Figure 4 of the ERG report

ERG additional work: Adjusted KM curve for OS for APN311-302

Administration of IL-2 does not provide additional benefit in OS



ERG: Addition of

[redacted]

Immunotherapy can delay, and possibly prevent mortality

Key: HR: hazard ratio

Adverse events in APN311-302

High-risk population

- Dose reductions or premature discontinuations of dinutuximab beta or IL-2 were [redacted] in patients receiving concomitant treatment with IL-2
- Mean [redacted] of dinutuximab beta was [redacted], as was the total amount of dinutuximab beta [redacted] of the study
- [redacted] of dinutuximab beta occurred [redacted] treatment ([redacted])
- Changes in dinutuximab beta treatment in both groups were predominantly because of toxicity - of those receiving IL-2, [redacted] had a [redacted]
- Exposure to [redacted] the two groups ([redacted]
- [redacted])
- There were 238 instances of infection - 106 instances in patients not receiving IL-2 and 132 instances in patients receiving IL-2
  - In the no IL-2 group, 48 of the infections were Grade 3 severity, and 2 were of Grade 4 severity
  - In the IL-2 group, 60 cases were Grade 3, and 6 were Grade 4

These figures are based on the 5-day infusion schedule as per APN311-302, rather than the 10 day continuous schedule used in UK practice and modelled

Adverse events – R/R population

Summary of adverse effects of special interest experienced by ≥20% of people and thought to be related to dinutuximab beta

Adverse effect of special warning or precaution of use[43]	APN311-202 (N=44)	APN311-303 (N=54)
Pain	28 (63.6%)	35 (64.8%)
Hypersensitivity reactions		
Hypotension	22 (50.0%)	32 (59.3%)
Capillary leak syndrome	15 (34.1%)	45 (83.3%)
Eye disorders[a]	10 (22.7%)	13 (24.1%)
Peripheral neuropathy	Unclear	Unclear
Infections and infestations[b]	13 (29.5%)	3 (5.6%)
Haematologic toxicities	Unclear	Unclear
Laboratory abnormalities	Unclear	Unclear

[a] SmPC specifies neurological disorders of the eye as the adverse effect with special warning or precaution for use.

[b] SmPC specifies systemic infections as the adverse effect with special warning or precaution for use.

Abbreviation: SmPC, summary of product characteristics

Source: Table 26 of the ERG report

ERG critique on adverse events

High-risk population

- APN311-302 gives data on the adverse effects associated with the addition of IL-2 to dinutuximab beta and isotretinoin
- As anticipated (based on the known adverse effect profile of IL-2), severe adverse effects occurred more frequently in people receiving IL-2 (46% with IL-2 vs 27% without IL-2; event rate not reported in CS)
- Capillary leak syndrome, platelet abnormalities, hypotension, infections, nausea or vomiting, fever, and pain related to dinutuximab beta were more common with concomitant administration of IL-2
- More than half of patients experienced a Grade 3 or Grade 4 level infection

R/R population

- Each person in APN311-202 and APN311-303 experienced a treatment-emergent adverse event (TEAE)
- The proportion of people experiencing a TEAE remained high throughout the studies
- Pain and hypotension were each experienced by a similar proportion of people in APN311-202 compared with APN311-303
- Considerably larger proportion of people experienced capillary leak syndrome in APN311-303 (83.3%) compared with APN311-202 (34.1%)
- Other frequently reported treatment-emergent adverse effects possibly related to dinutuximab beta were general disorders and administration site conditions

No direct evidence comparing dinutuximab beta with comparators available

Company performed naïve indirect comparisons for OS only

High-risk population
Dinutuximab beta + isotretinoin with/or without IL-2 vs. historical control

Historical controls from R1 phase of HR-NBL-1 (comparing BuMel vs. CEM as consolidation myeloablative therapy in high-risk neuroblastoma) n=450

Relapsed or refractory population
Dinutuximab beta plus IL-2 plus isotretinoin vs. no dinutuximab beta

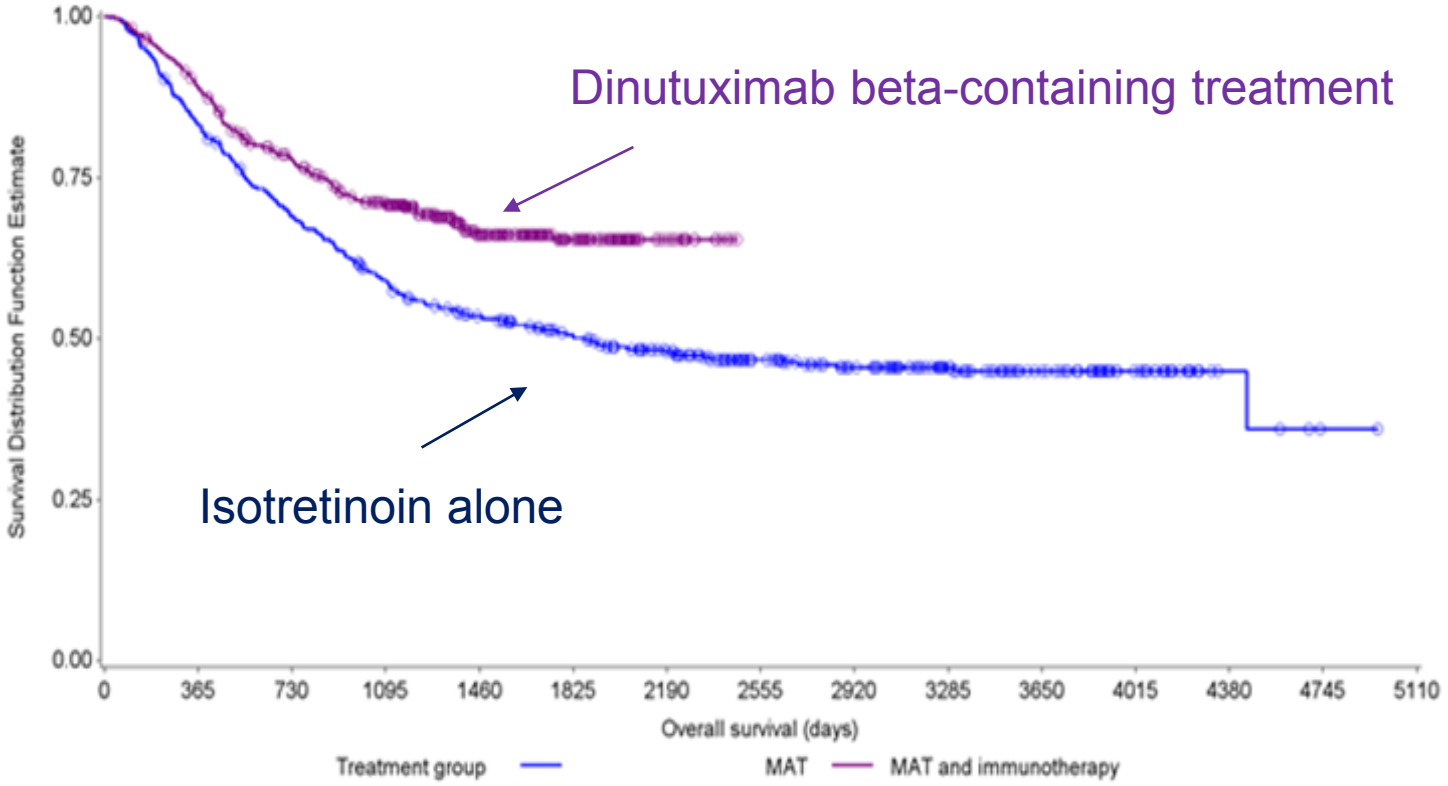
2 historical controls:
a) R1 phase of HR-NBL-1 who experienced relapse n=52
b) Garavanta retrospective study comprised only those with a date of initial diagnosis of 1999 or later. Patients received tumour resection, chemotherapy and MAT followed by ASCT, but no immunotherapy used n=29

- Difference in OS evaluated using the log-rank test
- HRs and 95% confidence intervals (Cis) provided for the indirect comparisons of the relevant APN311 study versus historical control from R1
- HR adjusted for prior treatment (BuMel vs CEM, MYCN status, and age at diagnosis and INSS stage)

➢ ID799 STA used HRs directly from RCT data

KM curves for OS of isotretinoin alone vs. dinutuximab beta-containing treatment

High-risk population



Source: Figure 10 of the ERG report

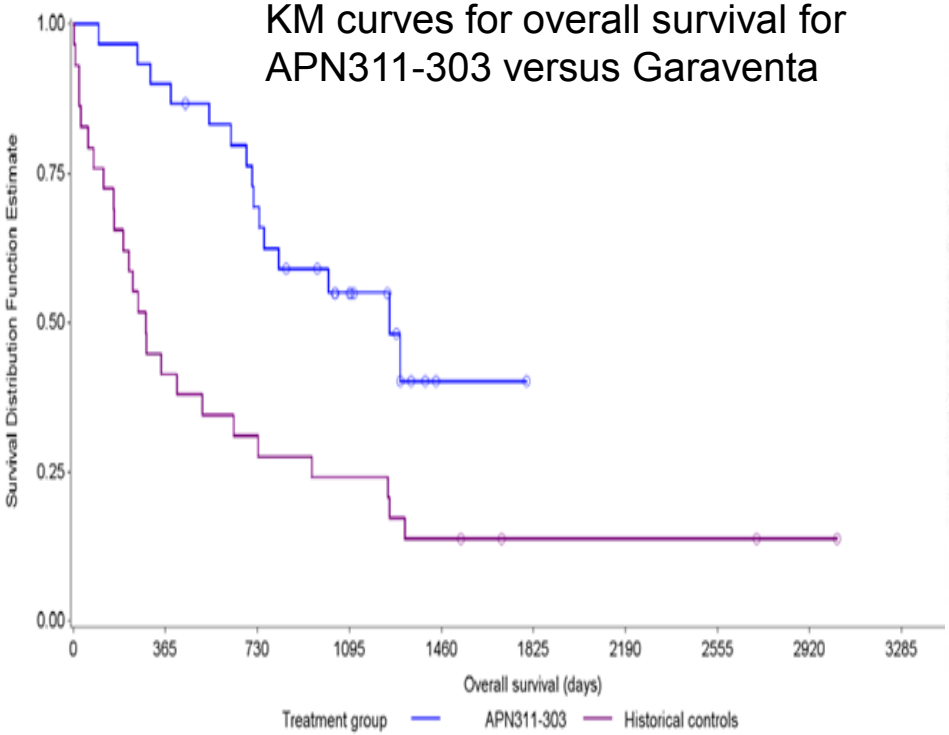
Dinutuximab beta in combination with isotretinoin with or without IL-2

[redacted]

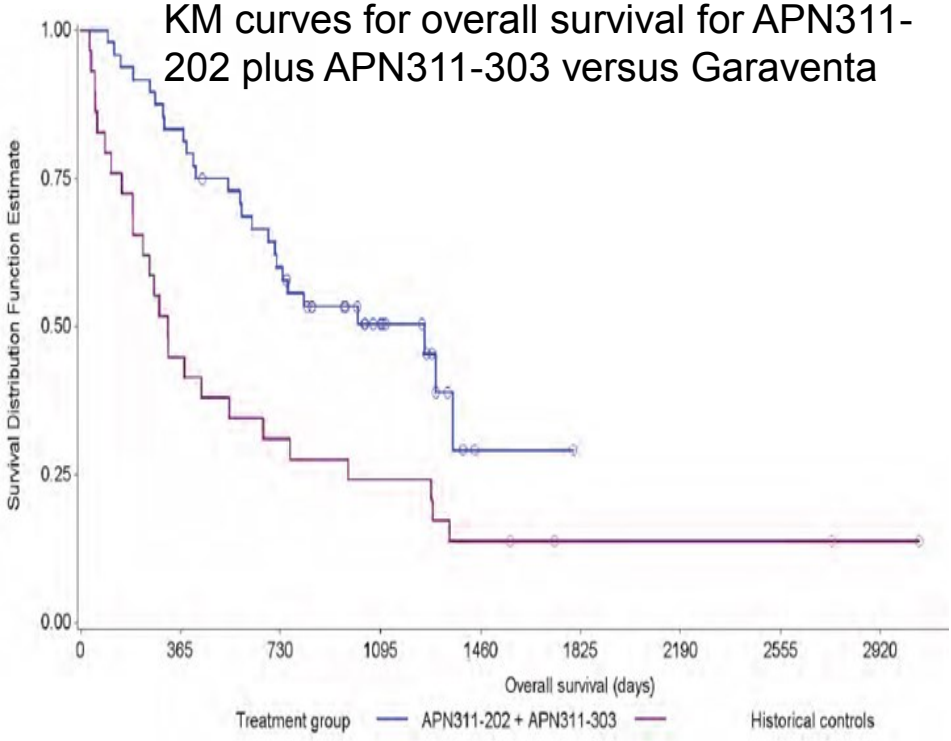
KM curves for OS

Relapsed/Refractory population

KM curves for overall survival for APN311-303 versus Garaventa



KM curves for overall survival for APN311-202 plus APN311-303 versus Garaventa



Source: Figures 14, 15 of the ERG report

[redacted]

ERG's critique of company's naïve indirect comparisons to estimate OS between treatments

- Indirect treatment comparison involving dinutuximab beta was not possible due to the lack of comparable clinical trials, company carried out a naïve comparison
  - ERG requested a Match Adjusted Indirect Comparison (MAIC) at clarification stage, but company did not provide
- ERG disagrees with company: naïve indirect comparisons versus historical controls at risk from the same type of bias arising from lack of randomisation but also from confounding

High-risk population vs historical control:

- APN311-302 and the historical control R1 are comparable but there is an imbalance between groups in proportion of people without residual disease – bias to results
- People in APN311-302 received BuMel as their consolidation myeloablative therapy ←→ R1: half of the people received CEM as their consolidation therapy

Relapsed/Refractory population vs. historical controls

- People in APN311-202 and APN311-303 might not be representative of those in the UK with these stages of disease
- Garavanta: historical control of 29 people; 24% of patients had progressive disease – different outcome to those who are not at that stage of disease; broad range of treatment
- Baseline characteristics not reported for cohorts
- Interpret results with extreme caution

Key issues: Clinical effectiveness

Overarching issues:

- Do the results of APN311-302 and the naive comparison provide robust estimates of treatment effectiveness in the high risk population to inform decision making?
- Are the estimates robust in the longer-term?
- Would a match adjusted indirect comparison (MAIC) provide more certainty regarding the treatment effectiveness of dinutuximab beta in the high risk population?
- Do the results of APN311-303 and APN311-202 and the naïve comparison provide a robust estimates of the treatment effect in the relapsed and refractory (R&R) population to inform decision making?

Other issues:

- Are the results of APN311-303 and APN311-202 for the R&R population generalisable to the NHS in England?
- Does the dosing schedule in APN311-302 (five daily infusions) reflect what is expected in NHS clinical practice?
- More than half of the people experienced a Grade 3 or Grade 4 level infections. Is the level of infection acceptable?

Cost-effectiveness evidence

Key cost-effectiveness issues (I)

- Clinical inputs:
  - Is the evidence base for the relapsed model fit for purpose and robust enough to inform decision making?
  - Is the evidence base for the high risk model fit for purpose and robust enough for decision making, in particular:
    - Company's naïve comparison?
    - ERG's alternative approach?
    - Is a match-adjusted indirect comparison (MAIC) or simulated treatment comparison (STC) required to provide a more robust estimate of treatment effect for the modelling?
- Model assumptions:
  - Is the company's approach to modelling administration based on body surface area appropriate? *(key driver)*
  - Is the modelling of hospitalisations appropriate?
  - Should the impact of infections have been captured in the modelling?
  - Is the modelling of the dosing schedule appropriate (continuous infusions over 10 days)?
  - Is the company's and ERG's 10-year cure assumption appropriate? (*upheld appeal point in TA507*)
  - Are the assumptions around treatment costs and resource use in the failure state appropriate?
  - Is the company's approach to modelling utility values appropriate?
  - Is the 1.5% discount rate for costs and health effects appropriate?

Key cost-effectiveness issues (II)

- What is the most likely cost-effectiveness estimate for the high risk population?
- Target population for this technology is a paediatric patient group – legal issues?
- Is end-of-life applicable?
- Innovation?
- Equalities issues?

Company's model structure

Partitioned-survival (area-under-the-curve) model to assess cost-effectiveness of dinutuximab beta vs isotretinoin

Partitioned Survival Analysis with 3 states and starting age 3 years:

- **Event-free state** (EFS)
- **Failure state** (FS)
- **Death**

➢ ID799 model health states: stable, failure, and death

- Proportion of patients occupying the different health states from cycle 0 until the point of the cure threshold based on a cohort-based partitioned survival model
  - *Referred to as the 'short-term model'*
- Economic outcomes for the first five cycles (first five months) of the model are estimated in a decision-tree-based model
- The economic model after the cure threshold is also a cohort-based partitioned survival model
  - *Referred to as the 'long-term model'*
- Time is discretised into monthly cycles for the short-term model and yearly cycles for the long-term model
- lifetime horizon of 90yrs, no half-cycle correction applied, NHS & PSS perspective
- Discount rate 1.5% [ID799: 1.5%]

Focus of economic analyses

- Company provided 2 models
  - one in the high risk population
  - and one in the R/R population
- ERG has focussed its review on the high risk population
- It **did not consider the R/R population further** due to:
  - The evidence base for the relapsed model being extremely poor and unfit for purpose, hence it is not robust enough to inform decision making
  - The company's clarification response showed that the fully adjusted HR's produced a HR below 1 (when using APN311-202 study), therefore the results and the model results lack clinical meaningfulness
  - Dinutuximab beta is always given first line in the UK and clinicians would not retreat patients unless there was evidence supporting this (there are no ongoing or planned studies)
  - The company doesn't support retreatment with dinutuximab beta

Company's modelling assumptions

Element	ID910 Company assumption & ERG response	ID799 dinutuximab alpha committee conclusions
Dosage	Continuous infusion over the first 10 days ERG: 10 day continuous infusions reflect UK practice (clinical trial 5 days) → unclear if the method of admin impacts treatment effectiveness and the safety profile of the drug	Daily dose of 17.5 mg/m2 on days 4–7 during courses 1, 3 and 5 (lasting ~ 24 days) and on days 8–11 during courses 2 and 4 (lasting ~ 28 days) Course 6 includes treatment with isotretinoin alone
Cure model and threshold used	a) patients in EFS state for 5yrs are cured b) after 10yrs in EFS a patient assumed cured *(Base case).* ERG: 10yrs	10yrs (but appealed).
Mortality rate in cured state	5.6 factor applied to the age and gender matched mortality in the UK general population. ERG: agrees, but points out that difficult to estimate the increase	Annual standardised mortality ratio of 5.6 from the childhood cancer survivor study for stable health state.
Costs and resource use in Failure state	Administration cost for FS was based on procurement cost for chemotherapy drugs (£2,620.54) ERG: cost of a hospital day (£934/day) should be used to calculate the admin costs per cycle (total of £4,670 for 10 days in the hospital). Should be adjusted for wastage	Cost of a hospital day should be used to calculate the admin costs per cycle.

*assumptions used in ID799 dinutuximab alpha are included for reference

Element	ID910 Company assumption & ERG response	ID799 dinutuximab alpha committee conclusions
HRQOL	12.5% decrement associated with having the disease compared with the general population based on portwine et al ERG: agrees with having a constant utility decrement applied after the cure threshold, but a few concerns remain about plausibility	13% reduction in general population utility estimate based on Portwine et al – committee agreed reasonable but uncertain
Adverse events	Assumed that utility values for each health state do not differ by treatment arm. Company did not identify any studies from the literature review that estimated the impact of adverse events on patients' QOL, therefore did not include utility values or decrements in the analysis. ERG: unclear if the administration method bears any effect on dinutuximab beta's safety profile → conducted scenario analysis	Adverse reactions during treatment were severe (as reflected in the utility values of 0), and the effects stopped when treatment ended
Admin – Body surface area	Median BSA from APN311-302 (0.63m^2, 4 vials) used for most of the cost calculations. For patients with a BSA greater than 0.83m2, 6 vials may be required to achieve the recommended dose. Company assessed impact in a scenario analysis ERG: Company did not provide the BSA categories for APN311-302, but from the maximum height and weight provided in the CSR, the ERG estimated a maximum BSA of 1.66m^2 in the trial. Remains uncertain what percentage of patients would have a BSA greater than 0.83m2 and thus require 6 vials of treatments	4.8% of patients included in ANBL0032 had a body surface area over 1 metre^2 Weighted average to account for additional vials needed for BSA>1m2
Hospitalisations	APN311-302 study: mean hospitalization days not reported Model: total of 54 days most due to receiving IL-2, 15 days without IL-2. Hospitalisations for infections not included ERG: Most of the hospitalisations were due to receive IL-2 with dinutuximab	Mean of 35 hospital days based on hospitalisation data from ANBL0032.

Element	ID910 Company assumption & ERG response	ID799 dinutuximab alpha committee conclusions
Treatment effectiveness	**Dinutuximab arm:** KM curves from the 302 study for the 7yrs that KM data were available, then parametric curves (Gompertz) to extrapolate for the 3yr horizon of the short term model. **Isotretinoin arm:** unadjusted KM data from the historical control R1 used to estimate OS Hence **naïve comparison** of KM (and fitted data) from unadjusted 302 data, with unadjusted R1 data was carried out ERG: Severe concerns with the estimation of treatment effectiveness in the economic analysis (disagrees with the approach of using OS and EFS KM data for dinutuximab beta for seven years, and then using estimated survival data for three years; lack of appropriate: methods; PH assumptions; expert opinion; uncertain use of piecewise approach; log-cumulative hazard plots)	ANBL0032 trial (n=226; International, multicentre, partly randomised, event-driven trial of dinutuximab alpha, GM-CSF, IL-2, and isotretinoin vs isotretinoin)
EOL	Company does not explicitly state that they are requesting that dinutuximab beta be considered in the end of life setting, but they provide a rationale for end of life considerations ERG: end-of-life criteria not met (life expectancy is uncertain; life extension not available, data immature)	Life expectancy: median 4yrs (doesn't meet criterion) Life extension: 33.7mo (2.81 LYs), (meets this criterion) EOL not met overall

ERG's comment on company's model structure

- Company's modelling approach and structure is unnecessarily burdensome and removes transparency from the formulae and calculations within the model -- leads to a higher probability of errors in formulae, and a lower probability of all errors being identified during the ERG's review process
- Time horizon (90 years) reasonable
- Half-cycle not applied: for the monthly cycles, this is generally fine, the yearly cycles in the long-term model should have been adjusted
- Quantification of the survival benefit associated with dinutuximab beta has a high degree of uncertainty
- ERG accepts the 1.5% discount for the base case analysis, but advises exploring the impact of the discount in an additional scenario analysis with a discount rate of 3.5%

ERG's comment on comparators used in the model

- The treatment and comparator arms in the model, include IL-2 as a treatment, even though this is not reported in the CS

- Patients in the trial received six cycles of isotretinoin treatment, people in the model received *only five cycles* → unclear why the company modelled five cycles of treatment with isotretinoin

- 10 continuous infusions reflects current practice in the UK, but unclear if the method of administration (daily vs. continuous) would have had any impact in terms of treatment effectiveness and the safety profile

- Issue with CEM (carboplatin, etoposide, melphalan) in R1: likely to be a poor reflection of the maintenance treatment for neuroblastoma patients in the UK. Clinical outcomes for R1 patients are negatively biased due to half of the patients receiving CEM instead of BuMel as consolidation therapy, before receiving isotretinoin
  - implications are that the baseline health of the population receiving isotretinoin is likely to be poorer than that of the population receiving dinutuximab beta plus isotretinoin. To have a valid estimate of relative effectiveness of dinutuximab beta plus isotretinoin compared with isotretinoin, it needs to be adjusted for the type of consolidation therapy.

Company's estimation of treatment effect in the high risk model

OS

- **Dinutuximab arm:**
- used KM curves from APN311-302 for the time period where KM data were available (approximately seven years in APN311-302), and then used a parametric curve to extrapolate the clinical data for the rest of the short-term model's time horizon (three years)
- The final OS and EFS curves used in the model are therefore based on the respective KM curves available, followed by a parametric tail fitted with Gompertz models for both clinical outcomes
- **Isotretinoin arm:** unadjusted KM data from the historical control R1 used to estimate OS

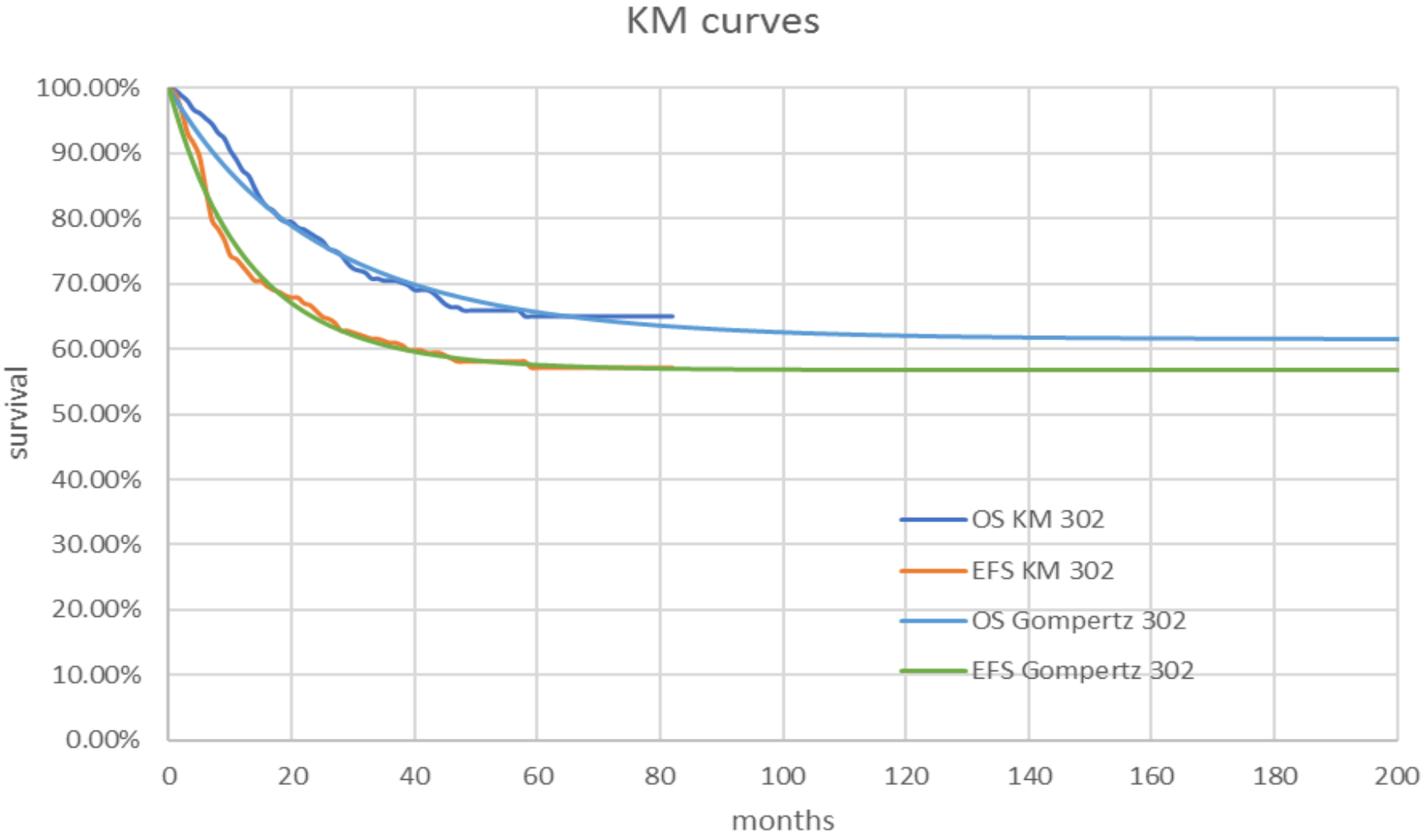
Estimating treatment effectiveness in the model was based on a **naïve comparison** of KM (and fitted) data from unadjusted APN311-302 data with unadjusted R1 data

EFS

- Absolute separation between OS and EFS is estimated in every cycle
- Using the following formula: [OSisotretinoin – (OSdinutuximab – EFSisotretinoin)]

Company's modelling of treatment-effectiveness

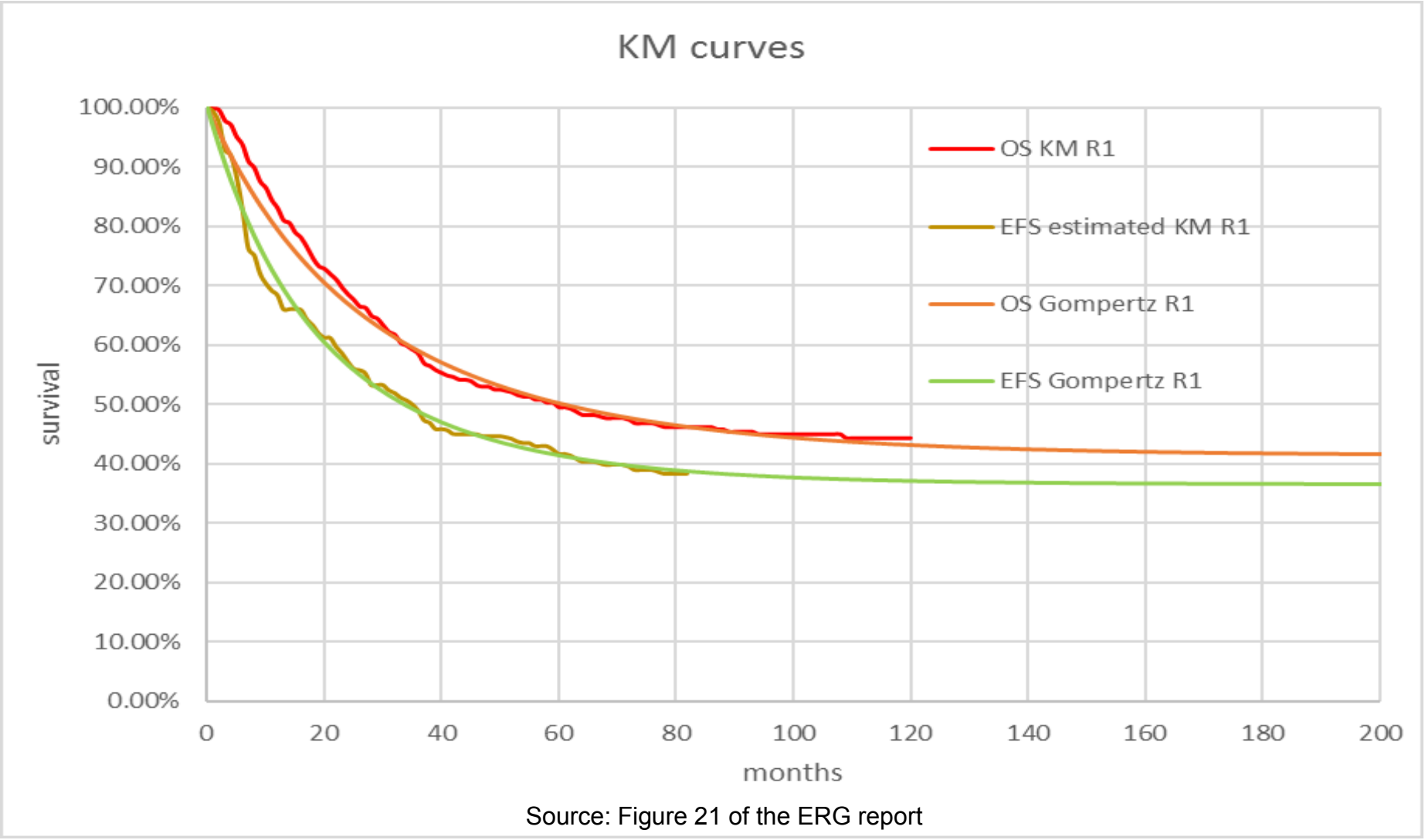
Kaplan-Meier data for OS and EFS for APN311-302 along with the fitted Gompertz curves



Source: Figure 20 of the ERG report

Company's modelling of treatment-effectiveness

KM data for OS for isotretinoin from R1 and estimated KM data for EFS for isotretinoin from R1 along with the fitted Gompertz curves



Source: Figure 21 of the ERG report

ERG critique: of company's modelling of treatment effectiveness

Two overarching concerns:

1. **Lack of maturity of OS data and non-existence of EFS data in historical control R1**
2. **Naïve (unadjusted) analysis of the relative treatment effectiveness of dinutuximab beta compared with isotretinoin**
   - Results in sampling error plus systematic error due to imbalance in prognostic factors and effect modifiers
   - Clinical outcomes for R1 patents are negatively biased due to half the patients receiving CEM instead of BuMeL as consolidation before receiving isotretinoin
   - ERG requested a MAIC of the full 302 population vs. the group receiving isotretinoin alone in the Yu et al RCT to provide a better comparison than using R1

Company's adjusted HRs for direct comparison of OS in APN311-302 vs. historical control R1

At clarification, the company provided HRs and 95% CIs for the indirect comparisons of OS in the APN311-302 study versus historical control R1, adjusting for prior treatment (BuMel vs CEM), MYCN status, and age and INSS stage at diagnosis

- ERG was concerned about the process for estimating the adjusted OS HR, and is unclear if it included all covariates

[redacted]

ERG used the OS HR for exploratory analysis (results need to be interpret with caution)

Source: Table 36 of the ERG report

Health related quality of life in the model (I)

- HRQOL not captured in APN311-302 study. Health state utility values were estimated by applying utility decrements to age-specific UK EQ-5D general population norms
  - EQ-5D norms only available for 18-75yrs+, so company used a logistic regression to estimate interpolated utility values for age 0 onwards
  - To estimate utilities for EFS and failure states for each cycle, the company applied a decrement for the UK EQ-5D general population values to reflect that patients have neuroblastoma
- Company assumed that utility values for each health state do not differ by treatment arm
- Company did not identify any studies from the literature review that estimated the impact of adverse events on patients' QOL, therefore did not include utility values or decrements associated with adverse events in the analysis

HRQOL in the model (II)

Summary of utility assumptions for the high-risk population for dinutuximab alpha [ID799] and dintuximab beta

Health state	Methods and assumptions	
	Dinutuximab alpha	**Dinutuximab beta EUSA**
Stable (0-5 years)	0.81 utility value based on patients with residual disease from Barr et al. 1999	• 12.5% decrement applied to age-specific UK EQ-5D general population norms • Decrement calculated using utility value for survivors of high risk neuroblastoma (0.84), compared with the utility value for the general population (0.96). • Both values obtained from the study by Portwine et al. 2016 and are based on the HUI3
Stable (5+ years)	• 12.5% decrement applied to age-specific UK EQ-5D general population norms • Utility value for survivors of high risk neuroblastoma (0.84), compared with the utility value for the general population (0.96) • Both values were obtained from the study by Portwine et al. 2014 and are based on the HUI	
Failure	• 0.56 utility value based on patients with recurrent disease from the study by Barr et al.,2016	• 41.7% decrement applied to age-specific UK EQ-5D general population norms • Decrement calculated using HUI2 utility value for patients with recurrent disease (0.56) from Barr et al. 2016, compared with the HUI3 utility value for general population (0.96) ofrom the study by Portwine et al. 2016
Age adjusted UK EQ-5D general population norms	EQ-5D = 0.9508566 + 0.0212126*male – 0.0002587*age – 0.0000332*age^2 based on paper by Ara et al. 2010	U(age)= 1/(1+e^(α*age+β))
Abbreviations: HUI, health utility index; EQ-5D, euroqol-5 dimensions		

Source: Table 43 of the ERG report

ERG critique of HRQOL in the model

- ERG cannot draw any final conclusions on which values should be used to estimate quality of life in the economic model
  - Although seems more appropriate to account for the impact of age for the entire model, for both the EFS and the FS health states, the decrements applied to the UK general population remain a source of uncertainty
  - ERG disagrees with the methodology used to adjust for age and considers that the published algorithm by Ara et al. 2010 should have been used instead
  - The ERG cannot anticipate the impact of using a different methodology for adjusting for age in the final ICER
- Company assumed no difference in utilities in the model by treatment arms
  - AEs are substantially worse for patients on dinutuximab beta than on isotretinoin
  - This approach is potentially overestimating the quality-adjusted life year (QALY) gain associated with dinutuximab, as the impact of its AEs are not being captured on patients' quality of life

Failure health state costs and resource use

- In the CS, the administration cost used for the failure state was based on a procurement cost for chemotherapy drugs rather that the delivery of the therapy
  - ID799 dinutuximab alpha: ERG concluded that given the failure state treatment regimen will be delivered as inpatient care over 5 days (topotecan/cyclophosphamide is given intravenously for 5 days), an inpatient hospital cost would have been more appropriate
  - ERG agree with conclusion in ID799, the cost of a hospital day (£934 per day) should have been used to calculate the administration costs per cycle (amounts to a total of £4,670 for 10 days in the hospital. The chemotherapy procurement cost used in the model originally was £2,620.54)
  - Failure state costs should also be adjusted for wastage
- In the CS, once patients enter the failure health state, they accrue the costs associated with the failure state until death
  - ERG: The treatment regimen associated with the failure state should only be given until further disease progression or up to one year without progression. More appropriate to calculate the proportion of newly relapsed patients entering the failure state in each cycle and track disease progression for these patients
  - Likely that the FS treatment costs are being overestimated in the analysis

Company's base case results

High-risk population

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£190,521	13.97	-	-	£22,338
Dinutuximab beta + isotretinoin	£311,569	19.39	£121,048	5.42	
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years					

Source: Table 53 of ERG report

- In response to factual accuracy check, the company provided a revised ICER calculated using an MAIC approach
  - No supporting documentation was provided, hence the ERG has not had an opportunity to critique these results

- ID799: Company base-case ICER: £49,000 (without PAS)
- ID799: Committee's most plausible ICER: £88,100 (without PAS)

Costs: Body surface area

When the maximum BSA is considered, the impact on the final ICER is considerable

- One of the main cost effectiveness drivers. Median BSA from APN311-302 (0.63m2) has been used for most of the cost calculations in the model
- Data seem reasonably reflective of what would be seen in UK clinical practice, but the estimates used are based on median values instead of mean BSA values
- In patients with an average BSA of 0.63m^2 →4 vials of dinutuximab beta are required
- In patients with a BSA greater than 0.83m^2, 6 vials may be required to achieve the recommended dose for dinutuximab beta
- Company does not provide the BSA categories for APN311-302, from the maximum height and weight provided in the CSR, ERG estimated a maximum BSA of 1.66m^2 in the trial
  - Remains uncertain what percentage of patients would have a BSA greater than 0.83m^2
- Company assessed the impact of changing the BSA estimate used in the economic model on the final ICER – *lower BSA ICER: £9,083; upper BSA ICER: £61,576*

ERG model corrections

Company's approach	ERG's corrections
Long-term model has annual cycles	Applied a half-cycle correction in the long-term model
5.6 increase in mortality factor applied to only female mortality	Applied to weighted male and female mortality in the UK population
Company included cost of treatment with IL-2 in the isotretinoin arm of the model	ERG does not see a clinical justification for this→ removed the costs of IL-2
Used 7.5 hospital days for the 1. cycle and 2.5 days for the 2. cycle	Included 10 days for hospitalisation
100% of patients in the dinutuximab arm assumed to receive IL-2 in	Changed the 100% assumption to 51% of patients (based on proportion in 302)
Not included the administration costs associated with treatment with IL-2	Included it
Undiscounted total costs for the stable and failure states of the short-term model	Replaced these with discounted costs
First row of costs and QALYs in the Excel model wasn't included	Included it in the model
Discounting factor estimated on a monthly basis instead of an annual basis	Corrected this to reflect annual discounting in the analysis

Impact of ERG's model corrections to company base case

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£172,236	13.61	—	—	£31,366
Dinutuximab beta + isotretinoin	£336,172	18.83	£163,808	5.22	

Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

Source: Table 56 of ERG report

- ERG **does not consider that a naïve comparison of APN311-302 and R1 data is a reliable method for estimating treatment effectiveness** for use in the company base case
- The ERG used the only available evidence to explore an alternative approach

ERG exploratory analysis: incorporating the OS HR to estimate the OS curve for isotretinoin

Two additional corrections were implemented:

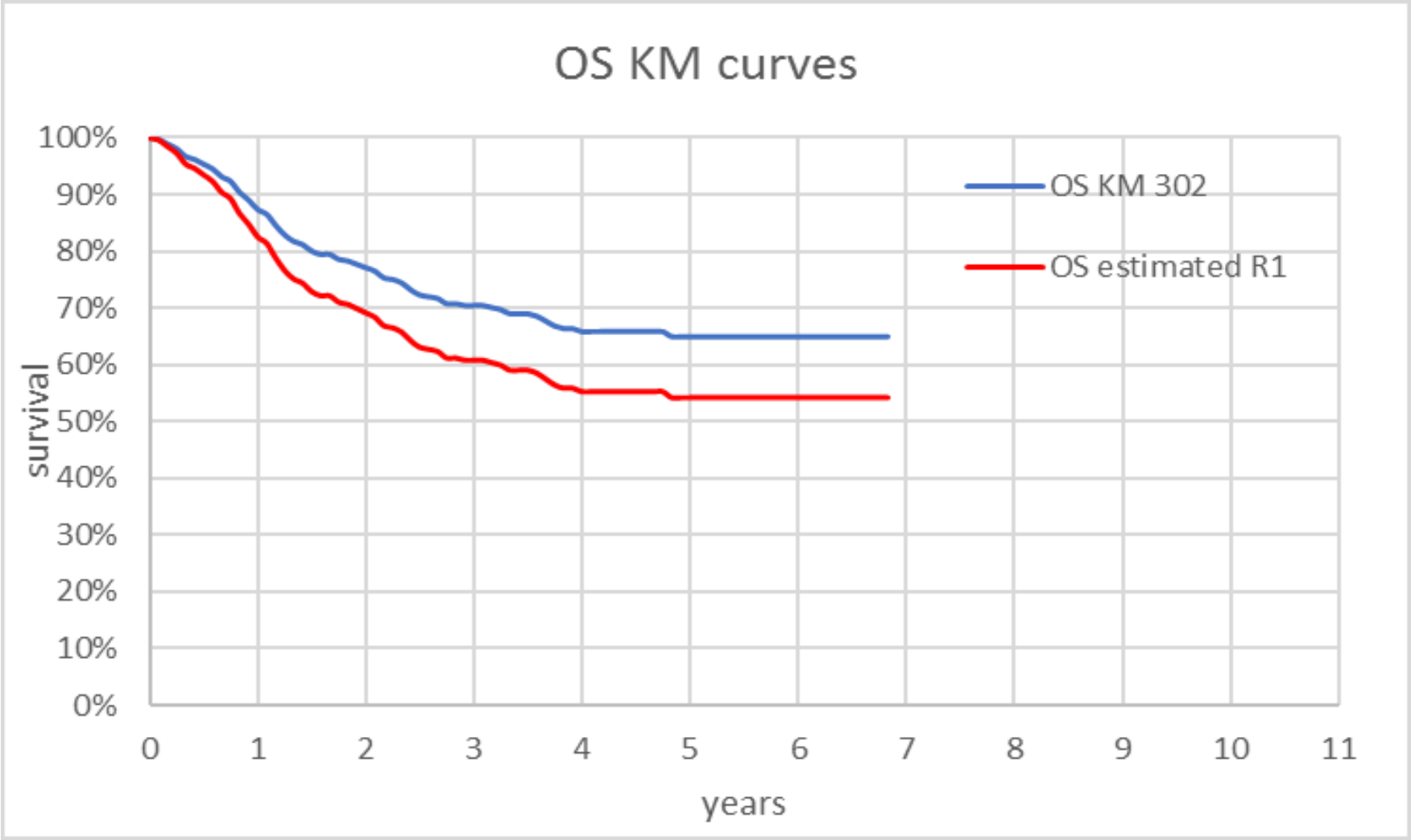
1. Restructuring the high-risk economic model to incorporate the use of the OS HR ([redacted]) to estimate OS for isotretinoin.

2. Using the relative difference between the OS HR and the EFS HR (for dinutuximab alpha compared with isotretinoin from ID799) and applying it to the adjusted OS HR estimated for dinutuximab beta of [redacted]. The ERG's estimated EFS HR for dinutuximab beta compared with isotretinoin is 1.656/1.319*[redacted]=[redacted]

   The ERG also replaced the dinutuximab beta KM curves for OS and EFS by the fitted and extrapolated Gompertz curves in the short term model to estimate OS after the 7yr KM OS curve. In doing so the ERG capped the EFS curve by the OS curve in the isotreinoin arm of the model, as they curves cross at 70 months

ERG's exploratory analysis for OS (I)

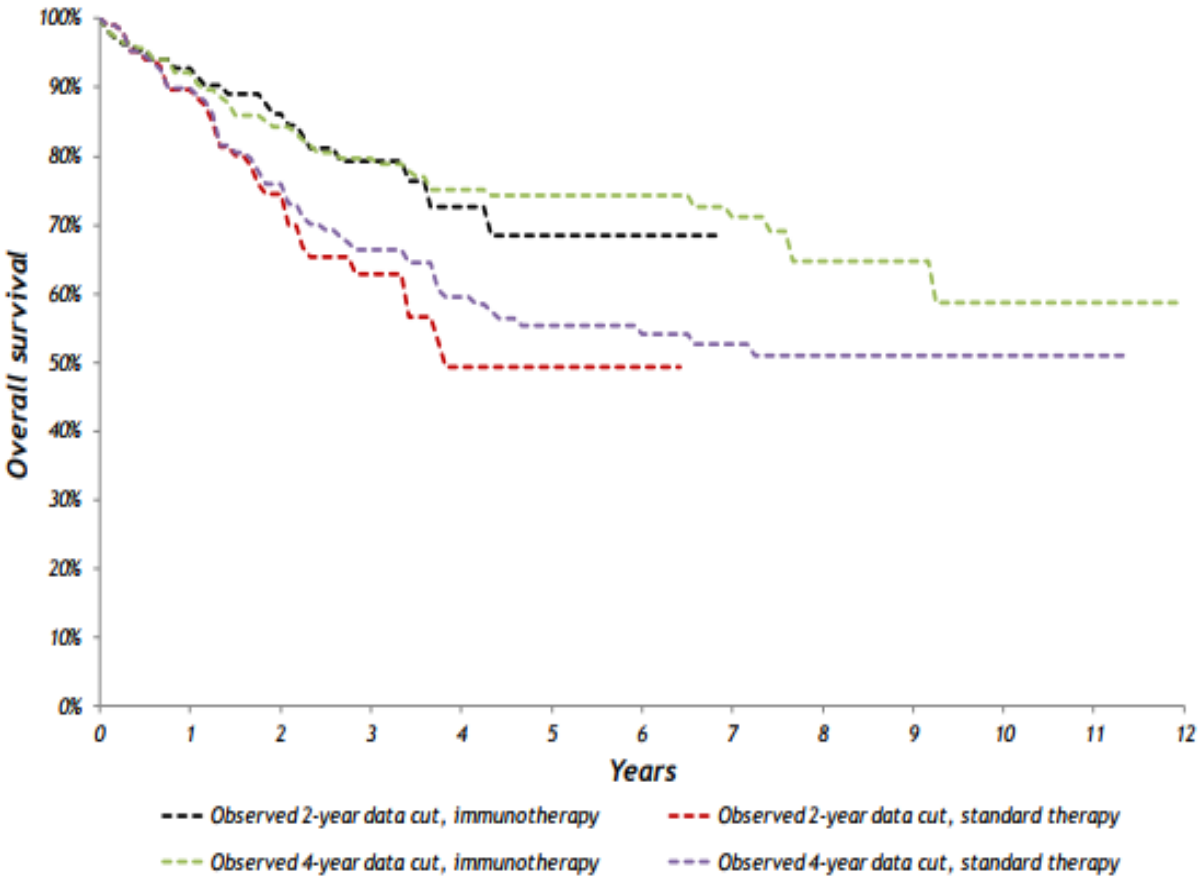
Unadjusted OS curve for dinutuximab beta and estimated isotretinoin OS curve with adjusted HR



Source: Figure 24 of the ERG report

ERG's exploratory analysis for OS (II)

Observed OS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis – **dinutuximab alpha**



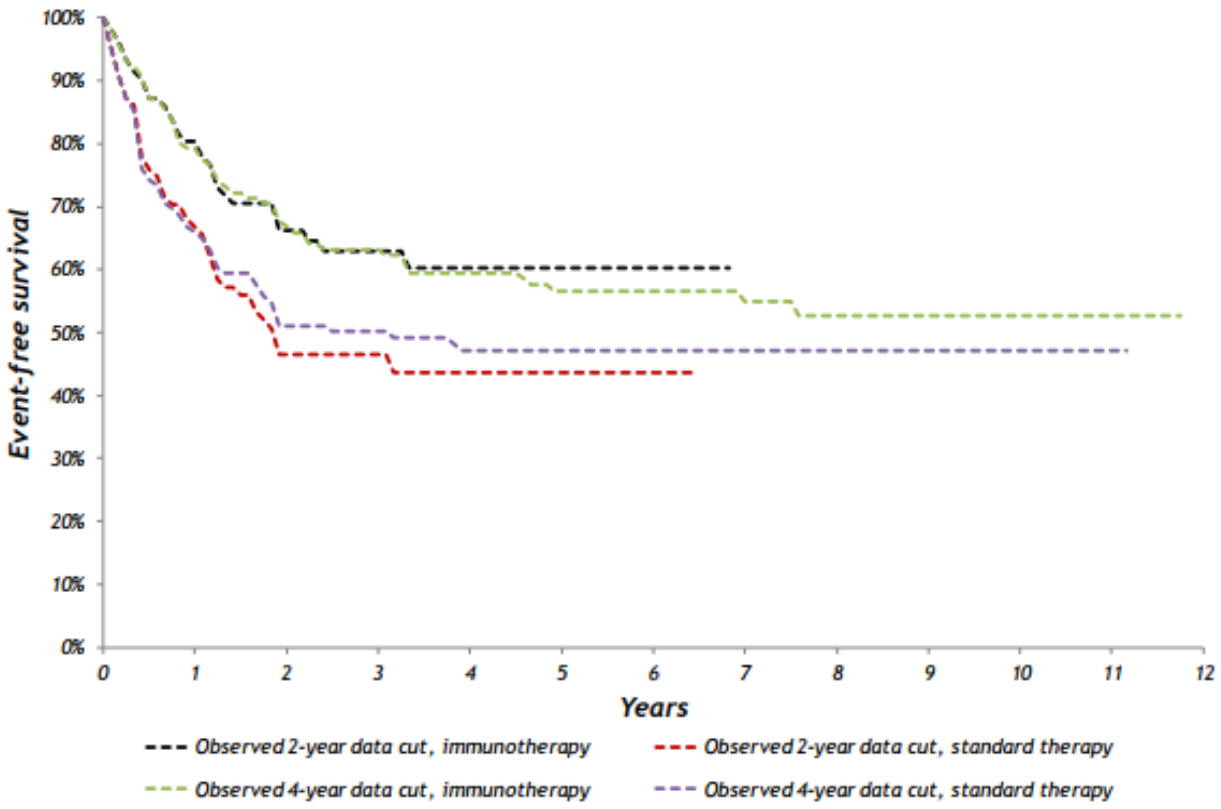
Source: Figure 25 in ERG report

- Observed data for immunotherapy and standard therapy appear to converge between 6.5 and 11 years in the updated analysis
- At 5 years, there were still 65% of patients at risk in the dinutuximab alpha arm and 47% of patients in the isotretinoin arm

- Seems plausible that the relative effectiveness of dinutuximab beta might decrease over time

ERG's exploratory analysis for EFS (I)

Observed EFS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis – **dinutuximab alpha**

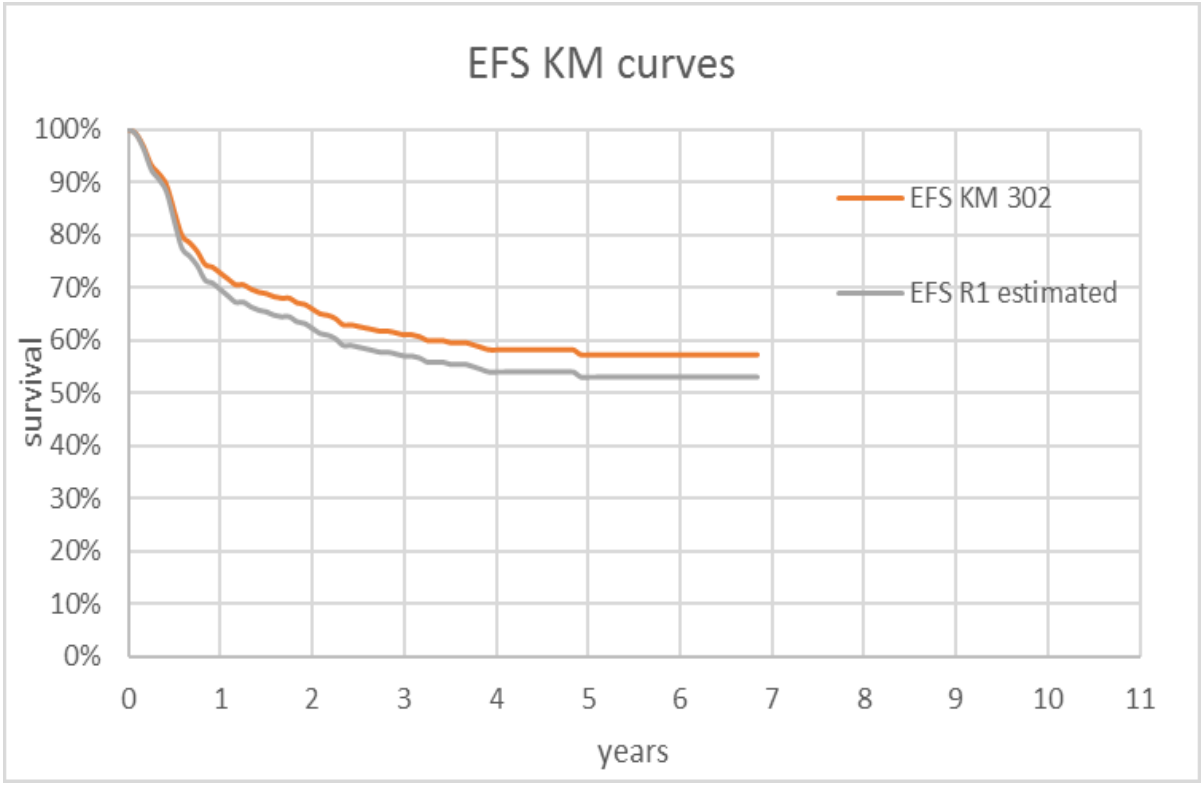


Source: Figure 27 in ERG report

- Observed data for immunotherapy and standard therapy appear to converge between 4.5 and 11 years in the updated analysis
- From year 7.5, dinutuximab alpha is associated with a gain in EFS by 7%
- Dinutuximab alpha curve seems similar to the shape of the EFS KM curves for dinutuximab beta from APN311-302 when the longer follow-up data is considered
- Seems plausible that the relative effectiveness of dinutuximab beta might decrease over time

ERG's exploratory analysis for EFS (II)

Unadjusted EFS curve for dinutuximab beta and estimated isotretinoin EFS curve with adjusted HR



Source: Figure 28 in ERG report

- Direct comparison between the dinutuximab alpha and beta curves is flawed
- ERG took the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission and applied it to the adjusted OS HR estimated for dinutuximab beta
- 1.656/1.319* [redacted] = [redacted]
- At year 7, the EFS curves seem to be separated by approximately 4%
- Dinutuximab beta is expected to delay events, rather than prevent them

Summary of ERG's exploratory analyses

Problem in CS	ERG's amendment	Level of mitigation	Proposed approach
Naïve comparison of OS data	Use of adjusted HR for OS	**Problem partially mitigated** Some adjustment for patients' characteristics and previous treatments was applied HR estimation method is flawed andunlikely that the use of HRs is an appropriate method of analysis	**An indirect comparison of dinutuximab beta versus isotretinoin and versus dinutuximab alpha should be undertaken** **The major methods applicable in this case are an MAIC and/or an STC**
Naïve comparison of EFS data + lack of EFS data for isotretinoin in historical control R1	Taking the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission and applying it to the adjusted OS HR estimated for dinutuximab beta	**Problem partially mitigated** Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis, through the adjusted OS HR EFS HR carries the same flaws as the OS HR It relies on the naïve comparison of the relative treatment effectiveness of dinutuximab alpha vs isotretinoin and isotretinoin beta vs isotretinoin	
Robustness of the final analysis			
Economic analysis unfit for purpose. Resulting ICERs are meaningless	**Economic analysis unfit for purpose**	**Problem partially mitigated**	**As above**

Source: Table D in ERG report

ERG conclusions on the exploratory analysis

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£29,898	16.12	—	—	£111,858
Dinutuximab beta + isotretinoin	£331,939	18.82	£302,041	2.70	

Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

Source: Table 57 of ERG report

The **ERG does not consider that the changes made to the company's model are robust enough** to provide results suitable for decision making

A more **robust estimate of the treatment effect is required before a meaningful ICER can be produced**

- The ERG identified issues relating to the estimation of utility values and costs in the economic analyses, however these only become relevant once the fundamental issues around treatment effectiveness are addressed

ERG: Further analyses required (I)

Once the fundamental issues around the estimate of treatment effect are addressed for use in the base case, the following analyses should be carried out:

1. Changing the assumption that patients entering the failure state of the economic model receive chemotherapy for the rest of their lives. The partitioned survival model should be changed to estimate newly progressed patients in both the dinutuximab beta and isotretinoin arms of the model.
   - Once newly progressed patients are estimated, an assumption needs to be made for treatment duration.
   - An assumption should also be made for the resource use required to manage relapsed patients who have gone off chemotherapy treatment, but are still alive and in the failure state;
2. The cost estimations regarding the chemotherapy regimens used in the failure state should include wastage;
3. The cost of treatment administration in the failure state should use the cost of an inpatient stay (£4,670 for five days), instead of procurement cost for chemotherapy drugs, which is used in the base case model (£2,620.54);

ERG: Further analyses required (II)

4. Concomitant medication costs in the stable state should include wastage for gabapentin;
5. The proportion of patients receiving IL-2 in the dinutuximab beta arm of the model should be explored (using 41% to reflect that 41% of children in APN311-302 had residual disease at baseline and therefore would require IL-2 as a concomitant medication as per dinutuximab beta's licence).
6. The published multiple regression to estimate age-specific UK EQ-5D in the model by Ara *et al.* should be used to estimate mean EQ-5D HSUVs for individuals in the general population.
7. A weighted analysis of costs taking into consideration the proportion of patients falling into different BSA categories.
8. A discount rate of 3.5% (instead of 1.5%) for costs and benefits should be used to explore structural uncertainty in the analysis;
9. Probabilistic sensitivity analysis should be undertaken to incorporate the impact of varying relative treatment effectiveness estimates on the final ICER.

End-of-life
Criteria not met

NICE criterion	Company assessment	ERG assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Survival in both relapsing and high-risk patients is expected to be shorter than 2 years Median survival for relapsing patients (Garaventa control) was 318 days High-risk patients included in the SIOPEN HRNBL1 study and who did not receive immunotherapy (R1 control), the median survival was 629 days	Median survival of 629 days is uncertain It is unclear whether the data cited are post-relapse Company reports a median OS of 1,869 days and a mean OS of 2,447.1 days for historical control R1 End of life criterion of life expectancy of has not been met for high-risk neuroblastoma
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Immunotherapy with dinutuximab beta and 13-cis RA with or without IL-2 has shown to provide statistically significantly better OS for patients with high-risk neuroblastoma Median OS time was longer in APN311-202+ APN311-303 patients compared with the historical control patients (1254 days vs. 318 days, respectively)	Log rank test indicated that there is a statistically significant difference between dinutuximab beta vs. isotretinoin in OS in high-risk neuroblastoma ($p < 0.0001$), but an estimate of the additional survival is not yet available ERG considers that OS data for APN311-302 are immature For relapsed neuroblastoma ERG considers that the populations of APN311-202 and APN311-303 are not representative of relapse in the UK

Source: Table 58 in ERG report

Innovation

- Dinutuximab beta Apeiron's main benefit stands in its continuous infusion scheme, which shows major improvements of the safety profile by reducing pain and associated i.v. morphine use
- Together with the possibility of receiving the treatment in outpatient setting, will facilitate patients remaining on therapy and receiving the full cycle of treatment, optimizing the possibility of long-term benefits

Equalities issues

- Company: There are no equality issues surrounding the use of Dinutuximab beta Apeiron for the indicated patient population
- ERG & experts: No equalities issues identified

Key cost-effectiveness issues (I)

- Clinical inputs:
  - Is the evidence base for the relapsed model fit for purpose and robust enough to inform decision making?
  - Is the evidence base for the high risk model fit for purpose and robust enough for decision making, in particular:
    - Company's naïve comparison?
    - ERG's alternative approach?
    - Is a match-adjusted indirect comparison (MAIC) or simulated treatment comparison (STC) required to provide a more robust estimate of treatment effect for the modelling?
- Model assumptions:
  - Is the company's approach to modelling administration based on body surface area appropriate? *(key driver)*
  - Is the modelling of hospitalisations appropriate?
  - Should the impact of infections have been captured in the modelling?
  - Is the modelling of the dosing schedule appropriate (continuous infusions over 10 days)?
  - Is the company's and ERG's 10-year cure assumption appropriate? (*upheld appeal point in TA507*)
  - Are the assumptions around treatment costs and resource use in the failure state appropriate?
  - Is the company's approach to modelling utility values appropriate?
  - Is the 1.5% discount rate for costs and health effects appropriate?

Key cost-effectiveness issues (II)

- What is the most likely cost-effectiveness estimate for the high risk population?
- Target population for this technology is a paediatric patient group – legal issues?
- Is end-of-life applicable?
- Innovation?
- Equalities issues?

Authors

- **Orsolya Balogh**
  Technical Lead
- **Fay McCracken**
  Technical Adviser
- with input from the Lead Team **William Turner, Peter Hall and Malcolm Oswald**

Additional slides

Baseline characteristics in APN311-302

High-risk population

Parameter	Dinutuximab beta plus isotretinoin (N=180)	Dinutuximab beta + isotretinoin + IL-2 (N=190)	All (N=370)
Gender, n (%)	116 (64.4)	120 (63.2)	236 (63.8)
	64 (35.6)	70 (36.8)	134 (36.2)
Age at randomisation (years)	180	189	369
	3.55 (2.23)	3.79 (2.97)	3.68 (2.63)
	3.00	3.00	3.00
	0.6, 19.0	0.7, 20.0	0.6, 20.0
MYCN status, n (%)	69 (41.6)	83 (46.4)	147 (44.0)
	87 (52.4)	94 (52.5)	178 (53.3)
	10 (6.0)	2 (1.1)	12 (3.5)
	14	11	25
INSS stage at initial diagnosis	1 (0.6)	–	1 (0.3)
	16 (8.9)	18 (9.5)	34 (9.2)
	159 (88.3)	169 (88.9)	328 (88.6)
	4 (2.2)	3 (1.6)	7 (1.9)

ERG: trial population is representative of those with high-risk neuroblastoma likely to be eligible for treatment with dinutuximab beta in England

Reported event-free survival at different time points for dinutuximab alpha and isotretinoin

High-risk population

Year of follow up	Estimate (SE or 95% CI)	
	Dinutuximab alpha plus isotretinoin, IL-2 and GM-CSF	Isotretinoin alone
2	66% (SE ±5%)	46% (SE ±5%)
3	62.8% (95% CI: 53.9% to 71.7%)	46% (SE ±6%) 50.9% (95% CI: 41.6% to 60.2%)
4	59.3% (95% CI: 50.3% to 68.4%)	48.3% (95% CI: 38.9% to 57.7%)
5	56.5% (95% CI: 47.3% to 65.7%)	42% (SE ±5%) 48.3% (95% CI: 38.9% to 57.7%)

Abbreviations: CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; IL-2, interleukin 2; SE, standard error.

Reported overall survival at different time points for dinutuximab alpha and isotretinoin

High-risk population

Year of follow up	Estimate (SE or 95% CI)	
	Dinutuximab alpha plus isotretinoin, IL-2 and GM-CSF	Isotretinoin alone
2	86% (SE ±4%)	75% (SE ±5%)
3	79.5% (95% CI: 72.1% to 87.0%)	56% (SE ±6%) 67.3% (95% CI: 58.4% to 76.1%)
4	75.1% (95% CI: 67.1% to 83.1%)	61.0% (95% CI: 51.8% to 70.3%)
5	74.2% (95% CI: 66.1% to 82.3%)	59% (SE ±8%) 57.0% (95% CI: 47.5% to 66.4%)

Abbreviations: CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; IL-2, interleukin 2; SE, standard error.

Main baseline characteristics for APN311-302 versus historical Control R1

Parameter	Isotretinoin alone (N=450)	Dinutuximab beta plus isotretinoin with or without IL-2 (N=370)	Total (N=820)
Gender, n (%)			
Male	275 (61.1)	236 (63.8)	511 (62.3)
Female	175 (38.9)	134 (36.2)	309 (37.7)
Age at initial diagnosis (years)			
Mean (SD)	3.24 (2.18)	2.46 (2.60)	3.34 (2.38)
Median	2.65	2.90	2.70
Min, Max	0.1, 16.8	0.0, 19.5	0.0, 19.5
Missing	0	1	1
Age groups (years), n (%)			
<1	5 (1.1)	28 (7.6)	33 (4.0)
≥1.5[b] to <1.5	56 (12.4)	25 (6.8)	81 (9.9)
>1.5 to ≤5	322 (71.6)	249 (67.3)	571 (69.6)
>5	67 (14.9)	67 (18.1)	134 (16.3)
Missing	0	1 (0.3)	1 (0.1)
MYCN status, n (%)			
Amplified	215 (47.8)	152 (41.1)	367 (44.8)
Not amplified	204 (45.3)	181 (48.9)	385 (47.0)
Missing	31 (6.9)	37 (10.0)	68 (8.3)
INSS stage at initial diagnosis			
Local	59 (13.1)	35 (9.5)	94 (11.5)
4	391 (86.9)	328 (88.6)	719 (87.7)
4S	0	7 (1.9)	7 (0.9)

Cancer Drugs Fund

Decision points

Starting point: drug not recommended for routine use

Proceed down if answer to each question is yes

1. Why is drug not recommended? Is it due to clinical uncertainty?

2. Does drug have plausible potential to be cost-effective at the current price, taking into account end of life criteria?

3. Could data collection reduce uncertainty

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection feasible?

Recommend enter CDF

Define the nature of clinical uncertainty and the level of it. Indicate research question, required analyses, and number of patients in NHS in England needed to collect data

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dinutuximab beta Apeiron (dinutuximab beta) for high-risk neuroblastoma – [ID910]

Document B

Company evidence submission

Version 2

June 2017

File name	Version	Contains confidential information	Date
DocumentB-Dinutuximab beta Apeiron [noACIC]	**2.0**	**No [noACIC]**	**28/06/2017**

Contents

Tables and Figures **4**

1. Decision problem, description of the technology and clinical care pathway **8**

1.1 Decision problem **8**

1.2 Description of the technology being appraised **11**

1.3 Health condition and position of the technology in the treatment pathway **12**

1.3.1 Brief overview of disease or condition for which technology is indicated 12

1.3.2 Summarize clinical pathway of care in a diagram showing context and proposed placement of technology within the pathway 17

1.4 Equality considerations **20**

2. Clinical effectiveness **21**

2.1 Identification and selection of relevant studies **21**

2.1.1 Research question 1: Treatment of high-risk neuroblastoma during maintenance phase 21

2.1.2 Research question 2: Treatment of patients with relapsed or refractory neuroblastoma 23

2.2 List of relevant clinical effectiveness evidence **25**

2.2.1 Supportive studies excluded from discussion 32

2.3 Summary of methodology of the relevant clinical effectiveness evidence **32**

2.3.1 Comparative summary of clinical trial methodology 32

2.3.2 Summary of baseline characteristics and demographics of trial participants 38

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence **45**

2.5 Quality assessment of the relevant clinical effectiveness evidence **50**

2.5.1 Methods for assessing risk of bias 50

2.5.2 Evaluate how closely trials reflect routine clinical practice in England 52

2.6 Clinical effectiveness results of the relevant trials **53**

2.6.1 APN311-302 53

2.6.2 APN311-303 56

2.6.3 APN311-202 58

2.7 Subgroup analysis **59**

2.7.1 APN311-302 59

2.7.2 APN311-303 60

2.7.3 APN311-202 61

2.8 Meta-analysis **62**

2.8.1 Meta-analysis qualitative overview 62

2.8.2 Studies providing evidence not related to dinutuximab beta (studies identified in the systemic literature review) 63

2.8.3 Pooled analysis of evidence related to dinutuximab beta (studies APN311-303 and APN311-202) 63

2.8.4 Comparison of outcomes 64

2.9 Indirect and mixed treatment comparisons **70**

2.9.1 Analysis of relevant studies vs historical controls 70

2.9.2 Summary of results of analyses of relevant studies vs historical controls 73

2.9.3 Uncertainties in the indirect and mixed treatment comparisons 84

2.10 Adverse reactions **85**

2.10.1 Studies reported in Section 2.2 85

2.10.2 Adverse events 86

2.10.3 Safety overview 95

2.11 Ongoing studies **100**

2.12 Innovation **101**

2.13 Interpretation of clinical effectiveness and safety evidence 102
2.13.1 Statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology..... 102
2.13.2 Discussion of the strengths and limitations of the clinical evidence base for the technology..... 107

3. Cost effectiveness 110
3.1 Published cost-effectiveness studies 110
3.2 Economic analysis (de novo analysis)..... 110
3.2.1 Patient population 110
3.2.2 Model structure 111
3.2.3 Key features of the de novo analysis..... 113
3.2.4 Intervention technology and comparators 113
3.3 Clinical parameters and variables 115
3.3.1 How are clinical data incorporated into the model? 115
3.3.2 Transition probabilities 117
3.3.3 Adverse reactions 118
3.4 Measurement and valuation of health effects..... 119
3.4.1 Health-related quality-of-life data from clinical trials 119
3.4.2 Mapping..... 119
3.4.3 Health-related quality-of-life studies 119
3.4.4 Adverse reactions 127
3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis .. 127
3.5 Cost and healthcare resource use identification, measurement and valuation 129
3.5.1 Resource identification, measurement and valuation studies 129
3.5.2 Appropriateness of NHS Ref costs/PbR tariffs 130
3.5.3 Intervention and comparators, costs and resource use 130
3.5.4 Health-state unit costs and resource use 135
3.5.5 Adverse reaction unit costs and resource use..... 137
3.5.6 Miscellaneous unit costs and resource use..... 138
3.6 Summary of base-case analysis inputs and assumptions 138
3.6.1 Summary of base-case analysis inputs 138
3.6.2 Rationale for inputs chosen in the base-case analysis 142
3.6.3 Assumptions 142
3.7 Base-case results 143
3.7.1 Base-case incremental cost-effectiveness analysis results 143
3.8 Sensitivity analyses..... 144
3.8.1 Probabilistic sensitivity analysis 144
3.8.2 Deterministic sensitivity analysis 147
3.8.3 Scenario analysis..... 148
3.9 Subgroup analysis..... 150
3.10 Validation 150
3.10.1 Validation of cost-effectiveness analysis 150
3.11 Interpretation and conclusions of economic evidence..... 151

4. References 152

5. List of appendices..... 158

Tables and Figures

Table 1: The decision problem 9
Table 2: Technology being appraised 11
Table 3: Neuroblastoma Clinical Signs & Symptoms 12
Table 4: International Neuroblastoma Staging System (INSS) 14
Table 5: International Neuroblastoma Risk Group Staging System (INRGSS) 14
Table 6: Modified International Neuroblastoma Risk Groups (mINRG; Matthay 2016) 15
Table 7: Eligibility criteria used in search strategy 22
Table 8: Eligibility criteria used in search strategy 24
Table 9: Tabular overview of dinutuximab beta clinical studies 26
Table 10: List of relevant studies investigating Dinutuximab beta Apeiron 28
Table 11: Comparative summary of methodology of APN311-202, -302, -303 33
Table 12: Demographics and baseline characteristics of patients in APN311-302 (FAS) 38
Table 13: Tumour characteristics (FAS, N=370) – APN311-302 39
Table 14: Demographic profile of patients enrolled in CU-LTI program - APN311-303 39
Table 15: Status at study entry by baseline disease status – APN311-303 40
Table 16: Clinical Prognostic factors - participants in APN311-303 41
Table 17: Demographics and disease history by disease type – APN311-303 41
Table 18: Baseline characteristics (demographics and disease history) of participants in APN311-202 43
Table 19: Disease status at baseline in APN311-202 43
Table 20: Relapse/Progression prior to immunotherapy in APN311-202 44
Table 21: Summary of statistical analyses 46
Table 22: Quality assessment results for APN311-202, APN311-303, and APN311-302 53
Table 23. Study APN311-302: 3-year event-free survival 53
Table 24: Study APN311-302: Event-free survival at 1 and 2 years 54
Table 25: Study APN311-302: Overall Survival at one, two and three years 54
Table 26: Study APN311-303: Overall response in patients with evidence of disease at baseline 56
Table 27: Study APN311-303: Event-free survival (EFS) and overall survival (OS) rates in relapsed and refractory patients 57
Table 28: Study APN311-202: treatment response in patients with detectable disease at baseline 58
Table 29: Pooled APN311-303 and -202 studies - treatment response at the end of treatment 64
Table 30: Pooled APN311-303 and -202 studies - Kaplan Meier results of overall survival 64
Table 31: Pooling analysis of studies reporting OS in mIBG-treated R/R patients 65
Table 32: List of additional analyses for Dinutuximab beta Apeiron 71
Table 33: Summary of patient groups 73
Table 34: Demographics and baseline characteristics of relapse patients for pooled APN311 studies 76
Table 35: Main patient demographics and disease characteristics, APN311-302 vs Historical Control R1 77
Table 36: Kaplan Meier results of overall survival 79
Table 37: Patient characteristics – APN311-303 vs Historical Control Garaventa 80
Table 38: Kaplan Meier Results of Overall Survival 80
Table 39: Kaplan Meier Results of Overall Survival 82
Table 40: Kaplan Meier Results of Overall Survival 83
Table 41: Summary of dinutuximab beta, IL-2 and 13-cis-RA administration in APN311 studies 86
Table 42: Overall summary of treatment-emergent adverse events (TEAEs) 87
Table 43: Most frequent TEAEs reported in cycle 1 (studies APN311-303 and APN311-202) 88
Table 44: Summary of grade 3 and 4 TEAEs occurring in >1 subject in any study APN311-202 & -303 89
Table 45: Summary of SAEs occurring in >1 subject in any study 91
Table 46: Toxicities in study APN311-302 (SAF; N=366) 92
Table 47: Adverse drug reactions reported in the clinical trials submitted 93
Table 48: Total number of patients with pain at any day of the cycle 95
Table 49: Occurrence of pain-related events reported by investigators and parents by cycle 96
Table 50: Intravenous morphine use (mean) per cycle in patients receiving morphine 97
Table 51. Dinutuximab beta Apeiron ongoing studies 100
Table 52: End-of-life criteria 108
Table 53: Summary list of published cost-effectiveness studies 110
Table 54: Target treatment population size estimate 111
Table 55: Features of the de novo economic analysis 113
Table 56: Adverse reactions considered for the cost-effectiveness analysis 119
Table 57: Health-related quality of life studies: results of the studies identified in the literature review 121
Table 58: Utilities applied in the model 128
Table 59: Summary of utility values for cost-effectiveness analysis 129
Table 60: Resource utilization for neuroblastoma survivors reported in Rebholz 2011 129
Table 61: Treatment regimens 130
Table 62: Drug costs 1st line 131
Table 63: Drug costs Relapsed/refractory model 131

Table 64: Administration and hospitalisation costs 1st line 132
Table 65: Administration costs 2nd line 133
Table 66: Concomitant medication costs 135
Table 67: Monitoring costs 135
Table 68: Costs and resources associated to Stable state in the economic model 136
Table 69: Costs and resources associated to Failure state in the economic model 137
Table 70: List of adverse reactions and summary of costs in the economic model 137
Table 71: List of all variables used in the economic model 138
Table 72: Base case results 143
Table 73: Summary of predicted resource use by category of cost 143
Table 74: PSA results for Dinutuximab beta Apeiron for the first-line population 146
Table 75: PSA results for Dinutuximab beta Apeiron for the relapsed/refractory population 146
Table 76: Utilities applied in the model for scenario analysis of conservative QALYs 149
Table 77: OS and EFS values applied in the model for scenario analysis of conservative EFS and OS 149
Table 78: Summary results of scenario analysis 150

Figure 1: Phases of multimodal therapy for high-risk neuroblastoma 18
Figure 2: Schematic for the Search 1 of clinical evidence systematic review 22
Figure 3: Schematic for systematic search 2 of clinical evidence systematic review 25
Figure 4: Study APN311-302 Event-Free Survival (FAS) 55
Figure 5: Study APN311-302 Overall Survival (FAS) 55
Figure 6: Study APN311-303 Overall Survival Kaplan Meier curve by disease type 57
Figure 7: Kaplan-Meier Overall Survival curves, APN311-302 vs Historical Control R1 79
Figure 8: Kaplan-Meier Overall Survival curves, APN311-303 vs Historical Control Garaventa 81
Figure 9: Kaplan-Meier Overall Survival curves, APN311-202+ -303 vs Historical Control R1 82
Figure 10: Kaplan-Meier Overall Survival curves, APN311-202 + -303 vs Historical Control Garaventa 84
Figure 11: Use of morphine in study APN311-303 96
Figure 12: Use of morphine in study APN311-202 97
Figure 13: Partitioned survival model- health states with OS and EFS curves 112
Figure 14: Model diagram for the first-line population 114
Figure 15: Model diagram for the Relapse/ Refractory population 114
Figure 16: Overall Survival in the APN311-302 Historical Control Report 115
Figure 17: Illustrations of survival curves for the first-line Population 117
Figure 18: Illustrations of survival curves for the Relapsed/refractory Population 118
Figure 19: Interpolated age-specific utilities (EQ-5D population norms) 128
Figure 20: Cost-effectiveness plane for Dinutuximab beta Apeiron for the first-line population with a £30,000/QALY threshold 145
Figure 21: Cost-effectiveness plane for Dinutuximab beta Apeiron for the relapsed/refractory population with a £30,000/QALY threshold 145
Figure 22: CEAC for Dinutuximab beta Apeiron for the first-line population 145
Figure 23: CEAC for Dinutuximab beta Apeiron for the Relapsed/refractory population 146
Figure 24: Tornado diagram for DSA results (ICER) for Dinutuximab beta Apeiron for the first-line population . 148
Figure 25: Tornado diagram for DSA results (ICER) for Dinutuximab beta Apeiron for the Relapsed/Refractory population 148

Abbreviations

13-cis RA. *13-cis retinoic acid also referred to as isotretinoin*
ADCC. *Antibody-dependent cell-mediated cytotoxicity*
ADR. *Adverse drug reaction*
AEs. *Adverse Events*
AIEOP. *Associazione Italiana di Ematologia e Oncologia Pediatrica*
ALT. *Alanine aminotransferase*
ASCT. *Autologous stem cell transplant*
AST. *Aspartate aminotransferase*
ATPP. *Adenosine tetraphosphate*
BM. *Bone marrow*
BNF. *British National Formulary*
BSA. Body surface area
BuMel. *Busulfan and melphalan hydrochloride myeloablative chemotherapy*
CCTs. *Controlled Clinical Trials*
CDC. *Complement-dependent cytotoxicity*
CEAC. *Cost-effectiveness acceptability curve*
CEM. *Carboplatin, etoposide and melphalan myeloablative chemotherapy*
CHMP. *Committee for Medicinal Products for Human Use*
CHO. *Chinese hamster ovary*
CI. *Confidence interval*
CLS. Capillary leak syndrome
CNS. *Central nervous system*
COJEC. *Cisplatin, vincristine, carboplatin, etoposide, cyclophosphamide*
CR. *Complete response*
CRF. *Case report form*, *Confirmation*
CRP. *C-reactive protein*
CRS. Cytokine release syndrome
CT. *Computed tomography*
CTX. *Cyclophosphamide*
CU-LTI. *Compassionate use - long term continuous infusion*
CUP. *Compassionate use program*
DSA. *Deterministic sensitivity analysis*
EBMT. *European Society for Blood and Marrow Transplantation*
eCRF. *Electronic case report form*
EFS. *Event-free survival*
EPAR. *European public assessment report*
EQ-5D. *EuroQol five dimensions questionnaire*, *EuroQol five dimensions questionnaire*
ERIC. *Education Resources Information Center*
EU. *European Union*
FAS. *Full analysis set*
GD2. *Disialoganglioside*
GFR. *Glomerular filtration rate*
GGT. *Gamma-glutamyl transferase*
GM-CSF. *Granulocyte macrophage colony-stimulating factor*
HACA. *Human anti-chimeric antibody*
HAMA. *Human anti-mouse antibody*
haplo-HSCT. *Haploidentical haematopoietic stem cell transplantation*
HDT+SCR. *High-dose therapy + stem cell rescue*
HRNBL1. *High-risk neuroblastoma study 1 of SIOPEN*
HRQoL. *Health-related quality of life*
HS. *Health state*
i.v.. *Intravenous*
ICER. *Incremental cost-effectiveness ratio*
IL-2. *Interleukin 2 also referred to as aldesleukin*
INPC. *International Neuroblastoma Pathology Committee*
INRC. *International Neuroblastoma Response Criteria*
INRGSS. *International Neuroblastoma Risk Group Staging System*
INSS. *International Neuroblastoma Staging System*
ITT. *Intention to treat, see also FAS*
IU. *International unit*
IVIG. *Intravenous immunoglobulin*
KM. *Kaplan Meier*
LDH. *lactate dehydrogenase*
mAbs. *Monoclonal antibodies*
MAT. *Myeloablative therapy*
mIBG. *Meta-iodobenzylguanidine*
MID/EOT. *Mid-evaluation/end of treatment*
mINRG. *Modified International Neuroblastoma Risk Groups*
MKI. *Mitosis-karyorrhexis index*
MNC. *Multinuclear cells*
MR. *Mixed response*
MRD. *Minimal residual disease*

MRI. *Magnetic resonance imaging*
MYCN. *V-Myc myelocytomatosis viral-related oncogene*
N/A. *Not applicable*
NCI CTC. *National Cancer Institute Common Toxicity Criteria*
NED. *No evidence of disease*
NHS. *National Health Service*
NK. *Natural killer (cells)*
NR. *No response*
NSAID. *Nonsteroidal anti-inflammatory drug*
OS. *Overall survival*
p.o.. *per ossum (by mouth/oral)*
PAS. *Patient access scheme*
PbR. Payment-by-results
PBSCR. *Peripheral blood stem cell rescue*
PD. *Progressive disease*
PFS. *Progression free survival*
PK. *Pharmacokinetics*
PP-RESP. *Per protocol population for overall response evaluation*
PPS. *Per protocol set*, *Per protocol set*
PP-SURV. *Per Protocol Set - survival analysis*, *Per protocol population for event free and overall survival*
PR. *Partial response*
PSA. *Probabilistic sensitivity analysis*
PSS. *Personal Social Services*
PT. *Preferred term*
QALYs. *Quality-adjusted life years*
QoL. *Quality of life*
R/R. *Relapsed/refractory*
RCTs. *Randomised Controlled Trials*
s.c.. *Subcutaneous*
S.D.. *Stable disease (no response)*
SAE. *Serious adverse event*
SAF. *Safety population or safety set*
SAP. *Statistical analysis plan*
SAS. *Statistical Analysis Software*
SCA. *Segmental chromosomal alterations*
SCR. *Screening visit*
SD. *Standard deviation*
SE. *Standard error*
SGPT. *Serum glutamate pyruvate transaminase*
SIOPEN. *International Society of Paediatric Oncology Europe Neuroblastoma*
SoC. *Standard of Care*
TEAEs. *Treatment-emergent adverse events*
TEM/IRN. *Temozolomide and irinotecan*
TOPO. *Topotecan*
TTFR. *Time to first relapse*
TVD. *Topotecan, vincristine, doxorubicin*
UK. *United Kingdom*
VAT. *Value-added tax*
VGPR. *Very good partial response*
WHO. *World Health Organization*

1.

2. Decision problem, description of the technology and clinical care pathway

2.1 *Decision problem*

The submission covers the technology's full marketing authorisation for this indication: *Treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures.*

In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first-line therapy, Dinutuximab beta Apeiron should be combined with interleukin 2 (IL-2).

This is relevant to NHS clinical practice; it would not be used in a wider population.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with high-risk neuroblastoma who have had myeloablative therapy and autologous stem cell transplant	Patients with high-risk neuroblastoma, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease.	The appraisal will consider dinutuximab beta within its marketing authorisation.
Intervention	Dinutuximab beta Apeiron (dinutuximab beta)	As per scope	N/A
Comparator(s)	1. Isotretinoin 2. Dinutuximab (subject to NICE guidance)	Isotretinoin alone (without immunotherapy)	Drug shortage and withdrawal of marketing authorisation in EU for Unituxin (dinutuximab or ch14.18/SP2/0), precludes its use as a comparator in this submission. Furthermore, there is currently no final NICE recommendation for this product or use established within the NHS.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival (OS) • Event-free survival (EFS) • Adverse effects of treatment • Tumour response rate • Health-related quality of life (HRQoL)	Event-free survival, was tracked in place of progression-free survival in the clinical trials. Tumour response rate was also tracked in the clinical trials.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Consideration should be given to alternative standardised and validated preference-based measures of health-related quality of life that have been designed specifically for use in children. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope	N/A

Subgroups to be considered	• People with relapsed disease • People with refractory disease	No subgroups will be considered in this submission.	The final indication from SMPC includes the high-risk neuroblastoma patients, as well as patients with history of relapsed/refractory neuroblastoma, with or without residual disease. Therefore, no subgroups are considered.
Special considerations including issues related to equity or equality	No comment from final scoping	Treatment of ultra-orphan group, approximately 41 newly diagnosed patients per year in the UK (for estimation of target population please refer to Table 54)	Neuroblastoma presents primarily in young children, and more rarely in adolescents, with 90% of cases diagnosed in patients aged under 10 years (Matthay et al., 2016). Equity of treatment for children and young people with cancer is a concern, as evident from the NICE Quality Standard QS55 "Cancer services for children and young people" (NICE, 2014) and NICE Cancer Service Guideline CSG7 "Improving outcomes in children and young people with cancer" (NICE, 2005). The Cancer Patient Experience Survey in 2010 (UK Department of health, 2010) found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer. Therefore, continued access, where appropriate, to a treatment such as Dinutuximab beta Apeiron should help to promote equality for both paediatric patients and those with rare forms of cancer.

2.2 *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	Dinutuximab beta Apeiron
Mechanism of action	Dinutuximab beta Apeiron (dinutuximab beta) is a monoclonal, chimeric (murine/human) antibody targeting the neuroblastoma tumour-associated carbohydrate, disialoganglioside (GD2), which is over-expressed by virtually 100% of neuroblastoma cells. By specifically binding GD2, dinutuximab beta triggers complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC), which leads to target cell lysis.
Marketing authorisation/CE mark status	Dinutuximab beta Apeiron currently has marketing authorisation (via centralised procedure, approved 8th May 2017) in the UK for the indication on the submission.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Dinutuximab beta Apeiron is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first-line therapy, Dinutuximab beta Apeiron should be combined with interleukin-2 (IL-2).
Method of administration and dosage	Dinutuximab beta Apeiron is given by i.v. infusion. Two modes of administration are possible: 1. A continuous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m^2 2. Or five daily infusions of 20 mg/m^2 administered over 8 hours, on the first 5 days of each course When IL-2 is combined with Dinutuximab beta Apeiron, it should be administered as subcutaneous injections of 6×10^6 IU/m^2/day, for 2 periods of 5 consecutive days, resulting in an overall dose of 60×10^6 IU/m^2 per course. The first 5-day course should start 7 days prior to the first infusion of dinutuximab beta and the second 5-day course should start concurrently with dinutuximab beta infusion (days 1 to 5 of each dinutuximab beta course).
Additional tests or investigations	No additional tests or investigations are required for dinutuxumab beta beyond those that are already part of current clinical practice to identify the population for whom the technology is indicated in the marketing authorisation
List price and average cost of a course of treatment	**Acquisition cost (excluding VAT):** £7,610 per vial **Average cost of a course of treatment:** For an average body surface area (BSA) of 0.63m^2 and an age of 3 years, a full course of treatment costs £152,200 – see Dinutuximab beta cost-effectiveness analysis (**Document B, Section 3.0**)
Patient access scheme (if applicable)	At present, no patient access scheme (PAS) has been proposed for Dinutuximab beta Apeiron.

1.3 *Health condition and position of the technology in the treatment pathway*

1.3.1 *Brief overview of disease or condition for which technology is indicated*

Neuroblastoma commonly refers to a spectrum of neuroblastic tumours, including neuroblastoma (NB), ganglioneuroblastoma (GNB), and ganglioneuroma (GN). Neuroblastoma is a genetically and clinically heterogeneous paediatric cancer which arises from the embryonic sympathetic nervous system during development of the neural crest, and has a diverse clinical presentation and prognosis depending on the tumour biology and cytogenetics (Yu et al., 2010, Matthay et al., 2016). Both nerve cells and cells of the medulla of the adrenal gland develop from neuroblasts in the foetus. Failure of these cells to mature into completely differentiated nervous or adrenal tissues leads to uncontrolled growth and division, which in turn develops into the tumour body of neuroblastomas.

Neuroblastoma tumours may vary in terms of location, histopathologic appearance, and biologic characteristics, as well as in their clinical behaviour, which can cover a broad spectrum from spontaneous regression, to maturation to a benign ganglioneuroma, or aggressive disease with metastatic dissemination leading to death. Tumours may appear anywhere along the sympathetic nervous system, but are most frequently found in the adrenal glands, or at other locations in the abdomen, chest, or pelvis. Unique features of these tumours are their high frequency of metastatic disease (approximately 50% of tumours at diagnosis are metastatic), and the tendency for spontaneous regression of tumours in infancy (London et al., 2011, Matthay et al., 2016). Bone, bone marrow, and liver are among the most frequently observed metastatic sites.

The most common presenting signs and symptoms in children diagnosed with neuroblastoma are given in Table 3 (Matthay et al., 2016, Orphanet).

Table 3: Neuroblastoma Clinical Signs & Symptoms

Common clinical signs & symptoms (depends on the location of primary tumour and locoregional/metastatic sites)	
• Palpable abdominal mass • Abdominal distention • Digestive problems • Discomfort • Pain • Bone pain/limping • Headache • Numbness or weakness • Fever • Weight loss • Nausea, vomiting • Pallor or bleeding • Renal impairment • Sweating • Paralysis (from spinal cord compression)	• Protruding eyeball (proptosis) • Blindness • Periorbital bruising/swelling • Drooping eyelid (ptosis) • Dizziness • Respiratory distress • Dysphagia • Circulatory problems • Coagulation disorders • Constipation • Diarrhoea • Problems with urination • Bladder or bowel dysfunction • Hypertension

The diagnosis of neuroblastoma is challenging because it can arise anywhere throughout the sympathetic nervous system, and is highly heterogeneous at diagnosis. Neuroblastoma is diagnosed through a combination of laboratory tests, radiographic imaging, and pathology. Elevated levels of catecholamines or catecholine metabolites can be detected in the urine of 90% of neuroblastoma patients (Matthay et al., 2016). Meta-iodobenzylguanidine (mIBG), an analogue of noradrenaline, is readily taken up by neuroblastoma cells, which has enabled radioiodinated (Iodine-123) mIBG to be used for diagnostic imaging (^{123}I-mIBG scanning). Computed tomography (CT) or magnetic resonance imaging (MRI) scans providing three-dimensional measurements of the primary disease site are used for preliminary assessment of tumours, whereas mIBG scintigraphy is more frequently used to evaluate the extent of metastatic spread, and is recommended prior to surgical excision (Maris et al., 2007, Matthay et al., 2016, Monclair et al., 2009). Radiographic images can also be used to identify the presence of image-defined risk factors (IDRFs) for both surgical excision of the tumour and tumour staging by risk classification (Matthay et al., 2016, Monclair et al., 2009).

In addition to radiographic imaging, the pathology of neuroblastoma is a valuable determinant of prognosis. Neuroblastoma can be classified based on the degree of neuroblastic differentiation (undifferentiated, poorly differentiated, and differentiating) and the mitosis-karyorrhexis index (low, intermediate, or high). Histologically, neuroblastoma is characterized by limited Schwannian cell production, stroma-poor cells, and abundant neuroblasts (Colon and Chung, 2011). The most recent classification guidelines from the International Neuroblastoma Pathology Committee (INPC) stratifies neuroblastoma tissues into 4 categories: neuroblastoma (Schwannian stroma-poor), ganglioneuroblastoma intermixed (Schwannian stroma-rich), ganglioneuroma (Schwannian stroma-dominant), and ganglioneuroblastoma nodular (composite Schwannian stroma-rich/stroma-dominant and stroma-poor).

Genomic characterization of neuroblastoma tumours is also assessed at diagnosis, and it is useful in defining patient prognosis. N-MYC, a master regulator of transcription that can activate genes, which allows sustained growth while repressing other genes that control cell differentiation, is associated with advanced tumour stage and disease progression (Huang and Weiss, 2013). MYCN gene amplification is therefore used as a biomarker for neuroblastoma risk stratification. The most malignant tumours have amplification of the MYCN oncogene, which is usually associated with poor survival, and detected in approximately 20% of tumours (Cohn et al., 2009). MYCN amplification is observed in 5-

10% of cases in infants up to 1 year, and in 20-30% of childhood and adolescent patients (Heck et al., 2009).

The likelihood of survival is dependent on several prognostic variables including the age of the patient, the tumour stage, and biological characteristics of the disease (e.g. MYCN oncogene status, tumour ploidy, and chromosomal aberrations). In the case of relapsed patients, time to first relapse (TTFR) is also highly prognostic of overall survival post-relapse (London et al., 2011). Age at diagnosis is highly prognostic, since patients under 18 months have better overall survival than those diagnosed after 18 months (Matthay et al., 2016).

To aid in risk stratification of neuroblastoma patients, several patient staging schemes have been proposed over the decades which consider different prognostic variables for risk assignment and recommendations for treatment. Since the mid-1990s many cancer centres have used the International Neuroblastoma Staging System (INSS) (Table 4) developed in 1986, which is a post-surgical staging system.

Table 4: International Neuroblastoma Staging System (INSS)

Stage	Description
1	Localised tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour could be positive)
2A	Localised tumour with incomplete gross excision; representative ipsilateral non-adherent lymph nodes negative for tumour microscopically
2B	Localised tumour with or without complete gross excision, with ipsilateral non-adherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes should be negative microscopically
3	Unresectable unilateral tumour infiltrating across the midline, with or without regional lymph node involvement; or localised unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, or other organs (except as defined by stage 4S)
4S	Localised primary tumour in infants younger than 1 year (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, or bone marrow (<10% malignant cells)

The INSS assessment is made after the completion of the initial surgical procedure, thus it is strongly dependent on the approach of the individual surgeon (Monclair et al., 2009). To develop a staging system based on preoperative diagnostic images, which offers a more robust and reproducible analysis of patients, the INRG Staging System (INRGSS) was proposed in 2009 (Cohn et al., 2009, Monclair et al., 2009); (Table 5).

Table 5: International Neuroblastoma Risk Group Staging System (INRGSS)

Stage	Description
L1	Localised tumour not involving vital structures as defined by the list of image-defined risk factors (IDRFs) and confined to one body compartment (neck, chest, abdomen, or pelvis)
L2	Locoregional tumour with presence of one or more IDRF
M	Distant metastatic disease (except stage MS). Non-regional (distant) lymph node involvement is metastatic disease.
MS	Metastatic disease in children <18 months, with metastases confined to skin, liver, and/or bone marrow

*Patients with multifocal primary tumours should be staged according to the greatest extent of disease as defined in the table.

Whereas the INSS was based on the extent of surgical excision at diagnosis and metastases, the INRGSS was designed to identify homogeneous pre-treatment risk groups to enable the comparison of clinical trials conducted internationally by different cooperative groups. The INSS has therefore been replaced by the INRGSS. A more recent update of risk classification scheme presented by the INRGSS is the Modified International Neuroblastoma Risk Groups (mINRG; Table 6).

Table 6: Modified International Neuroblastoma Risk Groups (mINRG; Matthay 2016)

Risk Group for Treatment	INRG stage	IDRFs in primary tumour	Distant metastases	Patient Age (months)	Histological category	Grade of differentiation	MYCN status	Genomic Profile	Ploidy
Very-low	L1	Absent	Absent	Any	GNB nodular, NB	Any	NA	Any	Any
Very-low	L1 or L2	Any	Absent	Any	GN, GNB intermixed	Any	NA	Any	Any
Low	L2	Present	Absent	<18	GNB nodular, NB	Any	NA	Favourable	Any
Low	MS	Present	Absent	≥18	GNB nodular, NB	Differentiating	NA	Favourable	Any
Low	L2	Any	Present	<12	Any	Any	NA	Favourable	Any
Intermediate	L2	Present	Absent	<18	GNB nodular, NB	Any	NA	Unfavourable	Any
Intermediate	L2	Present	Absent	≥18	GNB nodular, NB	Differentiating	NA	Unfavourable	Any
Intermediate	L2	Present	Absent	≥18	GNB nodular, NB	Poorly differentiated, undifferentiated	NA	Any	Any
Intermediate	M	Any	Present	<18	Any	Any	NA	Any	>1 (Hyperploidy)
Intermediate	M	Any	Present	<12	Any	Any	NA	Unfavourable and/or diploid	
Intermediate	MS	Any	Present	12-18	Any	Any	NA	Favourable	Any
Intermediate	MS	Any	Present	<12	Any	Any	NA	Unfavourable	Any
High	L1	Absent	Absent	Any	GNB nodular, NB	Any	Amp	Any	Any
High	L2	Present	Absent	≥18	GNB nodular, NB	Poorly differentiated, undifferentiated	Amp	Any	Any
High	M	Any	Present	12-18	Any	Any	NA	Unfavourable and/or diploid	
High	M	Any	Present	<18	Any	Any	Amp	Any	Any
High	M	Any	Present	≥18	Any	Any	Any	Any	Any
High	MS	Any	Present	12-18	Any	Any	NA	Unfavourable	Any
High	MS	Any	Present	<18	Any	Any	Amp	Any	Any

These risk stratifying groups have been updated from the original INRG report (Cohn 2009) to account for emergent genomic data and current treatment approaches. Favourable and unfavourable corresponds to the absence or presence, respectively, of segmental chromosome alterations. MYCN status: Amp, amplified; NA, non-amplified; GN, ganglioneuroma; GNB, ganglioneuroblastoma; NB, neuroblastoma; IDRF, image-defined risk factor

Children diagnosed with neuroblastoma are classified into four different risk groups according to the mINRG (Table 6): high-, intermediate-, low-, and very low-risk groups, which are based on their INRG stage (Table 5), age, and tumour biology. These risk groups are then used to define the recommended treatment guidelines. High-risk neuroblastoma according to the mINRG staging refers to patients with INRG stage L1 or L2 with MYCN

amplification, stage M and MS children under 18 months with MYCN amplification, stage M children over 18 months, and stage MS children under 18 months with an unfavourable genomic profile. In contrast to that, relapsed or refractory patients do not necessarily need to be diagnosed as high-risk neuroblastoma patients initially, since very-low, low, and intermediate risk patients without MYCN amplification can experience relapse or suffer from refractory disease.

Following disease staging, which involves assessment of tumour spread and risk factors for surgical removal, each patient is stratified into risk groups to determine the best course of treatment.

Neuroblastoma is a rare disease. The incidence is 10.2 cases per million of children under 15 years of age, and nearly 500 new cases are reported annually in the USA (Maris, 2010). In the EU, the annual incidence of neuroblastoma in the paediatric population (0-14 years) is 0.64 in 100,000 children and the incidence in the general population is 0.12 in 100,000 (RARECARE). Neuroblastoma is the most common extracranial tumour and most common malignancy diagnosed in the first year of life, accounting for approximately 28% of all cancers diagnosed in European and US infants (Heck et al., 2009, Maris, 2010, Matthay et al., 2016). The median age at diagnosis ranges from 18-23 months, and the majority of tumours (90%) are diagnosed in children under 10 years of age (Hoy, 2016, Matthay et al., 2016).

In the UK, neuroblastoma is the second most common childhood solid tumour, accounting for 8% of all childhood (0-14 years) cancers (Basta et al., 2016). The annual incidence of neuroblastoma in the UK varies between approximately 80 and 100 cases (Cancer Research UK). Between 1988 and 1997, the age-standardised incidence rate for both sexes in the British Isles was 9.1 cases per million population (Spix et al., 2006). During the same period, the five-year survival probability for all ages (0-14) in the British Isles was 49% (Spix et al., 2006). Survival amongst children diagnosed with high-risk disease (which accounts for approximately 50% of all neuroblastoma cases) remains poor, with 40-50% chance of long-term survival (Bagatell and Cohn, 2016, Maris, 2010). In 50% of high-risk cases, the patients relapse (Basta et al., 2016). Survival from relapsed, high-risk neuroblastoma is currently <10% (Park et al., 2012). In an analysis of relapsing patients from the INRG database, the 5-year OS was found to be 20% (London et al., 2011). Neuroblastoma remains one of the most difficult childhood cancers to cure with 5-year survival rates of 64.7% for patients diagnosed in UK and Ireland (Gatta et al., 2014).

1.3.2 *Summarize clinical pathway of care in a diagram showing context and proposed placement of technology within the pathway*

Neuroblastoma Management

First-line setting

The treatment of choice is risk category adapted, according to the risk-stratification schemes present in Table 5 and Table 6.

For **very low- and low-risk neuroblastomas**, treatment includes a “wait and watch” approach, particularly in infants <12 months of age, since tumours of this risk category can spontaneously regress without treatment. Patients without symptoms and/or unfavorable prognostic markers are therefore only observed closely (considered an option in case of perinatal neuroblastoma with small adrenal tumours). This approach is known to not negatively influence the outcome of a later initiated treatment, and therefore is frequently chosen in infants <12 months old (Tanaka et al., 2010). In other patients, treamtent encompasses surgery followed by observation and chemotherapy with or without surgery (for symptomatic disease or unresectable progressive disease after surgery).

For **intermediate-risk neuroblastomas**, the treatment encompasses chemotherapy (e.g. carboplatin, cyclophosphamide, doxorubicin, and etoposide) with or without surgery; surgery and observation (in infants); radiation therapy (only for emergency treatments, like progressive disease or life-threatening events related to the disease that does respond to treatment otherwise).

For **high-risk neuroblastomas**, the current treatment can be divided into three distinct phases (Maris, 2010, Matthay et al., 2016) (Figure 1):

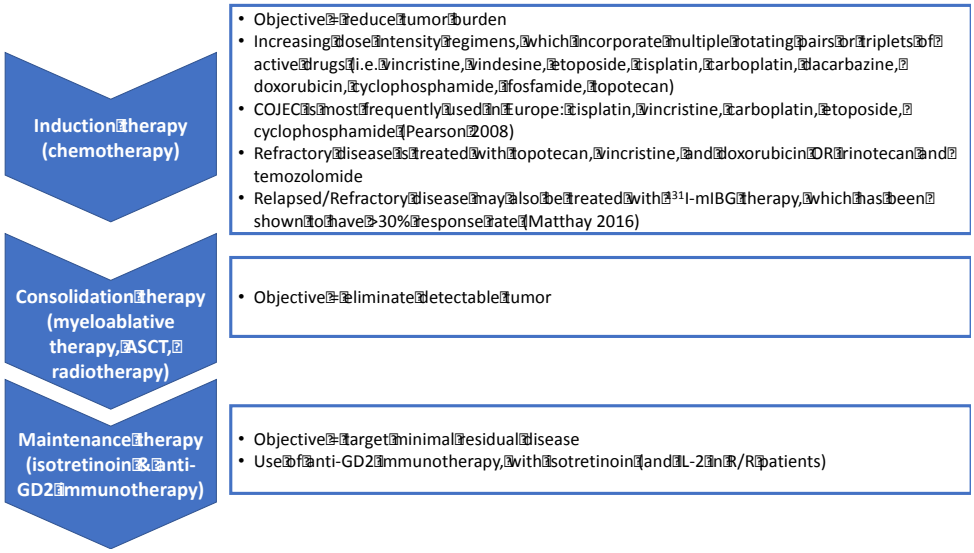
Induction of remission with intensive chemotherapy: The backbone of the most commonly used induction therapy includes dose-intensive cycles of cisplatin and etoposide alternating with vincristine, cyclophosphamide, and doxorubicin (Kushner et al., 2014). Topotecan was added to this regimen based on the anti-neuroblastoma activity seen in relapsed patients (Park et al., 2011). After a response to chemotherapy, resection of the primary tumour is usually attempted.

Consolidation of the remission: Myeloablative chemotherapy is utilised to eradicate minimal residual disease (MRD) using lethal doses of chemotherapy followed rapidly by rescue with autologous hematopoietic stem cell transfer (ASCT) to repopulate the bone marrow. Upon recovery from ASCT, external beam radiotherapy is administered to the primary tumour bed and sites of persistent metastatic disease (Bagatell and Cohn, 2016).

Maintenance therapy: Until 2010, standard maintenance treatment was considered to be 6 months of oral isotretinoin, given with the aim of differentiating any remaining neuroblasts (Matthay et al., 1999). Since 2010, with the publication of results from Yu et al. (Yu et al., 2010) some form of anti-GD2 antibody therapy has been included in maintenance therapy, and it is now considered the standard of care in many parts of the world. The maintenance phase is used to treat potential MRD following ASCT to reduce the risk of relapse (Matthay et al., 2009), through a combination of immunotherapy e.g. with dinutuximab and isotretinoin (Yu et al., 2010).

The utilisation of anti-GD2 immunotherapy is strongly recommended in numerous protocols with regards to high-risk neuroblastoma, as well as in relapsed or refractory patients who have received at least 2 previous treatments including autologous haematopoietic stem cell transfer (e.g. SIOPEN). The European organisation for neuroblastoma, SIOPEN, consists of 167 investigator centres in 15 European countries, Israel, and Australia. SIOPEN determined that it was not ethical to not propose anti-GD2 immunotherapy to patients, excluding the possibility of having a placebo arm without immunotherapy within randomised clinical trials. Clinical recommendations on the use of immunotherapy in high-risk neuroblastoma patients during maintenance phase will be published imminently (SIOPEN (2014), expert opinion).

Figure 1: Phases of multimodal therapy for high-risk neuroblastoma



Relapsed/refractory setting

Patients with very-low/low risk neuroblastoma (55% of all neuroblastoma patients, Cohn et al. (2009)) and intermediate risk (9% of patients, Cohn et al. (2009)) reach survival in approximately 90 and 70-90% of cases, respectively. Most favourable clinical results are

usually obtained in infants and good outcomes may be the result of restraint (spontaneous regression after observation) or surgery.

Despite intensive multimodal therapy, 52% of patients with high-risk neuroblastoma relapse with a dismal long-term outcome (Kushner et al., 2014). Historically, relapsed neuroblastoma has been treated with a combination of chemotherapy and radiotherapy for the purposes of palliation only. In more recent times, treatment has evolved comprising salvage chemotherapy, radiotherapy and surgery, and ^{131}I-mIBG therapy, and dinutuximab monoclonal antibody therapy with aldesleukin-2 (IL-2) and oral isotretinoin (13-cis RA).

Salvage regimens in the recent era have altered the natural disease course and prolonged post-relapse survival. Second line chemotherapies with mild to modest toxicities that have not been included in frontline treatment are often considered for salvage. Frequently used combinations are topotecan, vincristine, and doxorubicin (TVD), temozolomide and irinotecan (TEM/IRN), or topotecan and cyclophosphamide. Up to 60% of response or arrest of disease progression can be achieved. Depending on the type of relapse (localised vs metastatic), location of tumour, previous treatment history, etc. it may be that surgery or external beam radiotherapy are part of the treatment strategy. ^{131}I-mIBG (meta-iodobenzylguanidine) therapy may be an appropriate treatment option for children having mIBG avid (or mIBG positive) disease and has formed a core part of the treatment of relapsed neuroblastoma over the last few years. It may be expected to improve or consolidate the response to the intense chemotherapy.

A new aggressive treatment approach is being explored but further research is needed to show whether it can produce long lasting remissions. Haploidentical stem cell transplantation (haplo-HSCT) involves taking stem cells from a parent and transplanting them into the patient following myeloablative chemotherapy to completely destroy the existing bone marrow system. The transplant process effectively equips the patient with a new immune system, which is hoped to be able to target any remaining cancer cells in a way the patient's own immune system was unable to. The graft of donor stem cells is engineered in such a way that T and B cells are depleted, but large numbers of NK cells are infused.

Salvage regimens in the recent era have altered the natural disease course and prolonged post-relapse survival. Many of the factors at diagnosis that are prognostic of survival also influence survival after disease progression or relapse. Factors identified as most highly prognostic of poor survival were age ≥18 months, use of intensive multi-modality treatment at diagnosis, stage M (previously "stage 4" under INSS), elevated serum ferritin, elevated LDH, unfavourable histology, high MKI, and MYCN amplification; in addition, shorter time to first relapse was a significant adverse factor for survival.

Up to half of these patients achieve some response or stable disease, and survival after relapse is longer in patients who have received salvage therapy. In an INRG analysis of 2,266 patients who experienced first progression/relapse, the median time to relapse was 13 months, and 5-year OS from the time of first relapse was 20% (London et al., 2011). The longer survival after relapse is also likely due to early detection of disease recurrence thanks to the implementation of more sophisticated surveillance studies in recent years.

There is rationale for a child who has responded to second-line chemotherapy and/or mIBG therapy, and now has only MRD, to receive immunotherapy with dinutuximab and isotretinoin (13-cis RA) to try and achieve long-term remission.

Currently there are no NICE guidelines or pathways specifically addressing the treatment of neuroblastoma. There exists, however, three guidance documents related to the treatment of children with cancer or suspected of having cancer:

1) NICE Cancer Service Guideline CSG7: Improving outcomes in children and young people with cancer (NICE, 2005)
2) NICE Quality Standard QS55: Cancer services for children and young people (NICE, 2014)
3) NICE Guideline NG12: Suspected cancer: recognition and referral (NICE, 2015)

All of these guidance documents present a broad scope of goals for the delivery of cancer care to children and young adults in the UK. None of these documents specifically address the treatment or recommendations for management of neuroblastoma or specific subgroups of neuroblastoma patients.

1.4 *Equality considerations*

There are no equality issues surrounding the use of Dinutuximab beta Apeiron for the indicated patient population.

2. Clinical effectiveness

2.1 *Identification and selection of relevant studies*

A systematic review was conducted to identify all the relevant clinical evidence from the published literature regarding the clinical effectiveness of Dinutuximab beta Apeiron and relevant comparators in the treatment of both high-risk and relapsed/refractory neuroblastoma patient populations.

The systematic review was divided in two searches aimed at addressing two research questions. The first search (Research question 1) was aimed at specifically identifying evidence regarding the clinical effectiveness of therapies for the treatment of high-risk neuroblastoma patients during maintenance phase. The second search (Research question 2) was conducted to specifically identify evidence regarding the clinical effectiveness of therapies for the treatment of patients with relapsed/refractory neuroblastoma. Both searches were conducted on May 4th 2017.

2.1.1 *Research question 1: Treatment of high-risk neuroblastoma during maintenance phase*

A systematic search was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of dinutuximab beta and relevant comparators (i.e. isotretinoin) in maintenance phase treatment of high-risk neuroblastoma patients. Thus, the specific objective of this first search was to evaluate efficacy, safety, and toxicity of Dinutuximab beta Apeiron when included in the maintenance-phase therapy in high-risk neuroblastoma.

2.1.1.1 Search strategy

Searches were conducted in Medline, The Education Resources Information Center (ERIC), the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects), and Embase. Full details of the search strategy are provided in Appendix D.

2.1.1.2 Study selection process

Inclusion and exclusion selection criteria are shown in Table 7.

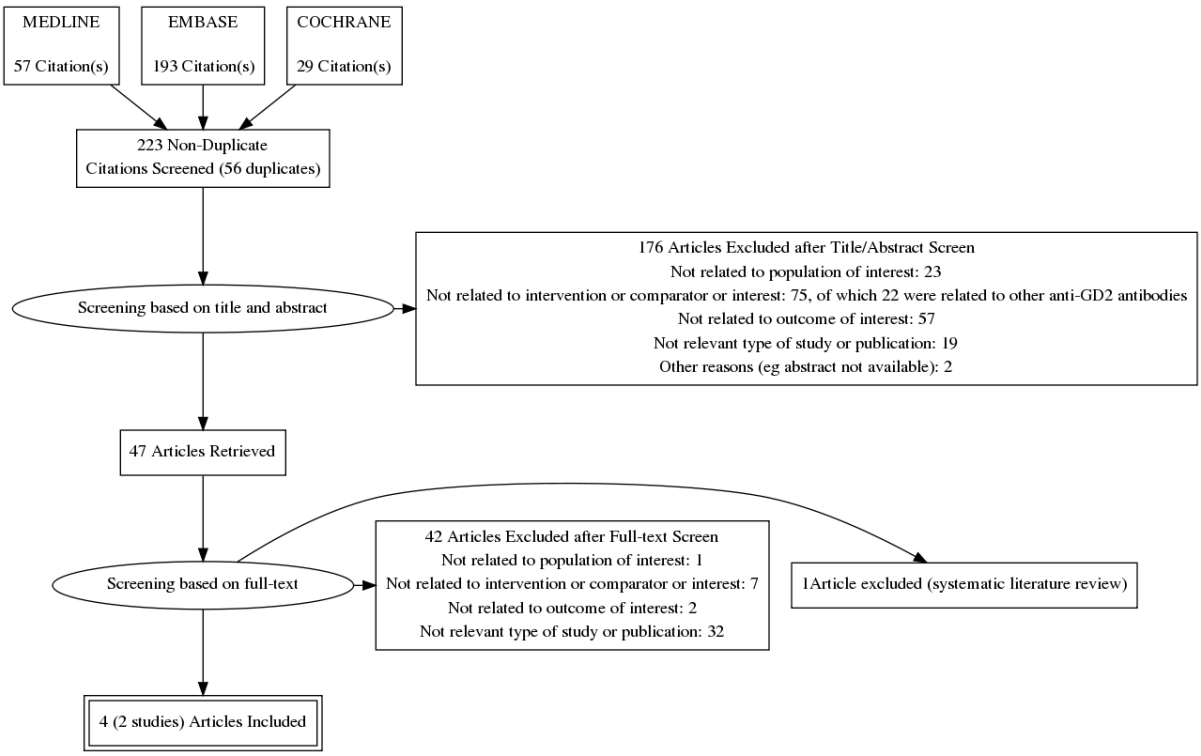
Table 7: Eligibility criteria used in search strategy

Inclusion criteria	
Population	Patients with high-risk neuroblastoma who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation.
Interventions	Dinutuximab beta in addition to current SoC
Comparators (Current SoC)	Isotretinoin
Outcomes	Efficacy outcomes: • Tumour response • Survival in terms of overall survival, progression-free survival, or event-free survival Safety or tolerability outcomes: • Mortality • Any AEs • Any toxicity reported
Study type	RCTs, CCTs, Reviews
Language restrictions	English Language
Exclusion criteria	
Population	Patients without high-risk neuroblastoma aged less than 12 months, as well as patients that have relapsed or are refractory to SoC
Intervention	Studies not investigating dinutuximab beta or isotretinoin treatment during maintenance phase in high-risk neuroblastoma patients, or studies utilizing dinutuximab antibody derived from alternative cell lines
Comparators (Current SoC for the relevant population)	Studies investigating the use of any other therapy different to the intervention (dinutuximab beta) or the current SoC (13-cis retinoic acid) during maintenance phase of high-risk neuroblastoma
Outcomes	Studies not reporting the outcomes listed in the final scope
Study type	Letters, editorials, comments, opinions, pharmacokinetic studies, pharmacodynamics studies, in vitro or animal studies, conference abstracts
Language restrictions	Non-English publications

Studies identified were initially assessed against the inclusion/exclusion criteria based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a "reason code" to document the rationale for exclusion. Papers included after this stage were then assessed based on the full text; further papers were excluded, yielding the final data set for inclusion.

Following assessment and exclusion of studies based on title, abstract and full text, we identified zero publications providing dinutuximab beta data in high-risk neuroblastoma patients. We then considered in our inclusion criteria publications investigating the clinical effectiveness of the comparator (13-cis-retinoic acid) regardless of the absence of dinutuximab beta in the treatment. In this way, we could identify 5 publications, one being a systematic literature review and the other 4 reporting 2 clinical studies. These studies and their main clinical outcomes are listed in **Appendix D** and summarised in **Section 2.8**. The schematic (PRISMA diagram flow) for this search is shown in Figure 2.

Figure 2: Schematic for the Search 1 of clinical evidence systematic review



A full list of excluded studies and reason for exclusion is provided in **Appendix D**.

2.1.2 *Research question 2: Treatment of patients with relapsed or refractory neuroblastoma*

A second systematic search was conducted to retrieve clinical relevant data from the published literature regarding the efficacy and safety of dinutuximab beta and relevant comparators in patients with relapsed or refractory neuroblastoma. In this case, relevant comparators (standard of care) included not only 13-cis-retinoic acid but also second-line chemotherapies, radiotherapy and surgery. Historically patients were having different types of treatment when they relapsed or when they were refractory after having received induction treatment, consolidation treatment, and autologous stem cell transplantation. For this reason we have included the most common treatments used in these patients as comparators. Thus, the specific objective of this search was to evaluate efficacy and safety of Dinutuximab beta Apeiron when included in the treatment of patients with relapsed or refractory neuroblastoma.

2.1.2.1 Search strategy

As for the research question 2, searches were conducted in Medline, The Education Resources Information Center (ERIC), the Cochrane Library (Cochrane Database of Searches were conducted in Medline, Embase, and the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database

of Abstracts of Reviews of Effects). Full details of the search strategy are provided in Appendix D.

2.1.2.2 Study selection

Inclusion and exclusion selection criteria are shown in Table 8.

Table 8: Eligibility criteria used in search strategy

Inclusion criteria	
Population	Patients with relapsed or refractory neuroblastoma at any level of risk
Interventions	Dinutuximab beta in addition to current SoC
Comparators (Current SoC for the relevant population)	• Isotretinoin • Interleukin-2 (IL-2) • The following (most common) second-line chemotherapies or high dose therapies: o BuMel (busulphan – melphalan) + ASCT o TVD (Topotecan – vincristine – doxorubicin) o TEM/IRN (temozolomide – irinotecan) o Topotecan + cyclophosphamide o Topotecan + cyclophosphamide + etoposide o mIBG treatment • Radiotherapy (localized) • Surgery
Outcomes	Efficacy outcomes: • Tumour response • Survival in terms of overall survival, progression-free survival, or event-free survival Safety or tolerability outcomes • Mortality • Any AEs Any toxicity reported
Study type	RCTs, CCTs, Reviews
Language restrictions	English Language
Exclusion criteria	
Population	Patients without relapsed or refractory neuroblastoma aged less than 12 months
Intervention	Studies not investigating dinutuximab beta (active substance) or any of the SoC treatments for the relevant population
Comparators (Current SoC for the relevant population)	Studies investigating the use of any other therapy different to the interventions or comparators stated in the inclusion criteria, or studies utilizing dintuximab antibody derived from alternative cell lines
Outcomes	Studies not reporting the outcomes listed in the final scope
Study type	Letters, editorials, comments, opinions, pharmacokinetic studies, pharmacodynamics studies, in vitro or animal studies, conference abstracts
Language restrictions	Non-English publications

Abbreviations: CCT, controlled clinical trial; RCT, randomised controlled trial; AEs, Adverse Events; SoC, Standard of Care.

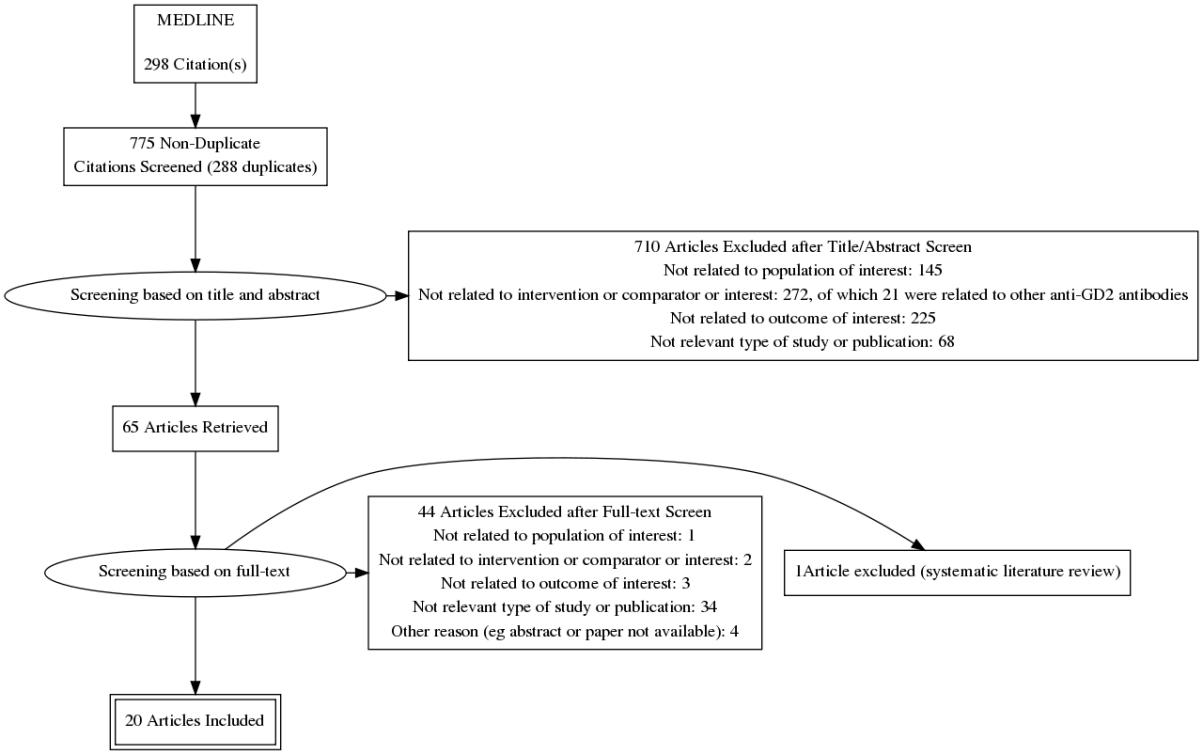
Studies identified were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a “reason code” to document the rationale for exclusion. Papers included after this stage were then assessed based on the full text; further papers were excluded, yielding the final data set for inclusion.

The second systematic search identified zero publications providing dinutuximab beta data in relapsed or refractory neuroblastoma patients. We then considered in our inclusion criteria publications investigating the clinical effectiveness of any relevant comparator regardless of the absence of dinutuximab beta in the treatment. In this way, we identified 22 publications, one being a systematic literature review and 21 corresponding to independent studies. These studies are summarized in **Appendix D**.

Among these studies, one study provided data on IL-2, 11 on radiotherapy (^{131}I-mIBG), and 9 on relevant second-line chemotherapy protocols. No relevant studies investigating 13-cis-retinoic acid or surgery in the targeted population (relapsed/refractory neuroblastoma) were identified. These studies and their main clinical outcomes are listed in **Appendix D** and summarised in **Section 2.8**.

The schematic (PRISMA flow diagram) for systematic search 2 is shown in Figure 3.

Figure 3: Schematic for systematic search 2 of clinical evidence systematic review



A full list of excluded studies and reason for exclusion is provided in **Appendix D**.

2.2 *List of relevant clinical effectiveness evidence*

EUSA Pharma has exclusive rights to the clinical study data from all SIOPEN- and Apeiron Biologics-sponsored Dinutuximab beta Apeiron studies. From the systematic literature reviews described in **Section 2.1**, no additional relevant studies have been performed outside these organizations and thus, all data necessary to address the remit and scope of

the technology appraisal is held by EUSA Pharma. All studies providing Dinutuximab beta Apeiron data are listed in this section. No RCT was performed with Dinutuximab beta Apeiron, apart from the study APN311-302 which compares the efficacy and safety of dinutuximab beta in first-line setting when administered with or without concomitant IL-2. This study was originally called APN311-301 and aimed at comparing 13-cis-RA treatment to 13-cis-RA treatment plus dinutuximab beta therapy in high-risk neuroblastoma. After the publication of the results of the US COG trial by Yu et al. in 2010, it was deemed unethical to treat patients without immunotherapy, thus the trial was stopped and re-designed as -302 as described in Table 10. Relevant studies regarding Dinutuximab beta Apeiron for the treatment of high-risk neuroblastoma and relapsed/refractory neuroblastoma, whether randomised or not, are presented in Table 9 and Table 10.

Table 9: Tabular overview of dinutuximab beta clinical studies

Study code Phase	NB Setting	Design	APN Scheme Dose(s) (mg/m^2/cycle) No. of cycles	Co-treatment	Patients Treated/planned Age	Assessments
Main study						
APN311-303 (Comp. Use)	R/R [a]	OL, uncontrolled, single-centre	24h / 10d 100 Up to 6 (each 35 days)	IL-2, 13-cis RA	54/54 >1 y to ≤45 y	Safety, Efficacy, Pharmacology ***Completed***
Supportive studies						
APN311-101 Phase I	R/R	OL, uncontrolled, multi-centre, dose-escalation	8h / 5d 50, 100, 150 1-3 (each 28 days)	none	15/12 [b] 15 in dossier >1 y to ≤21 y	Safety, Efficacy, Pharmacology ***Completed***
APN311-201 Phase II	R/R	OL, uncontrolled, multi-centre	8h / 5d 100 Up to 9 (each 28 days)	none (cycles 1-3), IL-2 (cycles 4-9)	35/35 [c] ≤21 y Amended to include a total 60 patients	Safety, Efficacy, Pharmacodynamics ***Ongoing***
APN311-202 Phase I/II	R/R	OL, uncontrolled, multi-centre, dose-escalation, dose-schedule finding	24h / 10d 100, 150, 210 5 (each 35 days)	IL-2, 13-cis RA	44/140 [d] >1 y to ≤21 y Recruitment extended	Safety, Efficacy, Pharmacology ***Ongoing***
APN311-301/302 Phase III	High-risk (first-line therapy)	OL, randomized, controlled, multi-centre	8h / 5d 100 5 (each 28 days)	301: 13-cis RA 302: IL-2, 13-cis RA	A: 34/34 <21 y B: 406/400 [f] <21 y Recruitment extended	Safety, Efficacy ***Ongoing***

[a] Also first-line patients have been accrued to a limited extent.
[b] A total of 16 patients were treated in the study. However, since the signed ICF for one patient could not be found at the time of data collection and analysis, only data from 15 patients were collected and are reported.
[c] Data cut-off date 28 Feb 2015 – last update 05 September 2016
[d] As of 17 Feb 2015. In amendment 1 to the protocol an expansion cohort of 100 patients was determined.
[e] Data cut-off date for manuscript: 03 July 2014 – CSR: 22 January 2016; updated addendum: 05 September 2016

Table 10: List of relevant studies investigating Dinutuximab beta Apeiron

Trial no. (acronym) Primary Study Reference	Population	Intervention
APN311-202 Analysis from data collected in the SIOPEN Long-Term Dinutuximab beta Apeiron (LTI) Study: A Phase I/II dose schedule finding study of dinutuximab beta continuous infusion combined with subcutaneous aldesleukin (IL-2) in patients with primary refractory or relapsed neuroblastoma	a) Primary refractory or relapsed neuroblastoma b) Aged 1-21 years c) With neuroblastoma diagnosed according to INSS d) Received at least 1 previous high-dose treatment followed by stem cell rescue after conventional therapy to reduce tumour burden e) Fulfilment of one of the following criteria: i. Primary refractory patients with stage 4 disease with at least 2 lines of treatment prior to high-dose therapy/autologous stem cell transplantation (ASCT), causing a delay from diagnosis to ASCT of over 9 months ii. Treated and responding relapse after primary stage 4 disease iii. Treated and responding disseminated relapsed neuroblastoma having received ASCT f) Patients may have had prior central nervous system (CNS) metastasis providing the following criteria were all met: i. The CNS disease had been previously treated ii. The CNS disease had been clinically stable for 4 weeks prior to starting the study iii. The patient was off steroids for CNS disease for 4 weeks prior to starting on study and during course of the study	100mg/m^2 treatment course of dinutuximab beta, administered as one continuous 10-day infusion at 10mg/m^2/day, in cycles of 35 to 49 days (depending on infusion duration), starting on Day 8 of each cycle, for a total of 5 cycles (only the first cycle was assessed for the dose schedule finding) Dinutuximab beta was combined with IL-2 and 13-cis RA

Trial no. (acronym) Primary Study Reference	Population	Intervention
APN311-303 (Lode et al., 2016) Retrospective analysis data collected during the administration of dinutuximab beta continuous infusion combined with subcutaneous aldesleukin (IL-2) in patients with high-risk neuroblastoma under a compassionate use program No randomisation, no blinding	a) ≥ 1 year and ≤ 45 years of age at treatment start b) Diagnosed with high-risk neuroblastoma according to INSS criteria (INSS stage 2, 3, 4, or 4S with MYCN amplification, or INSS stage 4 without MYCN amplification or relapsed or refractory neuroblastoma of any stage c) Off any standard or experimental treatments for at least 2 weeks prior to treatment start and fully recovered from short term major toxic effects d) No immediate requirement for palliative chemotherapy, radiotherapy or surgery e) ≥ 4 weeks after major surgery (e.g. laparotomy or thoracotomy) and fully recovered from any post-surgical complications f) Patients with seizure disorders were enrolled if on anticonvulsants and if seizure disorders were well controlled g) No dyspnoaea at rest and pulse oximetry >94% on room air h) Adequate bone marrow, liver, and renal function	Dinutuximab beta given in combination with fixed doses of subcutaneous aldesleukin (IL-2) and oral isotretinoin (13-cis-RA). Patients initially received i.v. dinutuximab beta in combination with s.c. IL-2 i. s.c. IL-2 was usually given at a dose of 6×10^6 IU/m^2/day. The majority of patients received it in two 5-day blocks (days 1-5 and 8-12). In these patients, IL-2 was given concurrently with dinutuximab beta on days 8-12. Initial patients, however, received IL-2 on days 1-5 only as they started with the combination of IL-2 and dinutuximab beta. Patients ≤ 12 kg were dosed according to body weight: 0.2×10^6 IU/kg/day ii. Dose level of dinutuximab beta was limited by tolerability although a target daily dose of 10 mg/m^2, which relates to a total dose of 100 mg/m^2/cycle was aimed for. Patients initially received 50 mg/m^2 in their first treatment cycle to assess feasibility and tolerability. The total duration of a cycle varied between 28 and 35 days. In each cycle, treatment ended with oral isotretinoin (13-cis-RA) after completion of dinutuximab beta infusion. iii. Patients received isotretinoin at a total daily dose of 160 mg/m^2/day administered in 2 equal oral doses twice a day for 14 days after completion of dinutuximab beta infusion. Patients ≤ 12 kg were given 5.33 mg/kg/day, divided into two equal doses given orally twice a day for 14 days

Trial no. (acronym) Primary Study Reference	Population	Intervention
APN311-302 (HR-NBL-1 / SIOPEN) (Ladenstein et al., 2014) Previously **APN311-301** Open-label with patients randomised to receive 13-cis-RA and dinutuximab beta, with or without IL-2	• Established diagnosis of neuroblastoma (NB) according to the INSS • Age < 21 years • High-risk NB, defined as either: o INSS stages 2, 3, 4 or 4s with MYCN amplification of any age below 21 years o INSS stage 4 without MYCN amplification aged ≥12 months at diagnosis, and in patients aged 12-18 months only in the presence of segmental chromosomal alterations (SCA) • No previous chemotherapy except for 1 cycle of etoposide and carboplatin (VP/Carbo) • Tumour cell material available for determination of biological prognostic factors	• 13-cis-RA administered orally at a dose of 160 mg/m^2/day over 14 days, every 4 weeks over 6 courses, started after completion of local irradiation, no later than Day 120 post PBSCR. 13-cis-RA was provided in 5mg and 20mg capsules depending on total daily dose required • Dinutuximab beta was administered as an 8-hour i.v. infusion at dose of 20 mg/m^2/day over 5 days, every 4 weeks over 5 courses. The first course starts 3 weeks after the initiation of 13-cis-RA • Patients randomised to receive dinutuximab beta and s.c. IL-2 started their immunotherapy with IL-2 at week 3. IL-2 was given according to the following treatment schedule: o Weeks 3, 7, 11, 15, and 19, IL-2 given at dose of 6 MIU/m^2/day over 5 days subcutaneously (Monday-Friday) o Weeks 4, 8, 12, 16, and 20, IL-2 given 2 hours after stop of antibody infusion at dose of 6 MIU/m^2/day over 5 days subcutaneously For 301: Comparison of dinutuximab beta + 13-cis-RA vs 13-cis-RA alone
Supportive Studies		

Trial no. (acronym) Primary Study Reference	Population	Intervention
APN311-101	Dose response trial	Patients received three 28-day treatment cycles, each consisting of 5 consecutive days of 8-hr intravenous infusions with dinutuximab beta (monotherapy). Although three doses were tested (10, 20 and 30 mg/m^2/day, data were only provided for the medium dose of 20 mg/m^2/day, i.e. a cumulative dose of 100 mg/m^2 per cycle
APN311-201 On-going feasibility study of using dinutuximab beta and IL-2 after haploidentical stem cell transplantation	a) Less than or equal to 21 years of age. b) Histologically confirmed neuroblastoma. c) Refractory to standard treatment (i.e. refractory disease) or relapse after previous autologous or allogeneic stem cell transplantation. d) Patient had undergone haploidentical stem cell transplantation prior to antibody infusion at least 60 days prior to starting immunotherapy. e) Serum glutamate pyruvate transaminase (SGPT) less than 2.5 times the upper limit of normal for age and total bilirubin less than 2 times the upper limit of normal for age. D-Dimers less than 2 times the upper limit of normal. f) Creatinine clearance or radioisotope glomerular filtration rate (GFR) greater than or equal to 40 ml/min/1.73 m^2. g) Cardiac shortening fraction greater than or equal to 20% by echocardiogram. h) Karnofsky/Lansky performance score (age appropriate) of greater than or equal to 50. i) Females of childbearing potential must have had a negative pregnancy test. Patients of childbearing potential must have agreed to use an effective birth control method. Female patients who were lactating must have agreed to stop breast-feeding. j) Written informed consent was obtained, and for minors a written agreement by parents or legal guardian. k) All institutional and national requirements for human studies were met.	The six-cycle regimen consisted of an 8-hour infusion (dinutuximab beta 20 mg/m^2/day) for 5 consecutive days administered every 4 weeks. If there was evidence of response after 6 cycles, patients could receive another 3 cycles. Interleukin-2 was added to cycles 4-9 at days 6, 8, 10 (1 x 10^6 IU/m^2/day s.c.).
Abbreviations: NB, neuroblastoma; INSS, International Neuroblastoma Staging System, INSS; CNS, central nervous system; ASCT, autologous stem cell transplant; RCT, randomised controlled trial; RA, retinoic acid; i.v., intravenous; s.c., subcutaneous		

2.2.1 *Supportive studies excluded from discussion*

Studies provided in Table 10 as Supportive Studies (APN311-101, and -201) have been excluded from further discussion due lack of long-term efficacy data. Of note, regarding study 301, this was the first design of the SIOPEN study which compared dinutuximab beta+13-cis RA with 13-cis RA alone. However, the main goal and treatment scheme were changed because meanwhile immunotherapy with dinutuximab together with GM-CSF, IL-2 and 13-cis-RA was shown to improve outcome compared with 13-cis-RA alone in high-risk neuroblastoma patients, and it was deemed unethical to treat patients with 13-cis-RA monotherapy. Thus, the aim of the maintenance phase of treatment was revised to investigate the benefit of adding IL-2 to treatment with dinutuximab beta and differentiation therapy with 13-cis-RA (Study 302).

It is noteworthy that none of the three single-arm investigator-sponsored trials had efficacy as a primary endpoint since these were Phase I/II trials to investigate the safety, pharmacokinetics, pharmacodynamics, and anti-tumour response. Their objectives were first to bridge to previous ch14.18 produced in other cell lines (i.e. ch14.18/SP2/0) and subsequently to evaluate a new way of delivering the cycle dose, as a continuous infusion rather than daily 8-hour infusions, in an attempt to reduce the well-known pain toxicity of anti-GD2 mAbs. Overall, none of the submitted studies included a comparative arm with patients who did not receive dinutuximab beta except for the very small APN311-301 trial (25 evaluable patients). In the absence of internal controls, the assessment of the efficacy of immunotherapy was performed by comparison to historical control data. All further analyses will deal only with clinical studies APN311-202, APN311-302, and APN311-303.

2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

2.3.1 *Comparative summary of clinical trial methodology*

Methodologies of the main clinical trials are summarised in Table 11.

Table 11: Comparative summary of methodology of APN311-202, -302, -303

Trial no. (acronym)	**APN311-202 (interim data analysis SIOPEN LTI Study)**	**APN311-302 (interim data analysis SIOPEN HRNBL1 Study)**	**APN311-303**
Primary study objective	Determine tolerable treatment schedule that reduces pain-toxicity profile of dinutuximab beta while maintaining immunomodulatory efficacy in primary refractory or relapsed neuroblastoma in patients (1-21 years old), using a prolonged continuous infusion in combination with s.c. aldesleukin (IL-2)	Test the hypothesis that the addition of s.c. IL-2 to dinutuximab beta immunotherapy in addition to differentiation therapy with 13-cis-RA following myeloablative therapy and autologous stem cell rescue will improve 3-year EFS in high-risk neuroblastoma patients	Retrospectively evaluate safety and assess the pain-toxicity profile of a prolonged continuous infusion of dinutuximab beta in combination with s.c. IL-2 followed by oral 13-cis-RA in patients with high-risk neuroblastoma treated under a compassionate use program (CU-LTI)
Secondary study objectives	1. To assess pain intensity and relief by appropriate medication with validated self-report tool 2. To validate, during the first cycle, the correlation between activated NK cells and dinutuximab beta level with antibody-dependent cellular cytotoxicity (ADCC) by using multinuclear cells (MNC) and serum from patients on Day 15 3. To determine systemic immune modulation/response resulting from the combined treatment of dinutuximab beta and s.c. IL-2 by repeated analysis of NK cell activation, soluble IL-2 receptor, ADCC, complement-dependent cytotoxicity (CDC) and anti-idiotype response (human anti-mouse antibody (HAMA), and human anti-chimeric antibody (HACA))	• To determine the tolerance of immunotherapy with dinutuximab beta with or without s.c. IL-2 in addition to 13-cis-RA following MAT • To collect data on selected, validated biological features, and determine the effect of these on EFS and overall survival	Retrospectively evaluate: • anti-tumour responses through clinical assessments in patients with measurable disease • overall survival and event-free survival • pharmacodynamics of dinutuximab beta • pharmacokinetics of dinutuximab beta
Trial design	Prospective, non-blinded, open-label, multi-centre study, consisting of dose schedule finding phase (Stage 1) followed by confirmatory phase (Stage 2)	Investigator-initiated, multi-centre, open-label, randomised, and controlled	Retrospective analysis of data from a compassionate use program
Method of randomisation	N/A	In the maintenance phase, patients were randomised to receive or not IL-2 in addition to dinutuximab beta with cis-13-RA. Randomisation of patients to the different treatment arms was done using a web-based system. Randomisation for the immunotherapy was stratified by national group and allocated by previous consolidation treatment (R1): BuMel vs CEM vs Non R1 patients.	N/A

Method of blinding (care provider, patient and outcome assessor)	N/A, the study was open-label	N/A, the study was open-label; placebo IL-2 injection was considered unethical in the patient population studied	N/A, the study was open-label

Eligibility criteria for participants	• ≥ 1 year and ≤ 45 years of age at treatment start (age limit ≤21 for trial cohorts only)
	• Diagnosis of high-risk neuroblastoma according to the INSS criteria, i.e. INSS stage 2, 3, 4, or 4s with MYCN amplification, or INSS stage 4 without MYCN amplification or relapsed or refractory neuroblastoma of any stage
	• Off any standard or experimental treatments for at least two weeks prior to treatment start and fully recovered from the short term major toxic effects
	• No immediate requirements for palliative chemotherapy, radiotherapy or surgery
	• ≥ 4 weeks after major surgery (e.g. laparotomy or thoracotomy) and fully recovered from any post-surgical complications
	• Patients with seizure disorders were enrolled if on anticonvulsants and if seizure disorders were well controlled
	• No dyspnoea at rest and a pulse oximetry >94% on room air
	• Adequate bone marrow. liver renal function
		1. Established diagnosis of neuroblastoma according to the INSS
		2. Age below 21y
		3. High-risk neuroblastoma, defined either as:
		  ○ INSS stages 2, 3, 4, or 4s with MYCN amplification below 21y
		  ○ INSS stage 4 without MYCN amplification aged ≥12 months at diagnosis, and in patients aged 12-18 months only in presence of segmental chromosomal alterations (SCA)
			Patients with high-risk, relapsed or refractory neuroblastoma diagnosed according to the INSS criteria between 1-45y, who have estimated life expectancy of at least 12 weeks and who could not get adequate treatment for their disease through routine medical treatment and/or were not eligible for clinical trials were included in the CUP

Number of patients (planned and analysed)	Planned: During the dose schedule finding phase (Stage 1) it was expected that 20 to 40 patients had to be enrolled to evaluate a cohort of 10 patients. In the confirmatory phase (Stage 2) 100 patients were planned. The study is still ongoing Analysed: The total number of patients for this interim analysis is 44 and consists of the 24 patients treated at 10 mg/m2 for 10 days during the dose schedule finding phase (Stage 1) of the study and the first 20 patients enrolled during the confirmatory phase (expansion cohort, Stage 2). All of these patients have completed study treatment and are therefore evaluable for this interim analysis.	400 patients were planned to enter modified R2 (randomisation 2). 406 patients were enrolled and randomised for modified R2 in APN311-302 between November 2009 and August 2013. A confirmation (CRF) was available from 385 patients. Data from these patients was used in the analysis described in this report.	54 planned and analysed

Settings and locations where the data were collected	Multiple centres across Europe (Germany, Austria, UK, Ireland, Italy, Spain, France), Israel and Australia	88 centres and investigators in 10 European countries, Israel and Australia	Single-centre, EU: University Children's Hospital Greifswald, 17475 Grefiswald, Germany
Duration of study	Five, 35-day cycles with: • dinutuximab beta: 10 day infusion on Day 8 to Day 17/cycle • IL-2: 10 days administered as two 5-day blocks (Days 1-5 and 8-12)/cycle • 13-cis-RA: 14 days on Day 19 to 32/cycle.	HRNBL1 study is ongoing with other open randomisation topics; duration is 5 cycles of 4 weeks	All patients were to be treated with up to 6 treatment cycles if there was no disease progression or unacceptable toxicity. Duration of each cycle was 28 to 35 days.
Trial drugs	Dinutuximab beta, IL-2, and isotretinoin (13-cis-RA)	During the immunotherapy phase: Dinutuximab beta, supplied as concentrated solution 4.5 ± 0.25 mg/mL, with or without commercially available IL-2 in addition to 13-cis-RA	Dinutuximab beta, supplied as concentrated solution of 4.6mg/ml, commercially available IL-2 and 13-cis-RA were used
Permitted and disallowed concomitant medications	dinutuximab beta treatment was preceded by premedication with gabapentin (10 mg/kg/dose once daily for 3 days) 3 days before the start of the dinutuximab beta infusion, as well as i.v. morphine as established in previous studies. Concomitant standard pain management was to be established with or without i.v. morphine and was to follow standard World Health Organization (WHO) guidelines Prohibited concomitant treatments while patients were enrolled in the trial: - Chemotherapy, hormonal anticancer therapy, or experimental anticancer medications other than those that were study-related. - Glucocorticoids, or other drugs with known immunosuppressive activity, were not to be used during and for 2 weeks prior to entry onto the trial except for life threatening symptoms. - Radiotherapy. - The use of i.v. immunoglobulin was strongly discouraged, because i.v. immunoglobulin could interfere with the antibody (dinutuximab beta) dependent cellular toxicity. Immunoglobulin i.v. was not to be given within 2 weeks of starting dinutuximab beta and 1 week after completing dinutuximab beta.	Premedication with anti-histamine medication was given prior to each dinutuximab beta infusion on Day 1 through Day 5 as allergic prophylaxis. During dinutuximab beta treatment, patients received mandatory pain treatment. Analgesic and anaphylactic prophylaxis included paracetamol, gabapentin, and morphine. Prohibited treatment during the immunotherapy phase: - Chemotherapy, hormonal anticancer therapy, or experimental anticancer medications other than study-related therapy. - Glucocorticoids or other drugs with known immunosuppressive activity, during and for 2 weeks prior to entry into this trial except for treatment of life-threatening symptoms. - Radiotherapy. - The use of i.v. immunoglobulin (IVIG) post-PBSCR was discouraged. If necessary, its use was to be limited to the first 100 days post-PBSCR, because IVIG might interfere with the antibody (dinutuximab beta) dependent cellular toxicity.	Concomitant medications were taken by all patients and each patient has received Hartmann's solution and has taken pain medications (e.g. paracetamol and metamizol).

		- For patients randomised in R2, IVIG was not to be given within 2 weeks of starting dinutuximab beta and 1 week after completing dinutuximab beta; i.e. if necessary, it could have been given during the first week and at any time from Week 22.	
Primary outcomes (including scoring methods and timings of assessments)	Primary endpoints for the dose schedule finding: • Pain-toxicity endpoint: • Intravenous (i.v.) morphine-free dinutuximab beta infusion schedule after the first 5 days (of infusion) during the first cycle in ≥80% of patients. • Efficacy endpoint: On Day 15 of the first cycle in ≥80% of patients: 1. An increase of 500% and/or an absolute minimum increase to ≥100 cells/µL of the CD16/CD56 positive activated NK cells; 2. A measurable dinutuximab beta level of at least 1 µg/mL.	3-year EFS, calculated from date of modified R2 randomisation. Disease progression or relapse, death from any cause and second neoplasm considered as events	Safety and tolerability evaluated by: • Pain intensity/ morphine use • Incidence, grade and type of adverse events, vital signs and changes in clinical laboratory assessments
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	Secondary endpoints for the dose schedule finding: 1) ADCC and activated NK cell concentrations above baseline levels in ≥80% of patients; 2) Appearance of soluble IL-2 receptor and CDC; 3) Detection of anti-idiotype response by appearance of HAMA and HACA; 4) Increase of absolute lymphocyte counts by 50% over baseline; 5) Increase of absolute NK cell numbers >1000 cells/µL in ≥80% of patients; 6) Dinutuximab beta concentration; 7) Anti-tumour response in patients with measureable disease (bone marrow [BM], skeletal lesions, soft tissue lesions, lymph nodes and/or primary tumour site) as measured by immunocytology, mIBG, CT and/or MRI;	• Overall survival, calculated from date of modified randomisation R2 to death from any cause • Cumulative incidence of relapse/progression • Cumulative incidence of death by disease progression, infection and other reason • Overall response based on the investigator's assessment • Toxicity • Relationship of response rates, survival, EFS, cumulative incidence of relapse or progressions with potential prognostic factors including MYCN amplification, age by categories (<1y, 1-1.5y, 1.5-5y, >5y) and disease status before immunotherapy	Efficacy evaluated by: • Response rate in patients with measurable/evaluable disease (skeletal lesions, soft tissue lesions, lymph nodes and/or primary tumour site, bone marrow) as measured by ^{123}I-mIBG scan, CT/MRI and/or bone marrow examination at the end of cycle 3 and at the end of treatment (after 5th or 6th cycle), and durability of response • Overall survival (OS) • Event-free survival (EFS), calculated as number of days from starting CU-LTI treatment until relapse or disease progression observed and detected by ^{123}I-mIBG scan, CT/MRI and/or bone marrow examination • Pharmacodynamic parameters: NK-cell activation, soluble IL-2 receptor, ADCC, CDC and

	8) Confirmation of the primary and secondary endpoints in the expansion cohort.		anti-chimeric antibody response (HACA), lymphocyte and absolute NK-cell count • Correlation between activated NK cells and dinutuximab beta level with ADCC • Pharmacokinetic parameters
Pre-planned subgroups	Efficacy data were analysed overall and separately for patients with relapsed, refractory or high-risk neuroblastoma. Analysis was also done for subgroups of patients with disease measureable by MRI/CT or mIBG and with no evidence of disease.	None	None

Abbreviations: NB, neuroblastoma; INSS, International Neuroblastoma Staging System; ASCT, autologous stem cell transplant; RCT, randomised controlled trial; 13-cis-RA, 13-cis retinoic acid; i.v., intravenous; s.c., subcutaneous; EFS, event-free survival; CU-LTI, compassionate use long-term infusion; IL-2, interleukin 2; CUP, compassionate use program; NK, natural killer; ADCC, antibody dependent cellular cytotoxicity; MNC, multinuclear cells; CHO, Chinese hamster ovary; CDC, complement-dependent cytotoxicity; HAMA, human anti-mouse antibody; HACA, human anti-chimeric antibody; MAT, myeloablative therapy; BuMel, busulphan and melphalan; CEM, carboplatin, etoposide, melphalan; SCA, segmental chromosomal alterations; CRF, confirmation; WHO, World Health Organisation; IVIG, intravenous immunoglobulin; PBSCR, peripheral blood stem cell rescue; CT, computed tomography; MRI, magnetic resonance imaging; mIBG, metaiodobenzylguanidine

2.3.2 *Summary of baseline characteristics and demographics of trial participants*

APN311-302

Patient characteristics at baseline in APN311-302 are summarised in Table 12 and Table 13. A total of 406 patients were enrolled in study APN311-302 by August 2013 in 10 European countries, Australia and Israel. The first patient was enrolled on R2 (immunotherapy randomisation) on 30 November 2009 and the last patient was enrolled on R2 on 12 August 2013. A confirmation CRF (case report form) was available from 385 patients. Data from these patients were used in the analysis submitted as part of this application. Demographic characteristics for the FAS are summarized in Table 12. Treatment groups were well balanced for demographic characteristics. The majority of patients were male (63.8%). The mean age of the study population at randomisation was 3.7 ± 2.6 (standard deviation, SD) years, ranging from 0.6 years to 20.0 years, and most patients (69.1%) were between 1.5 to 5 years old. Mean time from diagnosis to randomisation was 8.5 months.

Table 12: Demographics and baseline characteristics of patients in APN311-302 (FAS)

Parameter		Dinutuximab beta + 13-cis-RA (N=180)	Dinutuximab beta + 13-cis-RA + IL-2 (N=190)	All (N=370)
Gender, N (%)	Male	116 (64.4)	120 (63.2)	236 (63.8)
	Female	64 (35.6)	70 (36.8)	134 (36.2)
Age at randomisation (years)	n	180	189	369
	Mean (SD)	3.55 (2.23)	3.79 (2.97)	3.68 (2.63)
	Median	3.00	3.00	3.00
	Min, Max	0.6, 19.0	0.7, 20.0	0.6, 20.0
Age groups (years), N (%)	<1	5 (2.8)	5 (2.6)	10 (2.7)
	1 to 1.5	8 (4.4)	6 (3.2)	14 (3.8)
	>1.5 to 5	123 (68.3)	132 (69.8)	255 (69.1)
	>5	44 (24.4)	46 (24.3)	90 (24.4)
	Missing	-	1	1
Weight (kg)	n	179	189	369
	Mean (SD)	15.33 (5.24)	16.18 (7.51)	15.77 (6.51)
	Median	14.00	14.30	14.20
	Min, Max	6.4, 55.5	7.0, 54.4	6.4, 55.5
Height (cm)	n	134	152	286
	Mean (SD)	100.46 (16.03)	102.37 (18.80)	101.47 (17.55)
	Median	100.0	98.00	99.00
	Min, Max	71.0, 179.0	70.0, 172.0	70.0, 179.0
Time from diagnosis to randomisation (months)	n	180	190	370
	Mean (SD)	8.36 (1.93)	8.61 (3.23)	8.48 (2.68)
	Median	8.00	8.00	8.00
	Min, Max	6.0, 25.0	6.0, 48.0	6.0, 48.0

Abbreviations: 13-cis-RA = 13-cis retinoic acid, FAS = full analysis set, IL-2 = aldesleukin, Min = minimum, Max = maximum, SD = standard deviation, N = number of patients with observations

Tumour characteristics for the FAS are summarized in Table 13. Treatment groups were well balanced for tumour characteristics. The majority of patients (88.6%) had neuroblastoma stage 4 and about half of the patients presented with MYCN amplification.

Table 13: Tumour characteristics (FAS, N=370) – APN311-302

Parameter		Dinutuximab beta + 13-cis-RA (N=180)	Dinutuximab beta + 13-cis-RA + IL-2 (N=190)	Total (N=370)
MYCN status, N(%)	Amplified	69 (41.6)	83 (46.4)	147 (44.0)
	Not amplified	87 (52.4)	94 (52.5)	178 (53.3)
	Not available	10 (6.0)	2 (1.1)	12 (3.5)
	Missing	14	11	25
INSS[b] stage at initial diagnosis	2[a]	1 (0.6)	-	1 (0.3)
	3[a]	16 (8.9)	18 (9.5)	34 (9.2)
	4	159 (88.3)	169 (88.9)	328 (88.6)
	4S[a]	4 (2.2)	3 (1.6)	7 (1.9)

[a]MYCN amplified
Abbreviations: INSS = International Neuroblastoma Staging System, MYCN = N-myc proto-oncogene protein, FAS = full analysis set, IL-2 = aldesleukin, 13-cis-RA = 13-cis retinoic acid

APN311-303 (Retrospective analysis)

Patient characteristics at baseline in APN311-303 are summarised in Table 14,Table 15, Table 16 and Table 17. A total of 33 male (61.1%) and 21 female (38.9%) patients were enrolled and treated in this compassionate use program (see Table 14). The majority of the enrolled and treated patients (52, 96.3%) were Caucasian and the remaining patients were Asian (2, 3.7%). The ages of the patients ranged from 2 to 26 years with a median age of 6 years. The mean BSA was 0.839 m^2.

Table 14: Demographic profile of patients enrolled in CU-LTI program - APN311-303

Parameter		Number of Patients (n=54)
		N (%)
Gender	Male	33 (61.1%)
	Female	21 (38.9%)
Ethnicity	White/Caucasian	52 (96.3%)
	Black	-
	Asian	2 (3.7%)
Age (years)	n	54
	Mean (SD)	7.3 (4.7)
	Median	6.0
	Min, Max	2, 26
Weight (kg)	n	53
	Mean (SD)	22.33 (12.95)
	Median	17.40
	Min, Max	11.7, 75.1
Height (cm)	n	53
	Mean (SD)	116.1 (22.2)
	Median	110.0
	Min, Max	82, 188

Parameter		Number of Patients (n=54)
		N (%)
BSA (m^2)	n	53
	Mean (SD)	0.839 (0.307)
	Median	0.730
	Min, Max	0.53, 1.94
Abbreviations: Max = maximum, Min = minimum, SD = standard deviation, BSA = body surface area		

About half of the patients (56%) had relapsed neuroblastoma, i.e. the patients had experienced at least one relapse after previous neuroblastoma treatment, although they reacted adequately to the most recent treatment prior to immunotherapy. Fifteen patients (28%) had a refractory disease status and 9 patients (17%) had only received first-line neuroblastoma treatment with either a complete response or with minimal residual disease (Table 15). The majority of the enrolled and treated patients (24, 44.4%) had disease evaluable only by mIBG scan and/or BM histology, and 15 (27.8%) patients each had no evidence of disease or disease measurable by MRI and/or CT.

Table 15: Status at study entry by baseline disease status – APN311-303

Baseline Disease Status		Number of Patients (n=54)
		N (%)
Relapsed patients (N=30)	Measurable by MRI and/or CT	7 (23.3%)
	Evaluable only by mIBG and/or BM histology	16 (53.3%)
	No evidence of disease	7 (23.3%)
Refractory patients (N=15)	Measurable by MRI and/or CT	6 (40.0%)
	Evaluable only by mIBG and/or BM histology	7 (46.7%)
	No evidence of disease	2 (13.3%)
Patients with frontline therapy only (N=9)	Measurable by MRI and/or CT	2 (22.2%)
	Evaluable only by mIBG and/or BM histology	1 (11.1%)
	No evidence of disease	6 (66.7%)
Abbreviations: BM = bone marrow, CT = computed tomography, mIBG = meta-iodobenzylguanidine, MRI = magnetic resonance imaging		

Patients enrolled in the CU-LTI program had a mean time since the neuroblastoma diagnosis of 33.1 months. In 11 patients, neuroblastoma had been diagnosed prior to 1.5 years of age and 43 patients were over 1.5 years of age at the time of diagnosis (Table 16). Out of the 54 patients 30 patients had relapsed disease, 15 patients had refractory disease and 9 patients were treated with first-line therapy only.

As first-line therapy the majority of patients (N=50) received intensive multimodality treatment. Only four patients were observed only, had received standard chemotherapy or underwent surgery prior to being treated under the CU-LTI program. For more details on clinical prognostic factors please see Table 16.

Table 16: Clinical Prognostic factors - participants in APN311-303

Parameter		Statistics	Number of Patients (n=54)
Time since first diagnosis to screening visit (months)		N Mean (SD) Median Min, Max	54 33.1 (25.0) 25.0 9, 116
Age at first diagnosis (days)	< 547 ≥ 547	N (%) N (%)	11 (20.4%) 43 (79.6%)
INSS stage	1 2A 2B 3 4 4S Missing	N (%)	1 (1.9%) 1 (1.9%) - 4 (7.5%) 47 (88.7%) - 1
Baseline status	Relapsed Refractory Evidence of disease after first-line therapy No evidence of disease after first-line therapy	N (%)	30 (55.6%) 15 (27.8%) 3 (5.6%) 6 (11.1%)
LDH (µkat/L)		N Mean (SD) Median Min, Max	15 6.80 (5.19) 5.12 0.1, 21.0
Serum ferritin (µg/L)		N Mean (SD) Median Min, Max	12 1161.34 (1292.84) 638.00 79.1, 4458.0
Initial treatment	Observation, surgery, or standard chemotherapy Intensive multimodality	N (%)	4 (7.4%) 50 (92.6%)

Abbreviations: INSS = International Neuroblastoma Staging System, Max = maximum, Min = minimum, SD = standard deviation, LDH = lactate dehydrogenase

Table 17: Demographics and disease history by disease type – APN311-303

Parameter		Relapsed Patients[1] (N = 30)	Refractory Patients[1] (N = 15)	Frontline Patients[1] (N = 9)
Time since first diagnosis to SCR visit [months]	n Mean (SD) Median Min, Max	30 44.6 (27.3) 35.5 21,116	15 21.3 (11.7) 16.0 10, 55	9 14.2 (4.7) 14.0 9, 23
Age at first diagnosis, n (%)	< 547 days ≥ 547 days	4 (13.3) 26 (86.7)	6 (40.0) 9 (60.0)	1 (11.1) 8 (88.9)
INSS Stage, n (%)	1 2a 3 4	1 (3.4) 1 (3.4) 2 (6.9) 25 (86.2)	- - 1 (6.7) 14 (93.3)	- - 1 (11.1) 8 (88.9)
MYCN amplification, n (%)	no yes	17 (81.0) 4 (19.0)	9 (69.2) 4 (30.8)	3 (37.5) 5 (62.5)
Grade NB differentiation, n (%)	Differentiated Undifferentiated	6 (46.2) 7 (53.8)	8 (72.7) 3 (27.3)	1 (50.0) 1 (50.0)
MKI, n (%)	Low	1 (33.3)	2 (66.7)	-

	Intermediate	1 (33.3)	-	-
	High	1 (33.3)	1 (33.3%)	-
LDH (μkat/L)	n	8	6	1
	Mean (SD)	7.32 (3.72)	7.21 (6.81)	0.09 (.)
	Median	6.95	4.64	0.09
	Min, Max	2.9, 13.6	3.0, 21.0	0.1, 0.1
Serum ferritin (μg/L)	n	6	5	1
	Mean (SD)	1237	1279.00	159.00 (.)
	Median	(1746.77)	(712.55)	159.00
	Min, Max	341.85	1287.0	159.0, 159.0
		79.1, 4458.0	606.0, 2369.0	
Initial treatment, n (%)	Observation, surgery or standard chemotherapy	4 (13.3%)	-	-
	Intensive multimodality	26 (86.7%)	15 (100.0%)	9 (100.0%)

[1] Note: Missing values are not displayed
LDH = lactate dehydrogenase, Max = maximum, Min = minimum, MRI = magnetic resonance imaging, SD = standard deviation, SCR = screening visit; MKI = mitosis-karyorrhexis index

Six patients (11%) had INSS stage < 4 at diagnosis but suffered from disseminated or combined relapse, and therefore, are considered to have similar prognosis as stage 4 patients. Information on MYCN amplification status is missing for 12 patients (22%); it was positive in 13 patients (24%).

For 31 patients (30 with relapsed disease and 1 with refractory disease) the dates of previous relapses/progressions were documented. Most of the patients had experienced only 1 relapse/progression prior to enrolment to immunotherapy. The median time since the first relapse/progression to the start of immunotherapy was 12 months, the median time since the most recent relapse/progression was 10 months. The average time from the initial diagnosis to the first relapse/progression was 708 days (± 311) days, which would suggest a population with a relatively good survival prognosis.

First-line treatment included in most patients intensive combined chemotherapy followed by ASCT: 24 had BuMel+ASCT and 24 had CEM+ASCT. Salvage therapies of the recurrence included amongst others second-line therapy with irinotecan/temozolomide or topotecan/temozolomide, radiotherapy, and radionuclide therapy with mIBG.

APN311-202

Patient characteristics at baseline in APN311-202 are summarised in Table 18, Table 19 and Table 20. Table 18 summarizes the demographic characteristics and disease status at baseline for the FAS (full analysis set, which included all patients exposed to dinutuximab beta, and for whom baseline tumour assessments and at least 1 post-baseline tumour assessment were available). The majority of patients were male (63.6%) and from

Caucasian origin (87.8%). The mean age of the study population at start of treatment was 6.1 years, with a minimum of 1 year and a maximum of 17 years.

Table 18: Baseline characteristics (demographics and disease history) of participants in APN311-202

Parameter		Number of Patients (n=44)
Gender	Male	28 (63.6%)
	Female	16 (36.4%)
Ethnicity	White/Caucasian	36 (87.8%)
	Black	-
	Asian	1 (2.4%)
	Unknown	4 (9.8%)
	Missing*	3
Age at initial diagnosis (years)	n	44
	Mean (SD)	3.2 (2.0)
	Median	3.0
	Min, Max	0, 9
Age at start of treatment (years)	n	44
	Mean (SD)	6.1 (3.4)
	Median	5.0
	Min, Max	1, 17
MYCN amplification	No	39 (92.9%)
	Yes	3 (7.1%)
	Missing	2
INSS stage at initial diagnosis	1	1 (2.3%)
	4	41 (93.2%)
	4S	2 (4.5%)
Patients with refractory disease, n (%)		25 (56.8%)
Patients with relapsed disease, n (%)		19 (43.2%)

Abbreviations: INSS = International Neuroblastoma Staging System, max = maximum, min = minimum, SD = standard deviation, MYCN = v-myc myelocytomatosis viral related oncogene

Disease was measurable at baseline for 33 patients; for 21 patients (47.7%) measured by mIBG and/or BM histology and for 12 patients by MRI and/or CT (27.3%). Eleven patients (25%) had no evidence of disease at baseline (see Table 19). At baseline, 25 out of 44 patients (56.8%) had refractory disease and 19 (43.2%) had relapsed disease.

Table 19: Disease status at baseline in APN311-202

Disease Status		Number of Patients (n=44)
		N (%)
Relapsed patients	Measurable by MRI and/or CT	4 (21.1%)
	Evaluable only by mIBG and/or BM histology	8 (42.1%)
	No evidence of disease	7 (36.8%)
Refractory patients	Measurable by MRI and/or CT	8 (32.0%)
	Evaluable only by mIBG and/or BM histology	13 (52.0%)
	No evidence of disease	4 (16.0%)

Abbreviations: BM = bone marrow, CT = computed tomography, mIBG = meta-iodobenzylguanidine, MRI = magnetic resonance imaging

For a total of 23 patients the overall number of relapses/progressions and the date of the most recent relapse/progression was documented (Table 20). Sixteen out of the 23 patients experienced only 1 relapse/progression. Most patients (56.5%) experienced

relapse/progression of the combined type, i.e. not limited to one location. For 38 patients, the performance status before study treatment was evaluated. The minimum performance score was 80 and the maximum was 100 (mean 98.4 ± 4.4) at baseline.

Table 20: Relapse/Progression prior to immunotherapy in APN311-202

Parameter		Number of Patients (n=44)
Number of relapses/progressions	n	23
	Mean (SD)	1.5 (1.1)
	Median	1.0
	Min, Max	1, 6
Number of relapses/progressions (categories)	1	16 (69.6%)
	2	6 (26.1%)
	6	1 (4.3%)
Time from initial diagnosis to most recent relapse/progression (days)	n	16
	Mean (SD)	1099 (1091)
	Median	618.0
	Min, Max	253, 4123
Most recent relapse/progression type	Bone marrow alone	3 (13.0%)
	Combined	13 (56.5%)
	Other metastatic sites alone	1 (4.3%)
	Primary tumour site alone	2 (8.7%)
	Skeleton alone	4 (17.4%)
Abbreviations: INSS = International Neuroblastoma Staging System, Max = maximum, Min = minimum, MYCN = v-myc myelocytomatosis viral related oncogene, SD = standard deviation		

First-line treatment consisted of single courses or combinations of the following treatments: surgery, radiotherapy, chemotherapy, intensive chemotherapy and maintenance therapy with 13-cis-retinoic acid (RA). Most frequently patients received rapid COJEC followed by high-dose BuMel (busulfan and melphalan) + autologous stem cell transplantation (ASCT) treatment. About 55% of the patients received radiotherapy and 43% received 13-cis-RA maintenance therapy prior to immunotherapy.

As treatment of R/R disease, 14 patients received another intensive chemotherapy regimen followed by ASCT. Nine patients (20.5%) received radiotherapy as local therapy and 8 patients (18 %) underwent surgery. About 20% of patients received 13-cis-RA maintenance therapy.

Although the response to the most recent therapy was not recorded, all patients had to have responded adequately to their previous treatment and no patient had signs of progression at study entry. Most patients had evidence of disease at baseline before immunotherapy, either detected by $^{123/131}$iodine-meta-iodobenzylguanidine (mIBG) and/or bone marrow (BM) histology or measured by magnetic resonance imaging (MRI) and/or computed tomography (CT) (see Table 19).

2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

Details of the statistical analyses of relevant clinical trials are summarised in Table 21.

Table 21: Summary of statistical analyses

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
APN311-202	No hypothesis was stated. This clinical trial consisted of a dose schedule finding phase (Stage 1), followed by a confirmatory phase (Stage 2). The primary objective of this study was to find a tolerable treatment schedule which reduces the pain-toxicity profile of dinutuximab beta while maintaining immunomodulatory efficacy in patients (1-21y) with either primary refractory (≥2 lines of conventional treatment) or relapsed neuroblastoma by using a prolonged continuous infusion in combination with subcutaneous (s.c.) aldesleukin (IL-2).	All statistical analyses were performed using Statistical analysis software (SAS®) for Windows (Version 9.3). Data were presented in individual listings and summarized according to their data type. If appropriate, data were summarized over time. The following variables were not statistically described, but only given in listings: • medical history; • in-/exclusion criteria, pregnancy test; • physical examination; • check boxes, comments. All other data were analysed in a descriptive, exploratory manner and presented in summary tables. The analysis of all efficacy variables was based on the FAS population. EFS was defined as time between first day of IL-2 administration to date of relapse/progression or death. EFS for patients without progression/relapse or death at the time of analysis were censored at their last date of being known to be alive or at the database cut-off date, whatever came first. OS was defined as time between first day of IL-2 administration to death. OS of subjects not known to have died were censored at their last date of being known to be alive or at the database cut-off date, whatever came first. For both, EFS and OS was modelled by Kaplan-Meier estimators	*Determination of sample size* A total of up to 140 neuroblastoma patients is planned to enter this study. Initially, it was anticipated that between 30 and 60 patients were to be enrolled in the study; 20-40 within the dose schedule finding part of the study (dose schedule finding cohort) with an additional 20 patients enrolled during the confirmatory phase (expansion cohort). Later, Amendment 1 extended the confirmatory cohort (initially consisting of 20 patients) to an expansion cohort of a total of 100 patients. That means a maximum of 40 patients for the first stage of the study (dose schedule finding) and a (with Amendment 1 extended) total of 100 patients in the second stage of the study (confirmation). The total number of patients for this interim analysis was 44 and consisted of the 24 patients treated at 10 mg/m² x 10 days during the dose schedule finding phase of the study and the first 20 patients enrolled during the confirmatory phase (expansion cohort). All of these patients had completed study treatment and were therefore evaluable for this interim analysis. All populations were based on the 44 patients enrolled into the 24-patient dose-schedule finding phase and the original 20-patient confirmatory phase.	Data collected were entered into eCRFs (electronic case report forms). No data specified patient withdrawals.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
APN311-303	No hypothesis was stated. The authors aimed at retrospectively evaluate safety and assess the pain-toxicity profile of a prolonged continuous infusion of dinutuximab beta in combination with s.c. aldesleukin (IL-2) followed by oral 13-cis-RA in patients with high-risk neuroblastoma treated under a compassionate use program (CU-LTI). Only data collected through the compassionate use program was used and analysed.	The safety population (SAF) included all patients who were enrolled in this retrospective analysis. The analysis of all safety variables is based on this population. Only patients treated with study drug were enrolled. The full analysis set (FAS, intention-to-treat population, ITT) included all patients who were enrolled, and from whom a screening mIBG or CT/MRI was available. Two per protocol (PPS) populations were defined, PP-RESP for the overall response evaluation and PP-SURV for event free and overall survival. For the PP-RESP patients 1. with evidence of disease at screening assessment and 2. with MRI/CT at baseline and at MID/EOT (mid evaluation-end of treatment) evaluation or mIBG at baseline and at MID/EOT assessment and 3. receiving dinutuximab beta and IL-2 were considered. For the PP-SURV all patients receiving dinutuximab beta and IL-2 were considered. Efficacy data were analysed overall and separately for patients having received first-line therapy who had evidence or no evidence of disease at baseline, and patients with relapsed or refractory neuroblastoma (separately and together). All analyses were performed using SAS. Data is presented in individual listings and summarized – if appropriate over time - according to data type: 1. continuous data by mean, standard deviation, minimum, median, maximum 2. qualitative (nominal) data by absolute and/or relative frequencies. Overall survival (OS) and Event-Free Survival (EFS) were analysed using Kaplan-Meier methods.	No formal sample size determination was applicable for this retrospective study. All patients treated under CU-LTI were enrolled in this retrospective analysis.	*Data Management* Data collected under the CU-LTI program was entered onto paper case report forms (CRFs). When the CRFs had been completed, a monitor verified the source documents and reviewed the data. If subsequent review of the data resulted in queries being generated these were forwarded to the Investigator or designee for resolution. All data modifications resulting from review or querying of the data were electronically tracked. Any errors detected by either the monitor or the Investigator after CRF completion were communicated via query forms. In all cases the Investigator or designee and the monitor signatures were required. Coding of adverse events was performed using MedDRA dictionary Version 16.1. Patient Withdrawal N/A

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
APN311-302	Primary objective of this clinical trial was to test the hypothesis that the addition of subcutaneous aldesleukin (IL-2) to immunotherapy with dinutuximab beta in addition to differentiation therapy with isotretinoin (13-cis-RA) following myeloablative therapy (MAT) and autologous stem cell rescue (ASCR), will improve 3-year event-free survival (EFS) in patients with high-risk neuroblastoma.	Full analysis set (FAS): All patients randomised and treated with 13-cisRA, dinutuximab beta, or IL-2. Patients, who were randomised but not treated or for whom no treatment data are available, were excluded. Patients were analysed as randomised. Safety set (SAF): All patients randomised and treated with at least one dose of antibody (dinutuximab beta). Patients were analysed as treated. Per-protocol set (PPS): Subset of FAS, where patients were excluded if • Baseline disease evaluation was missing • Baseline disease evaluation: PD • MAT=No or missing • No dinutuximab beta antibody therapy • R2 Randomisation criteria not met or missing • Patients were analysed as treated. • Deviations from the SAP: • Patients not treated as randomised (i.e. patients randomised to concomitant IL-2 treatment who received no IL-2) were also excluded from the PPS. • The cumulative incidence of relapse and/or progressions was not related to potential prognostic factors Efficacy was analysed based on the full analysis set (FAS) and the per-protocol set (PPS). The primary endpoint, the 3-year EFS, was analysed using Kaplan-Meier methods. EFS was calculated as the number of days from randomisation until disease progression or relapse, death from any cause or secondary neoplasm. Overall survival was calculated as the number of days until death from any cause using Kaplan-Meier methods. Start of the observation period for 3-year EFS and OS was the date of the second (modified R2) randomisation.	The 3-year EFS in the group without IL-2; i.e. 13-cis-RA and dinutuximab beta) was anticipated to be 55%. This trial aimed to demonstrate an improvement of 12.5% by the addition of aldesleukin (IL-2). With a sample size of 400 patients, a recruitment period of 4 years, a minimum follow up of 2 years, and two-sided α = 5%, the study had a power of 80%.	*Monitoring and data management:* The study used a web-based system to collect data with remote data entry. For the immunotherapy part reported herein, separate paper 'confirmation, CRFs were used to collect selected data from participating centres. The paper CRF included information obtained from the web-based system used in the HRNBL1 study. The investigator was asked to confirm the information in the CRF, correct it if incorrect, and/or complete missing information. The additional paper CRF was used to confirm data previously collected within the web-based system and to eventually complete missing data of the web-based system used in the academic setting. No monitoring was performed on the paper CRF. Case report forms were reviewed by Ergomed personnel for omissions, apparent errors or values requiring further clarifications. Relevant errors/omissions were entered onto data correction forms and referred back to the investigator for resolution and subsequent correction. *Patient Withdrawal*: Patients who experienced progressive disease during or after induction, or after MAT were discontinued from the study. Patients were to be taken off dinutuximab beta if the following toxicities occurred: • Grade 3 (bronchospasm) and 4 (anaphylaxis) allergic reaction. • Grade 3 serum sickness. • Grade 4 severe, unrelenting neuropathic pain unresponsive to continuous infusion of narcotics and other adjuvant measures including lidocaine infusions.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
				• Neurotoxicity: 1) Grade 3 sensory changes interfering with daily activities >2 weeks after completing dinutuximab beta therapy; 2) Objective motor weakness; 3) Grade 3 vision toxicity (i.e. subtotal vision loss per toxicity scale). • Grade 4 hyponatremia (<120 mEq/L) despite appropriate fluid management. • Grade 4 capillary leak syndrome (Grade 4 includes ventilator support). • Grade 4 skin toxicity. Patients were to be continued to receive 13-cis-RA. If any (non-lethal) serious adverse event (SAE) occurred in a patient, his or her further treatment according to the study protocol had to be discussed with the national study co-ordinator immediately to decide together if continuation of immunotherapy was justifiable and could be recommended.

2.5 *Quality assessment of the relevant clinical effectiveness evidence*

2.5.1 *Methods for assessing risk of bias*

2.5.1.1 Was the randomisation method adequate?

Studies APN-202 and -303 were not randomized studies. Study -302 is an investigator-initiated, multi-centre, open-label, randomised, and controlled phase III trial in high-risk neuroblastoma patients, parts of which are currently still accruing. The study includes three main study phases: an induction phase, a consolidation (MAT) phase, and a maintenance phase. During the latter patients received immunotherapy, and were randomized to receive or not IL-2 together with Dinutuximab beta Apeiron and 13-cis-RA. Randomisation of patients to the different treatment arms was done using a web-based system. Randomisation for the immunotherapy was stratified by national group and allocated by previous treatment (R1: BuMel, R1: CEM, Non R1 patients).

2.5.1.2 Was the allocation adequately concealed?

Not applicable; the study APN311-302 was designed as a randomised, open-label, un-blinded study, thus treatment allocation was not concealed.

2.5.1.3 Were the groups similar at the outset of the study in terms of prognostic factors?

Treatment groups were well balanced for demographic and tumour characteristics at baseline in study APN311-302.

2.5.1.4 Were the care providers, participants, and outcome assessors blind to treatment allocation?

Study APN311-302 was open label, so neither patients nor providers were masked to treatment allocation. A placebo IL-2 injection was considered unethical in the vulnerable patient population studied. In addition, due to the expected adverse reactions of IL-2 administration full blinding would have been not possible.

2.5.1.5 Were there any unexpected imbalances in drop-outs between groups?

As expected, in study APN311-302 IL-2 treatment led to an increased frequency of SAEs, which consequently caused more dose reductions and premature discontinuations of dinutuximab beta and IL-2 in patients receiving IL-2 vs patients not receiving IL-2. In particular, 17.5% of patients receiving IL-2 experienced any SAE leading to withdrawal compared to 6% of patients in the dinutuximab beta+13-cis-RA arm (47 vs 16 SAEs, respectively). In total, 39.4% vs 78.3% of patients in whom treatment

completion status could be determined with and without IL-2, respectively, received at least 50% of the planned doses of dinutuximab beta or IL-2 (if applicable) in Cycles 1 to 5.

2.5.1.6 Is there any evidence to suggest that the authors measured more outcomes than they reported?

No, the Applicant reported the pre-specified primary and secondary outcomes.

2.5.1.7 Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

All of the 44 patients enrolled in the dose schedule finding phase and confirmatory phase in the APN311-202 study were included in the Safety Analysis Set (SAF) and in the Full Analysis Set (FAS/IIT). The SAF included all patients who were exposed to dinutuximab beta. The analysis of all safety variables was based on this population. included all patients who were exposed to study medication and for whom baseline tumour assessments and at least 1 post-baseline tumour assessment were available. The FAS population was the primary population for the various efficacy assessments. Missing data were not replaced.

Since study APN311-303 is a retrospective analysis of already available data, missing data were not considered protocol violation/deviation. The full analysis set (FAS/ ITT) included all patients who were enrolled, and from whom a screening mIBG or CT/MRI was available. All patients treated under CU-LTI who had received at least one dose of dinutuximab beta were included in the safety analyses (N=54). Two per protocol (PP) populations were defined, PP-RESP for the overall response evaluation and PP-SURV for event free and overall survival.

For the PP-RESP patients

- with evidence of disease at screening assessment and
- with MRI/CT at baseline and at MID/EOT evaluation or mIBG at baseline and at MID/EOT assessment and
- receiving dinutuximab beta and IL-2

were considered. For the PP-SURV all patients receiving dinutuximab beta and IL-2 were considered.

In study APN311-302, efficacy was analysed based on the full analysis set (FAS) and the per-protocol set (PPS). The FAS included all patients randomized and treated with 13-cisRA, dinutuximab beta, or IL-2, which were in total 385 (fifteen patients out of 400

received neither 13-cis-RA nor dinutuximab beta and IL-2 and were excluded from all data sets).

Patients, who were randomized but not treated or for whom no treatment data are available, were excluded. Patients were analysed as randomized. PPS was a subset of FAS, where patients were excluded if:

- Baseline disease evaluation was missing
- Baseline disease evaluation: PD
- MAT=No or missing
- No dinutuximab beta antibody therapy
- R2 Randomisation criteria not met or missing

Patients were analysed as treated. Missing data was not replaced.

2.5.2 *Evaluate how closely trials reflect routine clinical practice in England*

Until 2010, standard maintenance treatment was considered to be 6 months of oral isotretinoin, given with the aim of differentiating any remaining neuroblasts (Matthay et al., 1999). Since 2010, with the publication of results from Yu et al. (Yu et al., 2010), some form of anti-GD2 antibody therapy has been included in maintenance therapy, and it is now considered the standard of care in many parts of the world. Treatment of high-risk neuroblastoma in the UK has been and continues to be driven by the International Society of Paediatric Oncology (SIOPEN) clinical guidance protocol, the most recent version being based on the High-risk Neuroblastoma Study 1 of SIOP-Europe (HR-NBL-1/SIOPEN) from 2009 (SIOPEN, 2014). UK patients are therefore currently treated under this clinical trial.

Table 22: Quality assessment results for APN311-202, APN311-303, and APN311-302

	APN311-202	APN311-303	APN311-302
Was randomisation carried out appropriately?	N/A, not a randomized study	N/A, not a randomized study	Yes
Was the concealment of treatment allocation adequate?	N/A	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	N/A	N/A	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No	No
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

2.6 *Clinical effectiveness results of the relevant trials*

2.6.1 *APN311-302*

EFS and OS

The primary end-point for this study was the 3-year EFS, which was calculated from the date of randomisation. Disease progression or relapse, death from any cause and second neoplasm were considered as events. Overall survival, calculated from date of randomisation to death from any cause was recorded as secondary endpoint. Data for 3-year EFS, as well as EFS at 1 and 2 years are shown in Table 23 and Table 24 respectively. Overall survival data is shown in Table 25. Kaplan-Meier curves of EFS (FAS) and OS are presented in Table 23 and Table 24 respectively.

Table 23. Study APN311-302: 3-year event-free survival

		All patients	
		dinutuximab beta +13-cis-RA	dinutuximab beta +13-cis-RA+ IL-2
FAS	N	180[1]	190[2]
Events	n (%)	79 (44.1)	69 (36.5)
Censored	n (%)	100 (55.9)	120 (63.5)
EFS	KM estimate	55.4%	61.2%
Log-Rank test[3]	p-value[4]	0.3202	

13-cis-RA = 13-cis retinoic acid, EFS = event-free survival, FAS = full analysis set, IL-2 = aldesleukin, KM = Kaplan-Meier, N = number of patients, n = number of patients with observations.
1 1 patient with missing date of death and without progression was excluded from the analysis.
2 1 patient with missing date of death and without progression was excluded from the analysis.
3 Adjusted for previous treatment (busulfan and melphalan, carboplatin, etoposide and melphalan).
4 Note that the p-value refers to the overall EFS analysis and not only to the 3-year analysis.

Table 24: Study APN311-302: Event-free survival at 1 and 2 years

		All patients	
		dinutuximab beta +13-cis-RA	dinutuximab beta +13-cis-RA+ IL-2
FAS	N	180[1]	190[2]
1-year EFS	KM estimate	72.3%	72.3%
2-year EFS	KM estimate	63.2%	66.3%
Log-Rank test[3]	p-value[4]	0.3202	

13-cis-RA = 13-cis retinoic acid, EFS = event-free survival, FAS = full analysis set, IL-2 = aldesleukin, KM = Kaplan-Meier, N = number of patients, n = number of patients with observations.
1 1 patient with missing date of death and without progression was excluded from the analysis.
2 1 patient with missing date of death and without progression was excluded from the analysis.
3 Adjusted for previous treatment (busulfan and melphalan, carboplatin, etoposide and melphalan).
4 Note that the p-value refers to the overall EFS analysis and not only to the 3-year analysis.

Table 25: Study APN311-302: Overall Survival at one, two and three years

		All patients	
		dinutuximab beta +13-cis-RA	dinutuximab beta +13-cis-RA+ IL-2
FAS	N	180[1]	190[2]
Events	n (%)	60 (33.5)	56 (29.8)
Censored	n (%)	119 (66.5)	132 (70.2)
1-year OS	KM estimate	86.3%	87.9%
2-year OS	KM estimate	76.0%	75.4%
3-year OS	KM estimate	64.1%	69.1%
Log-Rank test[3]	p-value	0.6114	

13-cis-RA = 13-cis retinoic acid, EFS = event-free survival, FAS = full analysis set, IL-2 = aldesleukin, KM = Kaplan-Meier, N = number of patients, n = number of patients with observations.
1 One patient with missing date of death was excluded from the analysis.
2 Two patients with missing date of death were excluded from the analysis.
3 Adjusted for previous treatment (busulfan and melphalan, carboplatin, etoposide and melphalan).

Figure 4: Study APN311-302 Event-Free Survival (FAS)

13-cis-RA = 13-cis retinoic acid, FAS = full analysis set, IL-2 = aldesleukin. Two patients with missing date of death and without progression were excluded from the analysis.

Figure 5: Study APN311-302 Overall Survival (FAS)

13-cis-RA = 13-cis retinoic acid, FAS = full analysis set, IL-2 = aldesleukin. Three patients with missing date of death were excluded from the analysis.

Conclusion

In summary, 3-year EFS in the overall population was 61.2% in patients receiving IL-2 treatment and slightly lower (55.4%) in patients without IL-2 treatment. Event-free survival at 1 and 2 years after the immunotherapy phase was similar with IL-2 (72.3% and 66.3%, respectively) and without IL-2 treatment (72.3% and 63.2% respectively). The p-value (long-rank test, adjusted for previous treatment) for the difference in EFS and OS between patients treated with IL-2 and patients not treated with IL-2 treatments was 0.3202 and 0.6114 respectively. Thus, concomitant administration of IL-2 does not improve EFS nor OS.

2.6.2 *APN311-303*

Anti-tumour response

Anti-tumour response was evaluated in patients with evidence of disease at baseline and at least one assessment post-baseline (Table 26). At the end of treatment (i.e. 5-6 cycles or earlier in case of progressive disease), a response (CR+PR) was observed in 12/39 patients (31%) or in 12/37 evaluable patients (32.4%) with evidence of disease at baseline, while progression occurred in 17/39 patients (44%) or in 17/37 evaluable patients (45.9%). Two patients were not evaluable. The response rate was the same regardless of baseline status (MRI/CTI or mIBG/BM) although CR (3 cases) was only reported in patients with detectable disease by mIBG and/or BM histology. However, the duration of response (overall: median 313 days; range 71 – 847) was longer in patients with disease only detectable by mIBG/BM (median of 338 days; range: 97 - 659) compared to measurable disease with MRI/CT (median of 183 days; range: 71 - 847) as could be expected.

In patients with R/R disease, the response rate was only 10/36 (28%). Amongst the 15 patients without detectable disease at baseline, one was non-evaluable (no control) and two progressed under treatment.

Table 26: Study APN311-303: Overall response in patients with evidence of disease at baseline

			Response at end of cycle		Best Response (N=37)	End of treatment (N=37)
Category		**Statistics**	**1 to 3 (N=35)**	**5 to 6 (N=26)**		
Overall	Evaluable	N (%)	35 (100.0%)	26 (100.0%)	37 (100.0%)	37 (100.0%)
	CR	N (%)	5 (14.3%)	3 (11.5%)	5 (13.5%)	3 (8.1%)
	PR	N (%)	7 (20.0%)	8 (30.8%)	10 (27.0%)	9 (24.3%)
	S.D./no response	N (%)	15 (42.9%)	8 (30.8%)	12 (32.4%)	8 (21.6%)
	PD	N (%)	8 (22.9%)	7 (26.9%)	10 (27.0%)	17 (45.9%)
	Not evaluable	N	-	-	-	2

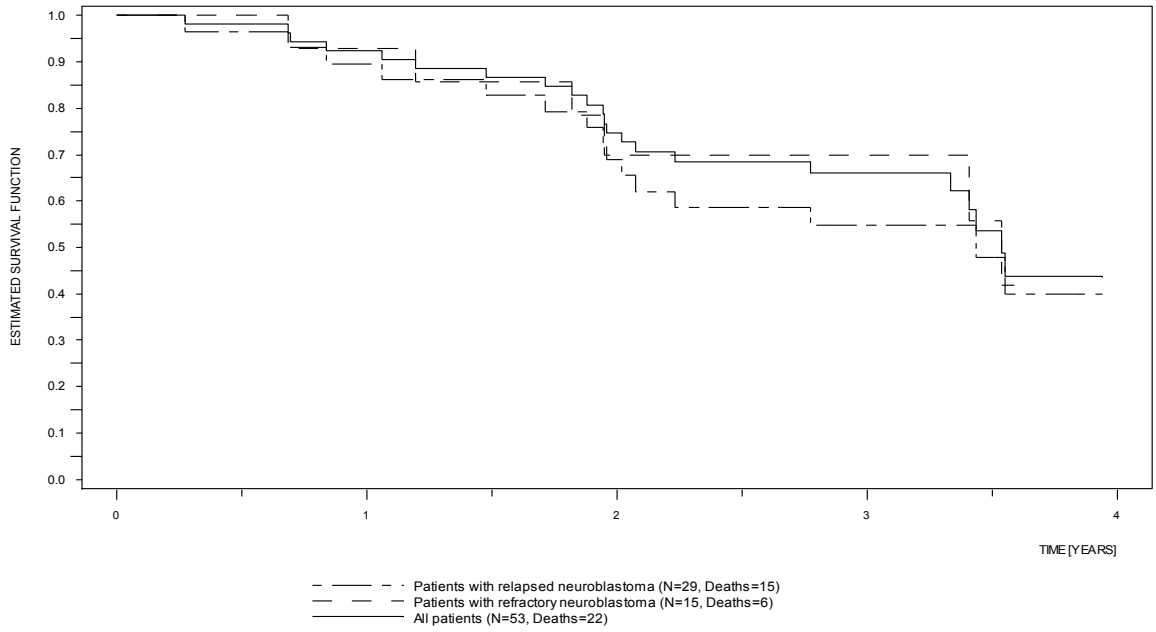
Overall survival and event-free survival

A summary of event-free and overall survival data for relapsed and refractory patients is presented in Table 27. An overall survival Kaplan Meier curve showing estimated survival up to 4 years is also shown (Figure 6).

Table 27: Study APN311-303: Event-free survival (EFS) and overall survival (OS) rates in relapsed and refractory patients

		Relapsed patients N=29	Refractory patients N=15
EFS	1 year	45%	58%
	2 years	31%	29%
OS	1 year	90%	93%
	2 years	69%	70%

Figure 6: Study APN311-303 Overall Survival Kaplan Meier curve by disease type



Conclusions

Treatment response in the 37 evaluable patients with evidence of disease amounted to 32,4% (8.1% CR, 24.3% PR), indicating antitumour activity. One-year and 2-year OS for relapsed patients amounted to 90% and 69% respectively, and similar values were observed for refractory patients (93% and 70% respectively). As for event-free survival, 45% and 31% of relapsed patients were reported to be event-free at one and two years respectively. Whereas a higher EFS rate was observed in refractory patients at one year (58%), a similar rate to that observed in relapsed patients was observed after 2 years (29%). In conclusion, long-term infusion of dinutuximab beta (together with IL-2 and 13-

cis RA treatment) showed a clinically meaningful therapeutic effect for continuous infusion treatment of dinutuximab beta, both based on response rates and OS results.

2.6.3 *APN311-202*

Anti-tumour response

The treatment response observed in patients with detectable disease at baseline is summarized in Table 28.

Table 28: Study APN311-202: treatment response in patients with detectable disease at baseline

	Statistics	End of 2nd cycle n (%) of patients (N=33)	End of treatment n (%) of patients (N=33)	Best response n (%) of patients (N=33)
No evidence of disease	N (%)	6 (19.4%)	6 (19.4%)	8 (25.8%)
Improved disease	N (%)	9 (29.0%)	8 (25.8%)	9 (29.0%)
Stable disease	N (%)	9 (29.0%)	5 (16.1%)	7 (22.6%)
Progressive disease	N (%)	6 (19.4%)	12 (38.7%)	7 (22.6%)
Mixed response	N (%)	1 (3.2%)	-	
Missing	N	2	2	2

At the end of the treatment (i.e. approximately 6 to 8 months after treatment initiation or earlier in case of progressive disease), a response was observed in 14/33 patients (42%) with evidence of disease at baseline. Two patients were non-evaluable. The treatment response was the same in patients with disease evaluable by mIBG/BM only (43%; 9/21) and in patients with disease measurable by MRI/CT (42%; 5/12). It was higher in refractory disease (48%; 10/21) than in relapsed disease (33%; 4/12). The range for the duration of response was very broad (5 weeks to 3 years); the median was about 2.3 years regardless of baseline status and disease type. No other factors were investigated.

Conclusion

A 10-day infusion schedule of 10 mg/m^2 dinutuximab beta (total dose 100 mg/m²) in combination with IL-2 and 13-cis-RA treatment had a reduced pain-toxicity profile of dinutuximab beta as shown by reduction both in treatment-related pain and morphine use, within a cycle and in consecutive cycles. This enabled at least parts of the treatment to be applied in an outpatient setting. Treatment response in the 33 evaluable patients with detectable disease at baseline amounted to 55.8% (25.8% no evidence of disease, 29.0% improved disease), indicating antitumour activity. In conclusion, a 10-day infusion schedule of 10 mg/m^2 dinutuximab beta (together with IL-2 and 13-cis RA treatment) was shown to be tolerable with a reduced pain-toxicity profile whilst maintaining immunomodulatory efficacy of dinutuximab beta, as based on response rates in patients with either primary refractory or relapsed neuroblastoma.

2.7 *Subgroup analysis*

2.7.1 *APN311-302*

A sub-group analysis was performed for EFS and OS in the FAS population. The sub-groups consisted of

- patients without evidence of disease at baseline (CR) and
- patients with evidence of disease at baseline (VGPR, PR, MR, NR, PD).

Treatment groups were compared using the log-rank test adjusted by previous treatment group (BuMel or CEM).

EFS was defined as the time between modified R2 randomisation to the date of disease progression, relapse, death, or occurrence of second neoplasm. 3-year EFS in the overall population was 61.2% in patients receiving IL-2 treatment and with 55.4% slightly lower in patients without IL-2-treatment (FAS, as randomized, (**Appendix E**). Similar trends like in the overall population were observed in both, patients with and without evidence of disease at baseline, i.e. slightly higher EFS rates with IL-2 treatment than without IL-2-treatment (53.8% vs 45.9% and 66.2% vs 61.7%, respectively, FAS). Compared with the overall population, the 3-year EFS was lower in patients with evidence of disease at baseline and higher in patients without evidence of disease at baseline.

EFS at 1 and 2 years after the immunotherapy phase was similar with IL-2 (72.3% and 66.3%, respectively) and without IL-2 treatment (72.3% and 63.2% respectively). In patients with evidence of disease at baseline the 1-year EFS was slightly higher with concomitant IL-2 treatment (72.3%) compared to no IL-2 treatment (66.6%); however, the 2-year EFS was similar in both groups (61.6% and 58.1%, respectively). No marked differences between groups in EFS at 1 and 2 years were observed in patients without evidence of disease at baseline (**Appendix E**).

Overall survival was 86.3%, 76.0% and 64.1% at 1, 2, and 3 years, respectively in patients not receiving IL-2 treatment. Adding IL-2 revealed similar OS rates at 1 (87.9%) and 2 years (75.4%) but a slightly higher OS rate at 3 years (69.1%, FAS, **Appendix E**). No marked differences in OS were observed in patients without evidence of disease at baseline, while for patients with disease at baseline the 3-year OS was slightly higher with concomitant IL-2 treatment (69.1%) compared to no IL-2 treatment (64.1%).

2.7.2 *APN311-303*

Efficacy data were analysed overall and separately for patients having received first-line therapy who had evidence or no evidence of disease at baseline, and patients with relapsed or refractory neuroblastoma (separately and together). EFS and OS were reported for the Per Protocol Set - Survival analysis (PP-SURV) populations, which included all patients who were treated with combined treatment (dinutuximab beta and IL-2) (N=53). One patient was excluded from this analysis set because the patient did not receive IL-2 treatment.

EFS results are presented for the PP-SURV in **Appendix E**. EFS in the overall PP-SURV population was [redacted] at one year, [redacted] at two years and [redacted] at three years. Analysed by disease type, the highest rate of events was shown for relapsed patients, followed by refractory patients and patients with evidence of disease (minimal residual disease [MRD]) after first-line therapy. In accordance, EFS times were lower in patients with relapsed or refractory neuroblastoma than in patients who received first-line therapy only.

In patients with relapsed neuroblastoma, EFS was 44.8% at one year, 31.0% at two-years and 24.1% at three-years. EFS in patients with refractory neuroblastoma was 58.2% at one year and 29.1% at two and three years. In patients with evidence of disease after first-line therapy, EFS was [redacted] at one, two and three years. EFS in patients without evidence of disease after first-line therapy was [redacted] at one year and [redacted] at two and three years.

EFS results based on disease status at baseline are presented in **Appendix E**. EFS in the overall PP-SURV population was [redacted] at one year, [redacted] at two years and [redacted] at three years. In the subgroup of patients with no evidence of disease at baseline, higher EFS rates were observed than in the other subgroups.

Overall survival results are presented for the PP-SURV in **Appendix E**. OS in the PP-SURV population was [redacted] at one year, [redacted] at two years and [redacted] at three years.

Analyzed by disease type, all [redacted] patients after first-line therapy survived during the first three years after immunotherapy (OS 100%). Of the [redacted] patients with no evidence of disease after first-line therapy, [redacted] patient (18-44) died after [redacted] days.

In patients with relapsed neuroblastoma, OS was 89.7% at one year, 69.0% at two years and 54.7% at three years. OS in patients with refractory neuroblastoma was 92.9% at one year and 69.8% at two and three years. Long-term OS rates were therefore

comparable for relapsed and refractory patients, with slightly better three-year OS results for patients with refractory neuroblastoma.

OS results based on disease status at baseline are presented for the PP-SURV in **Appendix E**. In all subgroups (disease measurable by MRI and/or CT at baseline, disease evaluable only by mIBG and/or MB histology at baseline, no evidence of disease at baseline) the vast majority of the patients survived the first year. Two-year and three-year OS was higher in the subgroup of patients with no evidence of disease at baseline as compared to the other subgroups. It should be noted, however, that the majority of the OS data was censored.

Overall, EFS in the PP-SURV population was [redacted] at one year, [redacted] at two years and [redacted] at three years. Analysed by disease type, EFS at one year was highest in patients without evidence of disease after first-line therapy ([redacted] in year one) and lowest in patients with evidence of disease (MRD) after first-line therapy ([redacted]). However, results should be interpreted with caution due to the small number of patients.

OS in the PP-SURV population was [redacted] at one year, [redacted] at two years and [redacted] at three years. All patients with first-line therapy, irrespective of evidence of disease or not at baseline, were still alive at the end of the analysis period. About [redacted] of relapsed and refractory patients were alive at one year and about [redacted] of relapsed and [redacted] of refractory patients were still alive at three years.

2.7.3 *APN311-202*

Efficacy data were analysed overall and separately for patients with relapsed, refractory or high-risk neuroblastoma. Analysis was also done for subgroups of patients with disease measureable by MRI/CT or mIBG and with no evidence of disease at baseline.

EFS results based on disease status at baseline are presented in **Appendix E**. EFS in the overall FAS population was [redacted] at 1 year and [redacted] at 2 years. Three-year EFS was not estimable. In the subgroup of patients with no evidence of disease at baseline, lower 1-year and 2-year EFS rates were observed than in the other subgroups.

Data presenting EFS results for patients with refractory or relapsed disease at baseline can be found in **Appendix E**. Analysed by disease type, relapsed patients showed a higher rate of events as compared to refractory patients. In patients with relapsed neuroblastoma, EFS was [redacted] at 1 year, [redacted] at 2 years. EFS in patients with refractory neuroblastoma was [redacted] at 1 year and [redacted] at 2 years.

OS results are presented for the FAS in **Appendix E**. OS in the overall FAS population was [redacted] at 1 year and [redacted] at 2 years. Three-year OS was not estimable. In all subgroups (disease measurable by MRI and/or CT at baseline, disease evaluable only by mIBG and/or MB histology at baseline, no evidence of disease at baseline) approximately [redacted] of the patients survived the first year. Two-year OS seemed to be slightly lower in the subgroup of patients with disease evaluable only by mIBG and/or MB histology at baseline as compared to the other subgroups. It should be noted, however, that the majority of the OS data was censored.

A table presenting OS results for patients with refractory or relapsed disease at baseline can be found in **Appendix E**. In patients with relapsed neuroblastoma, OS was [redacted] at 1 year and [redacted] at 2 years. In patients with refractory neuroblastoma, [redacted] survived the first year and 2-year OS was [redacted]

Overall, 1-year and 2-year EFS rates were [redacted] and [redacted], respectively. In the subgroup of patients without evidence of disease at baseline, lower 1-year and 2-year EFS rates were observed than in the patients with disease measurable by MRI and/or CT, or by mIBG and/or BM histology at baseline. Higher EFS rates were found in patients with refractory neuroblastoma as compared to relapsed neuroblastoma (1-year EFS: [redacted] vs. [redacted]; 2-year EFS: [redacted] vs. [redacted]).

Patients with primary refractory or relapsed neuroblastoma included in this study had an overall 1-year and 2-year OS rate of [redacted] and [redacted], respectively. Higher OS rates were found in patients with refractory neuroblastoma as compared to relapsed neuroblastoma (1-year OS: [redacted] vs. [redacted]; 2-year OS: [redacted] vs. [redacted]).

2.8 *Meta-analysis*

2.8.1 *Meta-analysis qualitative overview*

The outcomes of all the studies identified in the systematic review (previously described in **Section 2.1**) were assessed to determine the feasibility of performing a quantitative analysis (i.e. a network meta-analysis and pairwise meta-analysis) of clinical effectiveness outcomes for Dinutuximab beta Apeiron and relevant comparator therapies either in high-risk or relapsed/refractory neuroblastoma patients. Patients included in different arms of observational comparative, single arm studies or randomised clinical trials were considered as belonging to different “populations”. Tabulated outcomes data for these studies are provided in **Appendix D**. Relevant studies for the treatment of high-risk neuroblastoma patients during maintenance phase, as well as refractory or relapsed patients at any level of risk are presented in **Appendix D**.

However, a meta-analysis was found not to be feasible, because for most of the studies the treatment outcomes and regimens were heterogeneous and thus not comparable. Furthermore, most studies were either single-arm or did not share a common treatment, thus a meta-analysis of comparisons or network meta-analysis were not feasible.

Alternatively and when feasible, a pooled analysis for the reported outcomes was performed. This was the case for the studies reporting 1-year, 2-year, 3-year and 5-year overall survival (OS) in patients treated with ^{131}I-mIBG (Table 31). Here, weighted averages and 95% confidence intervals were calculated to obtain "quasi-quantitative" results regarding the OS observed upon this treatment. A pooled analysis was also performed for the dinutuximab beta studies APN311-303 and -202 performed in relapsed/refractory patients (see

Table 29 and Table 30).

For all other outcomes of interest (EFS, PFS, response to treatment, and safety outcomes), a qualitative summary of the outcomes reported in the studies identified in the systematic review is provided in **sections B2.10.3 to B2.10.5**.

2.8.2 *Studies providing evidence not related to dinutuximab beta (studies identified in the systemic literature review)*

A summary of the main clinical and safety outcomes reported in studies coming from the systematic literature review that were not investigating dinutuximab beta but did investigate relevant comparators is presented in **Appendix D**.

2.8.3 *Pooled analysis of evidence related to dinutuximab beta (studies APN311-303 and APN311-202)*

A pooled analysis to assess overall survival and treatment response of the patients from studies APN311-303 and -202 was performed. Overall survival analysis was done only on the pooled relapsed patients (48 patients who had experienced one or more relapses from the APN311-202 and APN311-303 studies [dinutuximab beta treatment]). The analysis of treatment response was done by pooling a total of 72 patients with detectable disease: 35 relapsed patients plus 34 refractory patients, and three patients with frontline therapy (patients that had only received first-line neuroblastoma treatment with either a complete response or with minimal residual disease).

A complete response (complete response plus partial response) was observed in 36.1% of patients, whereas stable disease (S.D.) and disease progression (PD) was reported in 18.1% and 40.3% of patients respectively (

Table 29). As for the survival analysis, OS in the APN311-202 and APN311-303 combined group was 83% at 1 year, 60% at 2 years and 50% at 3 years (Table 30).

Table 29: Pooled APN311-303 and -202 studies - treatment response at the end of treatment

Study	CR + PR [95% CI]	S.D. (95% CI)	PD (95% CI)	Not evaluable
APN311-303 and -202 (N = 72)	26 (36.1%) [25.12 ; 48.29]	13 (18.1%) [9.98 ; 28.89]	29 (40.3%) [28.88 ; 52.50]	4*

Table 30: Pooled APN311-303 and -202 studies - Kaplan Meier results of overall survival

Parameter		APN311-202 + APN311-303 (N=48)
Deaths	N (%)	26 (54.2)
Censored[b]	N (%)	22 (45.8)
Overall survival[a] (days)	Mean[c]	921
	Standard error	68.5
	Median	1254
	95% CI	686[d]
Overall survival rate at:	1 year KM estimate	0.83
	2 years KM estimate	0.6
	3 years KM estimate	0.5

Abbreviations: CI = confidence interval, KM = Kaplan Meier

[a]Overall survival defined as time from the starting point to the date of death from any cause

[b]For patients having no event (=death), censoring was done at the last date at which the patient was known to be alive

[c]The mean survival time and its standard error were underestimated for both group and total because the largest observation was censored and the estimation was restricted to the largest event time

[d]Estimation of the upper limit was not possible

2.8.4 *Comparison of outcomes*

2.8.4.1 OS: High-risk patients

The two studies retrieved in the systematic review for high-risk neuroblastoma patients treated with 13-cis-RA in first-line maintenance therapy reported Overall Survival (OS) outcomes. The COG ANBL0032 study reported 75% OS at 2 years (Yu et al., 2010). The CCG-3891 study presented OS values at later time points: 56% for 3y OS and 50% for 5 years (Matthay et al., 2009, Matthay et al., 1999). Clinical study APN311-302 reported the following numbers for the Dinutuximab beta Apeiron with 13-cis-RA arm (without IL-2) in first-line maintenance therapy for OS at 1, 2 and 3 years: 86.3%, 76.0%, 64.1%. Numerically those values are similar for the time point of 2 years OS, while OS at 3 years for Dinutuximab beta Apeiron is higher by 8.1% than dinutuximab. In conclusion, similar 2-year survival rates to those reported in the dinutuximab pivotal study (Yu et al., 2010)

were achieved without using GM-CSF and IL-2 cytokines, suggesting the benefit of adopting Dinutuximab beta Apeiron in the treatment of high-risk neuroblastoma patients.

2.8.4.2 OS: Relapsed/Refractory (R/R) patients

Of the 10 studies investigating mIBG therapy in relapsed/refractory NB patients, six studies provide OS data for time points ranging from 1 year to 5 years. It was possible to pool those outcomes together as multiple studies reported OS for 1,2 and 3 years. Table 31 presents summary of OS data for those studies, together with weighted averages and confidence intervals for different time points. Derived weighted averages for 1 year, 2 years, 3 years and 5 years OS were: 63.6%, 40.9%, 30.2% and 14%, respectively. OS numbers reported for pooled Dinutuximab beta Apeiron APN311-202 + APN311-303 studies in relapsed/refractory NB patients were 83%, 60% and 50% for 1 year, 2 years and 3 years OS, respectively (Table 30). Numerically those results were in favour of Dinutuximab beta Apeiron, with percentage difference close to 20% at any comparable time point (19.4% for 1 year OS, 19.1% for 2 years OS and 19.8% for 3 years OS).

Table 31: Pooling analysis of studies reporting OS in mIBG-treated R/R patients

Study/Authors	Number of patients	1y OS	2y OS	3y OS	5y OS
El-Sabban et al. (2013)	85	85.0%	58.0%	29.0%	14.0%
George et al. (2016)	44	65.0%			
Johnson et al. (2011)	76	60.0%	30.0%		
Matthay et al. (2007)	164	49.0%	29.0%		
Polishchuk et al. (2011)	39			32.8%	
Zhou et al. (2015)	218	67.3%	47.0%		
Weighted average		63.6%	40.9%	30.2%	14.0%
95% confidence interval		59.7% - 67.5%	36.8% - 45.0%	22.1% - 38.3%	6.6% - 21.4%

Of the nine studies investigating chemotherapy protocols (with or without stem cell transplantation) in relapsed/refractory NB patients, five studies reported OS data. For 1 year OS ranged between 40% to 63%, except for a relatively small group of patients (n=23) with ASCT from Simon et al. (2011), where 1 year OS was reported to be ~85%. 2-year OS was reported in a range of 31% to 41.8%, while 3-year OS was typically reported in a range of 15 – 33%, except for a wider range in Simon et al. (2011). Numerically at 1, 2 and 3 years, pooled Dinutuximab beta Apeiron APN311-202 + APN311-303 data in relapsed/refractory NB patients show higher OS values than those reported from chemotherapy protocols studies (typically over 20%).

Only one study reported 2-year OS for IL-2 therapy in relapsed/refractory NB patients. Reported value was 92% (± 6%) (Pession et al., 1998).

2.8.4.3 EFS: High-risk patients

Two RCTs evaluated the clinical effectiveness of 13-cis-retinoic acid therapy in patients with high-risk neuroblastoma who had previously completed induction therapy and autologous stem cell transplantation: CCG-3891(Matthay et al., 2009, Matthay et al., 1999, Park et al., 2009) and COGANBL0032 (Yu et al., 2010). Matthay and colleagues reported a 3-year event-free survival (EFS) of 46±6% (Matthay et al., 1999) and a 5-year EFS of 42±5% (Matthay et al., 2009). Using the same cohort of patients, a retrospective analysis was performed to investigate whether 13-cis-RA improved the outcome for a sub-group of patients with high-risk Stage 3 neuroblastoma (Park et al., 2009). For this sub-group of 23 Stage 3 patients randomised to 13-cis-RA, a higher EFS was observed (70±10%). Finally, in the COGANBL0032 study, another cohort of patients treated with 13-cis-RA was included as control arm, and for these a 2-year EFS of 46±5% was reported) (Yu et al., 2010). The APN311-302 study in high-risk patients reported higher EFS rates at two years in patients treated with Dinutuximab beta Apeiron and concomitant 13-cis-RA (63.2%, see **section B2.7**) than that reported with 13-cis-retinoic acid alone (46±5%). EFS rate at 2 years without IL-2 was identical to the 2-year EFS observed in the dinutuximab treatment arm of the Yu et al. study (Yu et al., 2010). All these results confirm the beneficial effect of treating high-risk neuroblastoma patients with dinutuximab beta during the maintenance phase.

2.8.4.4 EFS: Relapsed/Refractory (R/R) patients

Regarding the treatment of R/R patients, many studies have been published on the clinical outcome of several treatments, among them radiotherapy with ^{131}I-Metaiodobenzylguanidine (^{131}I-mIBG), IL-2 monotherapy and various chemotherapeutic protocols followed or not by stem cell transplantation (ASCT or SCR). Regarding radiotherapy, relatively low EFS rates have been reported, ranging approximately from 13% to 18%. A study by Johnson et al. (2011) reported EFS in relapsing patients receiving two consecutive ^{131}I-mIBG treatments. Ten patients on 76 (13.15%) did not present any event, defined as death or PD, in 3–25 months (median 10 months) after the initial ^{131}I-mIBG therapy. Another study by (Matthay et al., 2007) reported data on 164 patients with progressive, refractory or relapsed high-risk neuroblastoma, aged 2 to 30 years treated with ^{131}I-mIBG. The EFS for all patients at 1 year was 18%, with better results for patients with increasing age and patients who had fewer than three prior regimens. None of the selected studies provide head-to-head data for ^{131}I-mIBG versus

Dinutuximab beta Apeiron, but if compared indirectly, the ^{131}I-mIBG EFS outcomes are numerically lower by approximately 24% to 42% when compared to studies of Dinutuximab beta Apeiron effectiveness in relapsed and refractory patients, which have reported 1-year EFS of 42.1% and 60.0%, respectively (see **section B2.8.3**).

Regarding chemotherapy, there is great variability in the regimens used in second-line treatment, thus it is difficult to determine the precise outcome of patients treated with chemotherapy with or without stem cell transplantation. Two studies reported about EFS in patients treated with the most frequently used chemotherapeutic protocols: high-dose therapy + stem cell rescue (HDT+SCR) and topotecan (TOPO) + cyclophosphamide (CTX) regimens. A publication of 28 years of European data collection for neuroblastoma within the EBMT registry showed that EFS at 5 years in patients receiving HDT+SCR was 32% (Ladenstein et al., 2008). The addition of SCR has drastically improved OS in R/R patients, where chemotherapy alone, such as TOPO or TOPO+CTX have shown lower efficacy in terms of EFS. Indeed, these agents have shown an EFS at one, two, three and five years of only 33%, 10%, 4% and 1% respectively (London et al., 2010). As for ^{131}I-mIBG radiotherapy, none of the selected studies provided head-to-head data for these comparators. An indirect qualitative comparison of this evidence with EFS outcomes reported for Dinutuximab beta Apeiron in relapsed and refractory patients suggests a higher efficacy of dinutuximab beta, for which numerically higher EFS rates have been observed at any comparable time point (42.1% to 44.8% and 58.2% to 60% for 1-year EFS in relapsed and refractory, respectively; 31/ to 36.8% and 29.1% to 55.7% for 2-year EFS in relapsed and refractory, respectively; and 24.1% to 36.8% and 29.1% to 44.6% for 3-year EFS in relapsed and refractory, respectively (**section B2.8.3**).

2.8.4.5 PFS: High-risk patients

Any of the studies retrieved for high-risk patients treated with 13-cis-retinoic acid during maintenance therapy reported outcomes measured as progression free survival.

2.8.4.6 PFS: Relapsed/Refractory (R/R) patients

Outcomes measured as progression free survival were reported only in three papers investigating chemotherapy protocols. PFS at 1 year was around 35%, with values dropping to 21% at year 2 to about 12 – 15% at year 3. Reported median PFS range was 4.5 months to 1.2 years. There were no clinical study reports of Dinutuximab beta Apeiron reporting outcomes in PFS.

2.8.4.7 Treatment response: High-risk patients

Of the two studies retrieved with the systematic literature review, only the CCG-3891 reported treatment response outcomes in patients assigned to receive 13-cis-retinoic acid therapy. The overall response rate in these patients was 82% (CR+VGPR+PR), with a further 10% of patients having stable disease or mixed response. None of the assessable patients were reported as having disease progression (Matthay et al., 1999). As for the subgroup of Stage 3 patients, a CR or a VGPR was reported for 16 of 27 patients (59.2%).

2.8.4.8 Treatment response: Relapsed/refractory patients

Clinical effectiveness in terms of response to treatment in patients with relapsed or refractory neuroblastoma was reported in all studies retrieved from the SLR, although they were heterogeneous in terms of the criteria used for defining the type of treatment responses. Of the 20 studies, 9 utilized the International Neuroblastoma Response Criteria (INRC). All the other assessed overall response according to modified versions of the INRC (**see section 1.3.3 of Appendix D**).

The response to ^{131}I-mIBG therapy was considerably variable among studies. Complete responses ranged between 3.57% and 20%, whereas the rate of partial responses was higher, ranging from 16% up to 60%. When combining complete and partial responses, a wide range of results is also observed: overall response rates (CR+PR) between 27% and 80% were reported in the 10 studies investigating this therapy.

As for chemotherapy, heterogeneous responses were also observed among studies, which goes in line with the heterogeneity of the chemotherapeutic regimens evaluated. Different definitions of overall response were also noticed. An overall response rate defined as CR+PR+MR was reported in three studies and ranged between 32% and 63% (Ashraf et al., 2013, Donfrancesco et al., 2004, London et al., 2010). On the other hand, an overall response defined as CR+PR was reported in 2 studies: (Garaventa et al., 2003, London et al., 2010). The first study, which evaluated the antitumour activity of topotecan followed by vincristine and doxorubicin reported an overall response rate of 64% (95% CI 43-82%) in children with stage III or i.v. neuroblastoma who had been previously treated with chemotherapy and were diagnosed with either refractory or relapsed disease. The second study, which evaluated the efficacy of two other regimens, topotecan alone vs topotecan/vincristine/doxorubicin (TVD), reported lower responses rates upon treatment with TOPO (19%) and TOPO/CTX (32%).

Finally, after a median follow-up of 30 (16-64) months, 12 out of 17 patients (70.5%) were reported alive with no evidence of disease (NED) in the only study investigating IL-2 therapy in relapsed/refractory patients (Pession et al., 1998).

Besides the lack of head-to-head data or a feasible meta-analysis for comparison of Dinutuximab beta Apeiron with the relevant comparators, the considerable variation of responses, definition of responses and sample size of the reported studies render any qualitative comparison between these therapies and Dinutuximab beta Apeiron difficult to interpret.

2.8.4.9 Safety and toxicity outcomes: High-risk patients

Adverse events were reported in the two studies investigating 13-cis-RA in first-line maintenance therapy for high-risk NB patients. In Matthay et al. (1999) the most common adverse events of 13-cis-RA was the skin toxicity, but was rarely severe (grade 3 or 4 only in 2% of the patients). Other toxicities included renal toxicity (2%), elevations in aminotransferase levels (2%), gastrointestinal effects (2%). Catheter-related infections were observed in 12% of patients. In total, grade 3-4 toxic effects occurred in 17% of patients randomly assigned to 13-cis-isotretinoin. Yu et al. (2010) reported 22% of patients suffering from infections, of which 7% were catheter related in patients randomly assigned to 13-cis-isotretinoin. The most common toxic effects of grade 3 or 4 were: fever without neutropenia (6%), hyponatremia (4%), abnormal ALT (3%), vomiting (3%), hypokalemia (2%) and hypoxia (2%). In total, no grade 3-4 toxic effects were recorded for 37% of patients.

2.8.4.10 Safety and toxicity outcomes: Relapsed/refractory patients

Of the 10 studies investigating mIBG therapy in relapsed/refractory NB patients, 9 reports adverse events. All those studies mention blood and lymphatic system disorders related to myelosuppression, of which the most common were thrombocytopenia (in the range of 71 – 82%), which required platelet transfusion support and neutropenia (ranging from 33 to 82%). One study reported leukopenia in nine out of 10 patients. Other most common adverse effects were infections (in the range of 11 – 49%) and pain.

Of the 9 studies investigating chemotherapy protocols (with or without stem cell transplantation) in relapsed/refractory NB patients, six report adverse events. Five of those studies mention blood and lymphatic system disorders related to myelosuppression with the most common being thrombocytopenia (in the range of 42 - 96%), leukopenia (in the range of 61 – 94%), neutropenia (in the range 44% to 97%) and

anaemia (in the range of 27% to 88%). Severe systemic infections were in the range of 19 to 32%.

Only one study with 19 patients reported adverse events for IL-2 therapy in relapsed/refractory NB patients. For 5 patients (26%) platelets count dropped to values that required infusion. Other adverse events included diffuse rash with mild pruritus - 7 patients (37%), while mild diarrhoea and vomiting occurred in 2 patients only (11%).

Summary of adverse events of the Dinutuximab beta Apeiron studies APN311-202, -303 and -302 is presented in **section B2.12**.

2.9 *Indirect and mixed treatment comparisons*

Indirect and mixed treatment comparisons are not possible due to the lack of comparable clinical trials. Here analyses of relevant studies versus historical controls have been described, since these results are considered relevant to the decision problem due to the lack of a control arm (no immunotherapy) in the relevant clinical effectiveness studies.

2.9.1 *Analysis of relevant studies vs historical controls*

Table 32 presents additional analyses of clinical studies for Dinutuximab beta Apeiron.

Table 32: List of additional analyses for Dinutuximab beta Apeiron

Trial number (Acronym) Primary Study Reference	Design	Population	Intervention	Justification for inclusion
APN311-303 (vs Garaventa Historical Control)	Non-randomised, un-blinded. Retrospective analysis of data collected during the administration of dinutuximab beta continuous infusion combined with subcutaneous aldesleukin (IL-2) in patients with high-risk neuroblastoma under a compassionate use program	APN311-303: high-risk or relapsed/refractory neuroblastoma	APN311-303: long-term continuous infusion (LTI) regimen of dinutuximab beta. 10-day continuous infusion schedule of dinutuximab beta (100mg/m^2/cycle) given in combination with s.c. IL-2 ($6x10^6$ IU/m^2/day) and oral 13-cis-RA (160 mg/m^2/day). First 4 patients received 4 or 5 week cycles with various doses of dinutuximab beta in combination with various doses of IL-2, while remaining patients received 5-week cycles. Up to 6 cycles were administered.	Includes efficacy data (OS) relevant to the NICE decision problem
APN311-202 + APN311-303 (vs Garaventa Historical Control)	Investigator-initiated studies with no control arm since ch14.18 treatment is considered the standard of care for high-risk neuroblastoma patients since 2009 (Yu et al., 2010), and therefore placebo-controlled clinical studies are considered unethical.	APN311-202: relapsed or refractory neuroblastoma APN311-303: high-risk or relapsed/refractory neuroblastoma	APN311-202: long-term continuous infusion (LTI) regimen of dinutuximab beta. 10-day continuous (24h) infusion of dinutuximab beta (100 mg/m^2/cycle) given in combination with s.c. IL-2 ($6x10^6$ IU/m^2/day) and oral 13-cis-RA (160 mg/m^2/day). Patients received 5 week treatment cycles. Up to 5 cycles were administered. APN311-303: long-term continuous infusion (LTI) regimen of dinutuximab beta. 10-day continuous infusion schedule of dinutuximab beta (100mg/m^2/cycle) given in combination with s.c. IL-2 ($6x10^6$ IU/m^2/day) and oral 13-cis-RA (160 mg/m^2/day). First 4 patients received 4 or 5 week cycles with various doses of dinutuximab beta in combination	Includes efficacy data (OS) relevant to the NICE decision problem

			with various doses of IL-2, while remaining patients received 5-week cycles. Up to 6 cycles were administered.	
APN311-202 + APN311-303 (vs Historical Control R1)	See clinical design comments in line above	APN311-202: relapsed or refractory neuroblastoma APN311-303: high-risk or relapsed/ refractory neuroblastoma	See intervention comments in line above	Includes efficacy data (OS) relevant to the NICE decision problem
APN311-302 (HR-NBL-1/SIOPEN, vs Historical Control R1)	HRNBL1 of SIOP-EUROPE is an open-label, multicentre, randomised phase III trial and therapy optimisation study, which included three main phases (induction, consolidation, and maintenance) and also included several randomisation steps.	APN311-302: Briefly, inclusion criteria for patients: 1. Age below 21y 2. Diagnosed with high-risk neuroblastoma defined as: INSS stages 2, 3, 4, or 4s with MYCN amplification; INSS stage 4 without MYCN amplification aged ≥12 months and in patients 12-18 months only in presence of segmental chromosomal alterations (SCA)	In the maintenance phase of HRNBL1, which involved immunotherapy, patients were randomised (phase R2) to receive dinutuximab beta (8h i.v. infusion, 20 mg/m^2/day over 5 days, every 4 weeks over 5 courses) with or without s.c. IL-2 (6x10^6 IU/m^2/day) in addition to oral 13-cis-RA (160 mg/m^2/day)	Includes efficacy data (OS) relevant to the NICE decision problem
Abbreviations: MAT = myeloablative therapy, R1 = randomisation phase 1, OS = overall survival, IL-2 = interleukin 2 or aldesleukin, CHO = Chinese hamster ovary, 13-cis-RA = 13-cis retinoic acid, s.c. = subcutaneous, i.v. = intravenous				

2.9.2 *Summary of results of analyses of relevant studies vs historical controls*

2.9.2.1 Summary of Historical Control Treatment Groups and Efficacy Results

Dinutuximab beta has already been tested in various neuroblastoma patients with encouraging response rates. These studies were all investigator-initiated studies (Table 33) with no control arm since ch14.18 treatment is considered the reference treatment for high-risk neuroblastoma patients since 2009 (Yu et al., 2010) and therefore placebo-controlled clinical studies are considered unethical. To enable comparison of treatment with Dinutuxuimab beta Apeiron to neuroblastoma therapies without antibody treatment, it was decided to prepare a historical control report that compares patients who received dinutuximab beta therapy in studies APN311-202 and APN311-303 with a defined patient population that did not receive dinutuximab beta treatment. The historical control group was selected according to patient characteristics in studies APN311-202 and APN311-303. Two historical control group populations, Historical Control R1 and Historical Control Garaventa, discussed further below, were used to compare the effect of dinutuximab beta in neuroblastoma patients.

Data comparison of clinical trials APN311-202, -303 and -302 with historical controls will focus on OS data.

Table 33: Summary of patient groups

Investigator-initiated study	Historical control group
Patients with relapsed neuroblastoma in studies APN311-202 and APN311-303 APN311-202: Investigation of the safety and efficacy of dinutuximab beta treatment in patients with relapsed or refractory neuroblastoma under long-term continuous infusion (LTI) regimen. A total of 18 patients who had experienced 1 or more relapses since their initial diagnosis of neuroblastoma, and had received treatment for these events prior to immunotherapy were selected from study APN311-202. APN311-303: A retrospective analysis of data collected during administration of dinutuximab beta combined with s.c. IL-2 and oral 13-cis-RA in patients with high-risk or relapsed/refractory neuroblastoma under a LTI compassionate use program (CU-LTI). A total of 30 patients with a relapsed baseline disease status were treated under CU-LTI program of APN311-303.	Patients with relapsed neuroblastoma after high-dose chemotherapy and stem cell transplantation

2.9.2.2 Discussion of Historical Control R1

In the first randomisation phase (R1) of the HRNBL1 study, which occurred between 2002-2009, patients were randomised to different MAT regimens. The R2 randomisation phase, only started in 2009, ie, several years after the initiation of the R1 phase, compared dinutuximab beta immunotherapy following MAT with or without aldesleukin (IL-2) in addition to differentiation therapy with isotretinoin (13-cis-RA). Patients included in the R1 randomisation phase who received standard of care neuroblastoma treatment, including MAT but no immunotherapy, form a valid historical control group to patients receiving immunotherapy in addition to standard of care neuroblastoma treatment. The demographics and overall survival (OS) of R1 patients with relapse after 'first-line therapy', which included induction and consolidation chemotherapy as well as differentiation therapy with 13-cis-RA (Historical Control R1) are described and compared to relapsed patients from studies APN311-202 and APN311-303, where immunotherapy with dinutuximab beta was part of the maintenance therapy following relapse treatment.

For Historical Control R1, patients from the HR-NBL-1/SIOPEN study randomized for R1 (but not R2, as patients randomized for R2 received dinutuximab beta immunotherapy) with complete response (CR) after MAT (or after radiotherapy, if the tumour status after MAT was not available), for whom a subsequent relapse date was documented, were selected. Patients from the HR-NBL-1/SIOPEN study randomized for R1 with CR after MAT (or after radiotherapy, if the tumour status after MAT was not available), who experienced their first relapse before MAT (or radiotherapy, as applicable) were excluded.

In addition to the condition of relapsed neuroblastoma, the following selection criteria were applied to the Historical Control R1 patient group to ensure the best possible comparability between study patients and control patients:

1. Date of initial diagnosis ≥ 1999
2. Age at initial diagnosis ≥ 12 months
3. Age at first relapse ≥ 12 months
4. International Neuroblastoma Staging System (INSS) stage at initial diagnosis = 4 or type of first relapse not local

The starting point of studies APN311-202 and APN311-303 was the day immunotherapy treatment with dinutuximab beta and/or IL-2 started (whichever comes first). Since, after completion of first-line neuroblastoma treatment, there was no additional immunotherapy

treatment presumed for the patients who are part of the Historical Control R1 group, an auxiliary starting point had to be defined for the comparisons comprising patients of the APN311-303 and/or APN311-202 studies. For the Historical Control R1 group, the starting point was equal to the date of first relapse (as described above) plus the median time between first relapse and start of immunotherapy for the APN311-303 and/or APN311-202 patients. As only the date of the most recent relapse/progression is captured in the disease history of the APN311-202 study patients, solely those APN311-202 study patients could be included in the analyses determination of the auxiliary starting point who experienced exactly 1 relapse since initial diagnosis (as for these patients, date of most recent relapse is equal to date of first relapse). For the APN311-303 study and the patients with one relapse of the APN311-202 study, date of first relapse after diagnosis is used. Relapse for the Historical Control R1 group refers to the first relapse after diagnosis as well, as patients with a relapse before MAT (or radiotherapy, as applicable) will be excluded.

The use of this auxiliary starting point led to the following additional selection criterion to be applied to the Historical Control R1 group: patients who died before the auxiliary starting point or who had no follow-up afterwards had to be excluded.

2.9.2.3 Discussion of Historical Control Garaventa

In a retrospective study, Garaventa and colleagues investigated the outcome of neuroblastoma children with relapse or progression documented in the Italian Neuroblastoma Registry from 1979 to 2006 (Garaventa et al., 2009). These patients had received treatment according to the protocols of the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP), which included tumour resection, chemotherapy, radiotherapy, and myeloablation followed by ASCR, but no immunotherapy. While “follow-up was censored at 31 December 2006” for the analyses presented in Garaventa et al. (2009), the comparisons described in this historical data report were based on extended data with follow-up until 22 July 2014. Garaventa et al. (2009) described patients who had been diagnosed with neuroblastoma between 1979 and 2004. However, for this historical control comparison, only patients were selected that were diagnosed with neuroblastoma between 1999 and 2004. This period and no earlier period of first diagnosis was chosen since 1999 was the start of state of the art multimodal induction and consolidation chemotherapy in combination with maintenance therapy with 13-cis-RA (Matthay et al., 1999) which resulted in a significantly improved prognosis for high-risk neuroblastoma.

Treatment was thus comparable to the treatment used prior to immunotherapy in patients included in study APN311-303. Since neuroblastoma treatment regimens had changed over the decades, only data from historical control patients with a date of initial diagnosis ≥1999 were included in the historical control group.

Data from this time period seem to be the best comparison for the data collected in APN311-202 and APN311-303. The majority of patients reported in the Garaventa study should not have been treated with any anti-GD2 antibody, but it cannot be excluded that some of these patients received dinutuximab beta or dinutuximab within the scope of other studies. Assuming that ch14.18 antibody has a positive effect on OS, the fact that some of the historical control patients might have been treated with ch14.18 should reduce the difference in OS between the two treatment groups and thus was regarded as being conservative. Garaventa et al. (2009) reported 81 relapses in patients diagnosed between 1999 and 2004. Relapse was defined as the appearance of any new lesion(s) or deterioration of previous lesion(s). Timing of relapse was defined as “early relapse” or “late relapse” using a cut-off of 18 months after achieving complete response or very good partial response.

To further ensure comparability of data, historical control analyses were restricted to patients with relapsed neuroblastoma, patients who were ≥1 year of age at initial diagnosis/relapse and who presented with INSS stage 4 at initial diagnosis or nonlocal type of first relapse. The cut-off date for these patients follow-up was 22 July 2014. Since the historical control patients had not been treated with dinutuximab beta, an auxiliary starting point had to be defined; this was equal to the date of first relapse plus the median time between first relapse/progression and start of antibody therapy for the APN311-303 patients (~ 1 year). The historical cohort (see Table 34) included fewer females and more patients with stage 4 disease and MYCN amplification (i.e. less favourable prognosis) than the immunotherapy cohort but the time between diagnosis and first relapse was comparable.

Table 34: Demographics and baseline characteristics of relapse patients for pooled APN311 studies

	APN311-202 + APN311-303 N=48	Historical controls Garaventa N=29	Historical controls R1 N=52
Gender, [N (%)]			
Male	25 (52.1)	20 (69.0)	33 (63.5)
Female	23 (47.9)	9 (31.0)	19 (36.5)
Age			
Mean; years (SD)	4.4 (3.6)	4.3 (2.4)	4.2 (2.4)
Median; years	4.0	4.0	4.0
Min, max; years	0, 17	1, 13	1, 15
MYCN status [N (%)]			

Amplified	5 (10.4)	8 (27.6)	14 (26.9)
Not amplified	32 (66.7)	21 (72.4)	32 (61.5)
Missing	11 (22.9)	0	6 (11.5)
INSS stage at initial diagnosis, [N (%)]			
1	2 (4.2)	0	0 (0)
2A	1 (2.1)	0	0 (0)
3	2 (4.2)	1 (3.4)	1 (1.9)
4	42 (87.5)	28 (96.6)	51 (98.1)
Missing	1 (2.1)	0	0 (0)
1p deletion, [N (%)]			
No loss or aberration	6 (12.5)	11 (37.9)	-
Deletion and imbalance	-	1 (3.4)	-
Deletion	2 (4.2)	6 (20.7)	-
Imbalance	-	6 (20.7)	-
Missing	40 (83.3)	5 (17.2)	-
Number of relapses, [N (%)]			
1	36 (75.0)	20 (69.0%)	-
2	9 (18.8)	7 (24.1%)	-
3	-	2 (6.9%)	-
5	1 (2.1)	-	-
6	1 (2.1)	-	-
8	1 (2.1)	-	-
Type of first relapse, [N (%)]			
Combined	28 (58.3)	10 (34.5%)	-
Disseminated	16 (33.3)	17 (58.6%)	-
Local	4 (8.3)	2 (6.9%)	-
Time between diagnosis and first relapse			
Mean; years (SD)	2.34 (1.94)	1.87 (1.00)	2.26 (1.42)
Median; years	1.65	1.70	1.80
Min, max; years	1.0, 11.3	0.3, 5.8	1.0, 7.4
Missing; N (%)	6	0	0
Response to treatment of last relapse prior to starting point, [N (%)]			
CR	14 (29.2%)	7 (24.1%)	-
VGPR/PR/S.D.	34 (70.8)	8 (27.6%)	-
PD	0	7 (24.1%)	-
Missing	-	7 (24.1%)	-

2.9.2.4 APN311-302 vs Historical Control R1

Populations: The analysis population set (ALL) included 450 patients in the MAT group (Historical R1 control; no dinutuximab beta treatment) and 370 patients in the MAT and immunotherapy group (dinutuximab beta treatment).

Table 35: Main patient demographics and disease characteristics, APN311-302 vs Historical Control R1

Parameter		MAT (N=450)	MAT and immunotherapy (N=370)	Total (N=820)
Gender, N (%)	Male	275 (61.1)	236 (63.8)	511 (62.3)
	Female	175 (38.9)	134 (36.2)	309 (37.7)
Age at initial diagnosis (years)[a]	Mean (SD)	3.24 (2.18)	2.46 (2.60)	3.34 (2.38)
	Median	2.65	2.90	2.70
	Min, Max	0.1, 16.8	0.0, 19.5	0.0, 19.5
	Missing	0	1	1
Age groups (years), N (%)	<1	5 (1.1)	28(7.6)	33 (4.0)
	≥1.5 to <1.5	56 (12.4)	25 (6.8)	81 (9.9)

Parameter		MAT (N=450)	MAT and immunotherapy (N=370)	Total (N=820)
	>1.5 to ≤5	322 (71.6)	249 (67.3)	571 (69.6)
	>5	67 (14.9)	67 (18.1)	134 (16.3)
	Missing	0	1 (0.3)	1 (0.1)
MYCN status N (%)	Amplified	215 (47.8)	152 (41.1)	367 (44.8)
	Not amplified	204 (45.3)	181 (48.9)	385 (47.0)
	MIssing	31 (6.9)	37 (10.0)	68 (8.3)
INSS stage at initial diagnosis	local[b]	59 (13.1)	35 (9.5)	94 (11.5)
	4	391 (86.9)	328 (88.6)	719 (87.7)
	4S	0	7 (1.9)	7 (0.9)

Abbreviations: INSS = International Neuroblastoma Staging System, MAT = myeloablative therapy, MYCN = N-myc proto-oncogene protein, Min = minimum, Max = maximum, SD = standard deviation, N = number of patients with observations

[a]Age at initial diagnosis was calculated as (date of initial diagnosis – date of birth)/365.25. Half a year was defined as 183 days and a whole year as 365.25 days

[b]Local includes INSS stage 2, 2/3, 2A, 2B, and 3

Overall Survival: The date of death was missing for three R2 patients. These patients were excluded from the analyses of OS, so the total number of patients for OS analyses was 817. Overall, 353 of the 817 patients included in the OS analysis died, of whom 238 (52.9%) out of 450 patients died in the MAT group and 115 (31.3%) out of 367 died in the MAT and immunotherapy group. In the ALL analysis set (Table 36), the mean OS time was substantially longer in MAT patients (2447.1 days) than in the MAT and immunotherapy patients (1359.4 days). This is likely due to a longer follow-up time for the MAT group. Median OS time in the MAT group was 1869 days, while it was 4448 days in the total patient population. An estimation of the median OS time was not possible in the MAT and immunotherapy group, because <50% of patients was deceased.

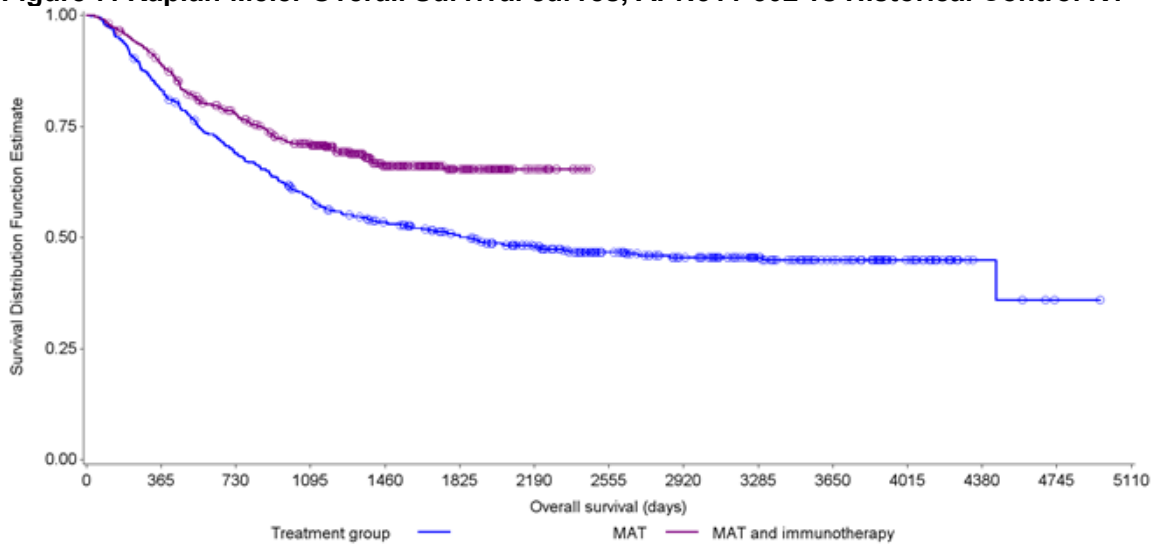
In the MAT group, OS was 83% at 1 year, 69% at 2 years, 59% at 3 years, and 50% at 5 years. In the MAT and immunotherapy group, OS was 89% at 1 year, 78% at 2 years, 71% at 3 years, and 65% at 5 years. The difference in OS between the MAT group and the MAT and immunotherapy group was statistically significant ($p < 0.0001$), in favor of MAT and immunotherapy. In a Cox regression model, INSS stage at initial diagnosis (combined stage 2 vs stage 4S, stage 3 vs stage 4S and stage 4 vs stage 4S) and MAT (BuMel /CEM) contributed significantly to OS ($p = 0.0011$ and $p = 0.001$ respectively), however, the treatment effect on OS remained significant when these two factors were added to the OS analysis ($p = 0.0139$).

Table 36: Kaplan Meier results of overall survival

Parameter		MAT (Historical Control R1) (N=450)	MAT and immunotherapy (N=367)	Total (N=817)
Deaths	N (%)	238 (52.9)	115 (31.3)	353 (43.2)
Censored[b]	N (%)	212 (47.1)	252 (68.7)	464 (56.8)
Overall survival[a] (days)	Mean[c]	2447.1	1359.4	2680.6
	Standard error	90.3	31.4	70.7
	Median	1869	-[d]	4448
	95% CI	1304-3302	-[e]	2221[f]
Overall survival rate[a] at:	1 year KM estimate	0.83	0.89	0.86
	2 years KM estimate	0.69	0.78	0.73
	3 years KM estimate	0.59	0.71	0.64
	5 years KM estimate	0.5	0.65	0.56
Log-rank test	p-value (two-tailed)		<0.0001	

Abbreviations: CI = confidence interval, KM = Kaplan Meier, MAT = myeloablative therapy
[a]Overall survival defined as time from the auxiliary starting point to the date of death from any cause
[b]Patients without an event were censored at the date of their last follow-up evaluation
[c]The mean survival time and its standard error were underestimated for both group and total because the largest observation was censored and the estimation was restricted to the largest event time
[d]Estimation of the median survival time was not possible
[e]Estimation of the upper and lower limits was not possible
[f]Estimation of the upper limit was not possible

Figure 7: Kaplan-Meier Overall Survival curves, APN311-302 vs Historical Control R1



2.9.2.5 APN311-303 vs Historical Control Garaventa

Populations: Fifty-four (54) patients were treated in this compassionate use programme. About half of the patients (56%) had relapsed neuroblastoma, i.e. the patients had experienced at least one relapse after previous neuroblastoma treatment, although they

reacted adequately to the most recent treatment prior to immunotherapy. Fifteen patients (28%) had a refractory disease status and 9 patients (17%) had only received first-line neuroblastoma treatment with either a complete response or with minimal residual disease.

Table 37: Patient characteristics – APN311-303 vs Historical Control Garaventa

Patient Characteristics		Historical Control Garaventa (N = 29)	APN311-303 (N = 30)
Period of diagnosis		1999-2004	2000-2010
Gender, n (%)	Male Female	20 (69.0) 9 (31.0)	15 (50.0) 15 (50.0)
Age (years) at initial diagnosis[1]	N Mean (SD) Median Min, Max	29 4.3 (2.4) 4.0 1, 13	30 4.8 (4.1) 3.5 1, 17
Age category at initial diagnosis[1], n (%)	≤ 5 years > 5 years	21 (72.4) 8 (27.6)	22 (73.3) 8 (26.7)
INSS Stage, n (%)	1 2A 3 4 Missing	0 (0.0) 0 (0.0) 1 (3.4) 28 (96.6) 0 (0.0)	1 (3.3) 1 (3.3) 2 (6.7) 25 (83.3) 1 (3.3)
MYCN status, n (%)	Amplified Not amplified Missing	8 (27.6) 21 (72.4) 0 (0.0)	4 (13.3) 17 (56.7) 9 (30.0)
Time between diagnosis and first relapse	N Mean (SD) 95% CI Median Min, max	29 1.87 (1.00) 1.70 0.3, 5.8 29	30 1.96 (0.85) 1.60 1.0, 4.3 30

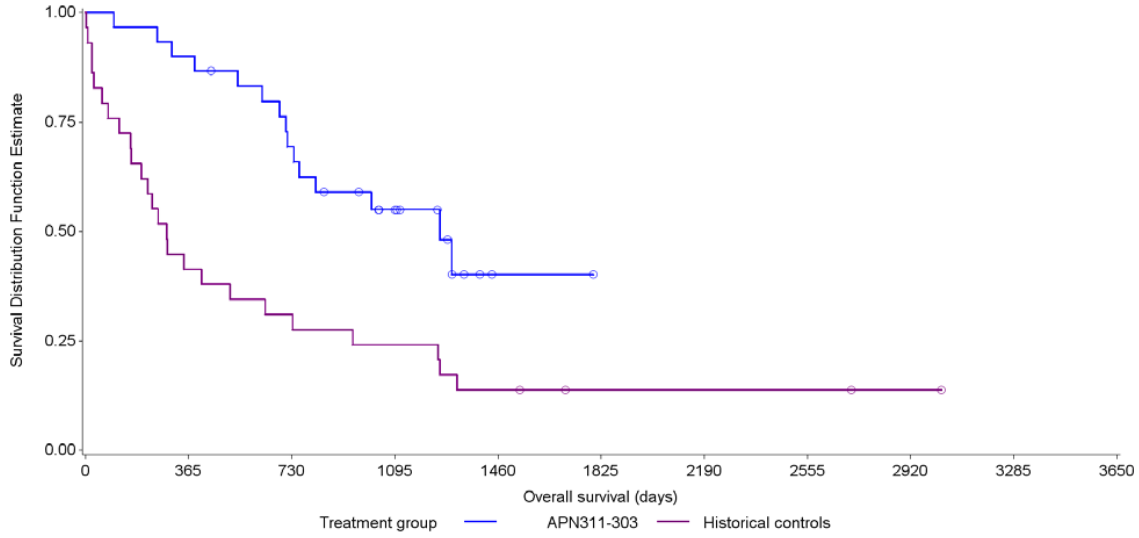
INSS = International Neuroblastoma Staging System, MYCN = v-myc myelocytomatosis viral related oncogene, SD = standard deviation
[1] Age was calculated as year of initial diagnosis – year of birth

Overall survival: The difference in OS between the two cohorts was highly significant (p = 0.0009) in favour of APN311-303 (Table 38). When adding prognostic factors for OS (ie, age at diagnosis, gender, MYCN amplification, and INSS stage) in a Cox model, the difference in OS time was still statistically significant (p = 0.002).

Table 38: Kaplan Meier Results of Overall Survival

Parameter		**APN311-303 (N=30)**	**Historical Control Garaventa (N=29)**
Overall survival rate at:	1 year KM estimate 2 years KM estimate 3 years KM estimate	0.90 0.69 0.55	0.56 0.46 0.28
Median (days) 95% CI		1254 715-NA	287 160-636
Log-rank test	p-value (two-tailed)	0.0009	

Figure 8: Kaplan-Meier Overall Survival curves, APN311-303 vs Historical Control Garaventa



APN311-202 + APN311-303 vs Historical Control R1:

Populations: This analysis set comprised 52 relapsed patients from the HR-NBL-1/SIOPEN study (Historical R1 control; no dinutuximab beta treatment) and 48 patients who had experienced one or more relapses from the APN311-202 and APN311-303 studies (dinutuximab beta treatment). The statistical analysis will be restricted to the variables which are comparable between the Historical Control R1 patients and relapsed patients from APN311-202 and APN311-303. It cannot be excluded that the Historical Control R1 patients may have been treated with dinutuximab beta within the scope of other relapse studies. Assuming that dinutuximab beta has a positive effect on OS, the fact that some of the historical control patients might have been treated with ch14.18 should reduce the difference in OS between the groups for comparison and thus was regarded as being conservative.

Overall Survival: Overall, 65 of the 100 patients died, of whom 26 (54.2%) out of 48 patients died in the combined APN311-202 and APN311-303 group and 39 (75%) out of 52 in the Historical Control R1 group. The median OS time was substantially longer in patients in the combined APN311-202 and APN311-303 group (1254 days) than in the Historical Control R1 (630 days). Mean OS times were 921 days vs. 911.4 days for the combined APN311-202 and APN311-303 group and Historical Control R1, respectively.

In the combined APN311-202 and APN311-303 group, yearly OS rates were clearly higher than in the Historical Control R1 group. OS in the APN311-202 and APN311-303 combined group was 83% at 1 year, 60% at 2 years and 50% at 3 years, compared to 56%, 46% and 28%, respectively, in Historical Control R1. The difference in OS between the combined APN311-202 + APN311-303 group and the Historical Control R1 group

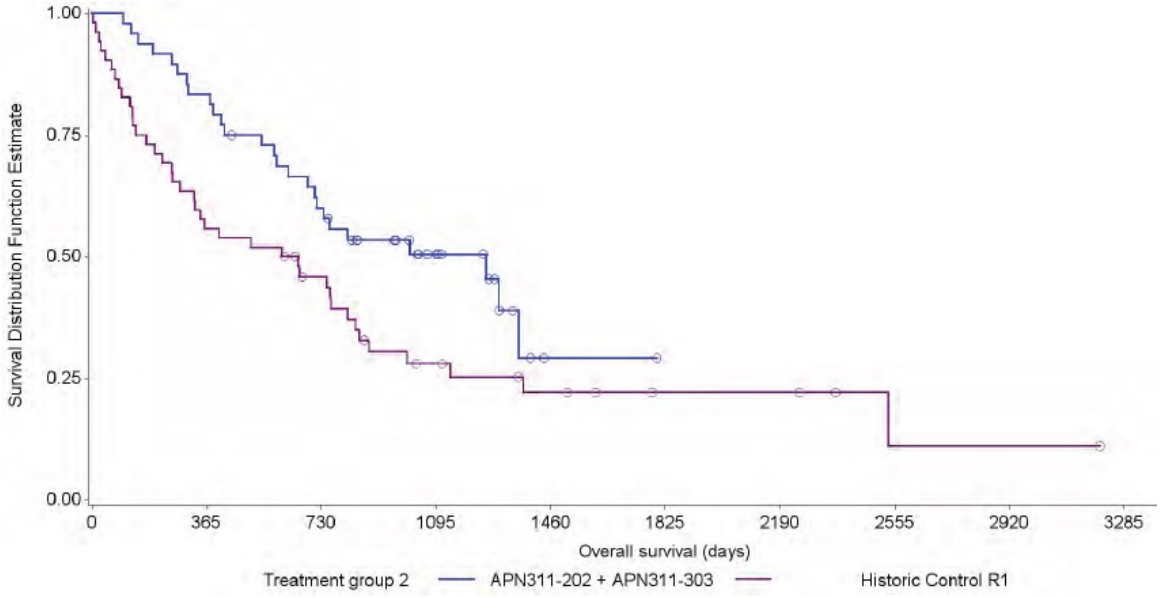
was statistically significant (p = 0.0302), in favor of dinutuximab beta treatment (Table 39). When adding prognostic factors for OS to the model, the treatment difference in OS time was still statistically significant (estimated hazard ratio 0.555 [95% CI 0.32,0.97], p = 0.0376).

Table 39: Kaplan Meier Results of Overall Survival

Parameter		APN311-202 + APN311-303 (N=48)	Historical Control R1 (N=52)	Total (N=100)
Deaths	N (%)	26 (54.2)	39 (75)	65 (65)
Censored[b]	N (%)	22 (45.8)	13 (25)	35 (35)
Overall survival[a] (days)	Mean[c]	921	911.4	1102.6
	Standard error	68.5	136.4	105.9
	Median	1254	630	757
	95% CI	686[d]	281-838	588-1004
Overall survival rate at:	1 year KM estimate	0.83	0.56	0.69
	2 years KM estimate	0.6	0.46	0.53
	3 years KM estimate	0.5	0.28	0.39
Log-rank test	p-value (two-tailed)	0.0302		

Abbreviations: CI = confidence interval, KM = Kaplan Meier
[a]Overall survival defined as time from the starting point to the date of death from any cause
[b]For patients having no event (=death), censoring was done at the last date at which the patient was known to be alive
[c]The mean survival time and its standard error were underestimated for both group and total because the largest observation was censored and the estimation was restricted to the largest event time
[d]Estimation of the upper limit was not possible

Figure 9: Kaplan-Meier Overall Survival curves, APN311-202+ -303 vs Historical Control R1



APN311-202 + APN311-303 vs Historical Control Garaventa

Populations: The analysis set used for comparison included 29 patients of the 81 relapsed patients from the Garaventa study (Historical Garaventa control; no

dinutuximab beta treatment) and 48 patients who had experienced one of more relapses from the APN311-202 and APN311-303 studies (dinutuximab beta treatment). Two patients from APN311-303 received dinutuximab beta treatment in the initial 'dose finding phase'. The other patients were treated according to the 10-day continuous infusion schedule of dinutuximab beta (100 mg/m^2/cycle).

Overall Survival: Overall, 51 of the 77 patients died, of which 26 (54.2%) out of 48 patients died in the APN311-202 + APN311-303 group and 25 (86.2%) out of 29 in the historical control group. In the analysis population set (Table 40), the median OS time was substantially longer in APN311-202 + APN311-303 patients (1254 days) than in the historical controls (318 days). Mean OS times were 921 days vs. 541.7 days for APN311-202 + APN311-303 and historical controls, respectively.

In the APN311-202 + APN311-303 group, OS was 83% at 1 year, 60% at 2 years and 50% at 3 years. In historical controls, less than half of the patients (45%) survived the first year, and OS was 31% and 24% at 2 and 3 years, respectively.

The difference in OS between APN311-202 + APN311-303 and the historical control group was statistically highly significant (p = 0.0031), in favor of APN311-202 + APN311-303.

Table 40: Kaplan Meier Results of Overall Survival

Parameter		APN311-202 + APN311-303 (N=48)	Historical Control Garaventa (N=29)	Total (N=77)
Deaths	N (%)	26 (54.2)	25 (86.2)	51 (66.2)
Censored[b]	N (%)	22 (45.8)	4 (13.8)	26 (33.8)
Overall survival[a] (days)	Mean[c]	921	541.7	777.5
	Standard error	68.5	93.5	58.7
	Median	1254	318	715
	95% CI	686[d]	191-667	441-1254
Overall survival rate at:	1 year KM estimate	0.83	0.45	0.69
	2 years KM estimate	0.6	0.31	0.49
	3 years KM estimate	0.5	0.24	0.4
Log-rank test	p-value (two-tailed)	0.0031		

Abbreviations: CI = confidence interval, KM = Kaplan Meier

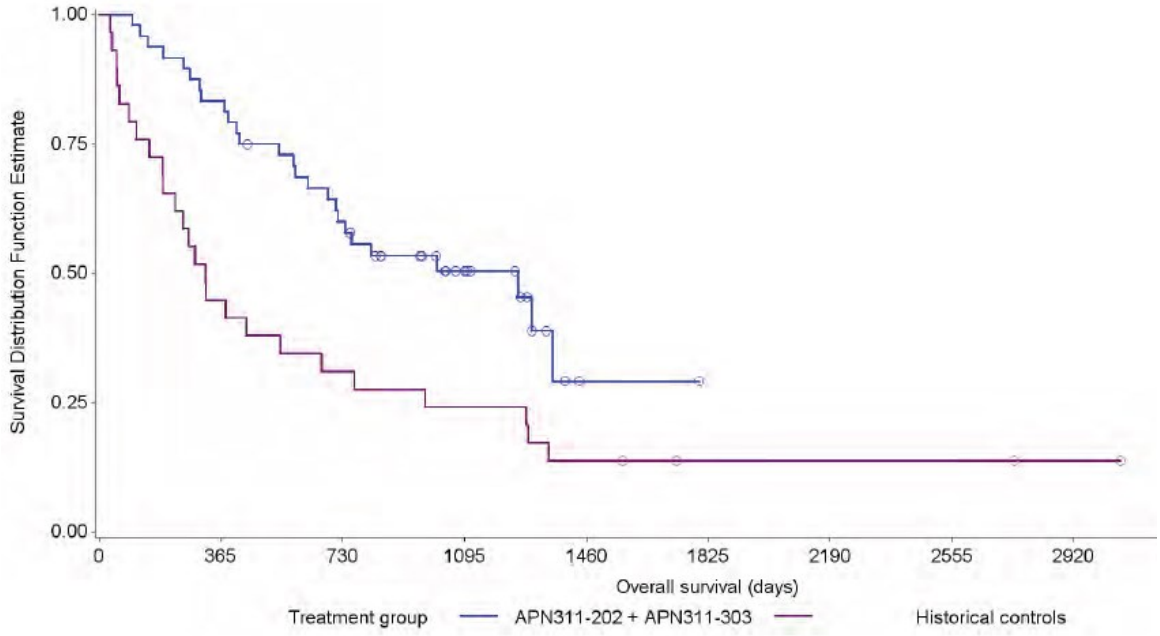
[a]Overall survival defined as time from the starting point to the date of death from any cause

[b]For patients having no event (=death), censoring was done at the last date at which the patient was known to be alive

[c]The mean survival time and its standard error were underestimated for both group and total because the largest observation was censored and the estimation was restricted to the largest event time

[d]Estimation of the upper limit was not possible

Figure 10: Kaplan-Meier Overall Survival curves, APN311-202 + -303 vs Historical Control Garaventa



2.9.3 *Uncertainties in the indirect and mixed treatment comparisons*

Overall, none of the submitted studies included a comparative arm with patients who did not receive ch14.18/CHO except for the very small APN311-301 trial (25 evaluable patients). In the absence of internal controls, the assessment of the efficacy of immunotherapy was performed by comparison to historical control data. As expected for compassionate use (study APN311-303), the patient population is extremely heterogeneous, including both first-line and refractory/relapsed patients. Furthermore, due to the retrospective nature of the data collection, there was a substantial amount of missing data, especially for prognostic factors; these data could not be retrieved in spite of the Applicant's review of the data. As a consequence of this design, population (selection bias), application of treatment (no prospective treatment protocol), data recording (possible lack of standardization) and measurement of outcomes could potentially be affected.

Tumour response, especially the occurrence of complete response (CR) may indicate anti-tumour activity of the treatment regimen but does not always relate to clinical benefit e.g. prolonged survival. Moreover, dinutuximab beta was combined with 13-cis-RA and IL-2 in most studies. Thus, it is not clear whether the reported responses are exclusively the result of dinutuximab beta treatment or of the other components of the applied regimen. Responses, including complete response, have also been reported for 13-cis-RA therapy. Given the fixed number of treatment cycles 5 (or 6), which was applied to

the vast majority of patients except in case of early disease progression, the best response is not necessarily the most clinically relevant outcome as it takes into account responses of very short duration. Evaluation at the end of treatment, which was usually performed 6-8 months after treatment initiation (except in case of early disease progression), provides a valuable indication of the disease outcome after such a period of time.

Event free survival is generally considered as an important efficacy endpoint, and this might even be used as primary endpoint when there is a good correlation between EFS and OS and a long median OS is anticipated. However, this endpoint is complicated by several methodological issues, including the exact definition of events and methods of disease status determination. The time points at which disease status was assessed during treatment and follow-up were not strictly pre-specified; consequently, it is not clear whether the exact time of disease progression was determined.

As efficacy data in terms of EFS and OS were not planned in the protocols, these have been collected retrospectively. The value of EFS results is considered limited due to the methodological issues previously mentioned and OS is considered the most important efficacy endpoint. As the proportion of censored subjects is high after 2 years, only outcomes during the first 2 years after treatment are currently considered reliable in the R/R setting.

Due to the small samples of treated patients and controls, these historical comparisons lack power but the point estimate and confidence interval do indicate survival benefit. In conclusion, the magnitude of the effect may differ but the trends are consistent and the replication of the results provides reassurance about the benefit even if its extent cannot be accurately quantified.

2.10 *Adverse reactions*

2.10.1 *Studies reported in Section 2.2*

Adverse reactions have been documented for the APN311-303 and 202. Severe adverse reactions and toxicities are available for the APN311-302 study.

2.10.1.1 Patient exposure

The overall safety database currently includes 514 patients that received dinutuximab beta: 98 patients as a continuous infusion over 10 days and 416 patients as short 8h-infusions. Overall, 281 patients received it in combination with IL-2 and 207 patients received antibody treatment without IL-2; 26 patients received both single-agent and

combination cycles, but with a low IL-2 dose. In addition, 13-cis retinoic was also administered to patients in studies APN311-202, -302 and -303. The dosing regimens of the three products are shown in the next table (Table 41).

Table 41: Summary of dinutuximab beta, IL-2 and 13-cis-RA administration in APN311 studies

Study		Dinutuximab beta Apeiron - i.v.	IL-2 – s.c.	13-cis-RA – p.o.	Cycles
APN311-303 (Compassionate Use)	Patient 1-4	Days 1-11 (10 days) Continuous (24h) 5-10 mg/m^2/day [a]	Days 1-5 (5 days) 6 x 10^6 IU/m^2/day	Days 15-28 (14 days) 80 mg/m^2/day b.i.d.	3-6 cycles, 1 cycle = 28-35 days
	Patient 5-54	Days 8-18 (10 days) Continuous (24h) 10 mg/m^2/day [a]	Days 1-5 & 8-12 (2 x 5 days) 6 x 10^6 IU/m^2/day	Days 19-32 (14 days) 80 mg/m^2/day b.i.d	5/6 cycles, 1 cycle = 35 days
APN311-202		Days 8-18 (10 days) Continuous (24h) 10 mg/m^2/day [a]	Days 1-5 & 8-12 (2 x 5 days) 6 x 10^6 IU/m^2/day	Days 19-32 (14 days) 80 mg/m^2/day b.i.d.	5 cycles, 1 cycle = 35 days
APN311-302	- IL2	Days 8-12 (5 days) Short-term (8h) 20 mg/m^2/day [b]	NA	14 days 80 mg/m^2/day b.i.d. Weeks: 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21, 22	5 cycles ch14.18 & IL-2, 6 cycles RA, start with RA 1 cycle = 4 weeks (28 days)
	+ IL2		Days 1-5 & 8-12 (2 x 5 days) 6 x 10^6 IU/m^2/day 2 h after stop of ch14.18 infusion		

It should be emphasized that the method of AE collection varied across studies. In particular, in the largest study (APN311-302) only SAEs were fully reported while for other AEs, a pre-defined list of 31 specific toxicities was used. All adverse events that were listed as toxicity were classified as at least possibly related to treatment. As the main study (APN311-303) is a retrospective analysis of patients enrolled into the compassionate use programme, safety was also retrospectively assessed from adverse events recorded from time of enrolment until 30 days after last study treatment.

Therefore, except for SAEs and some ADRs of specific interest, the evaluation will mainly focus on the 98 patients of the continuous infusion studies due to the specific toxicities of the transplantation setting, the restricted number of cycles administered in the PK bridging study. In the main (continuous infusion) studies 68/98 (69%) patients completed the planned 5-6 cycles. The main reason for treatment discontinuation was progressive disease and the number of patients having stopped treatment due to an ADR, as only reason or associated with PD, was 6 (6%).

2.10.2 *Adverse events*

The overall summary of treatment-emergent adverse events (TEAEs) is presented hereafter (Table 42).

Table 42: Overall summary of treatment-emergent adverse events (TEAEs)

Patients with	APN311-303	APN311-202	APN311-302
	N (%) patients (N=54)	N (%) patients (N=44)	N (%) patients (N=366)
Any AE	**54 (100.0%)**	**44 (100.0%)**	
Any AE possibly related to study drug a	54 (100.0%)	44 (100.0%)	
Any AE possibly related to IL-2	54 (100.0%)	44 (100.0%)	
Any AE possibly related to dinutuximab beta	54 (100.0%)	44 (100.0%)	
Any AE possibly related to 13-cis-RA	27 (50.0%)	ND	
Any serious AE	**12 (22.2%)**	**26 (59.1%)**	
Any serious AE possibly related to study drug[a]	6 (11.1%)	22 (50.0%)	
Any serious AE possibly related to IL-2	4 (7.4%)	18 (40.9%)	
Any serious AE possibly related to dinutuximab beta	6 (11.1%)	20 (45.5%)	
Any serious AE possibly related to 13-cis-RA	-	ND	
Any AE leading to discontinuation of study drugs[b]	**5 (9.3%)**	**10 (22.7%)**	
Maximal NCI CTCAE Grade[c]			
Grade 1 (mild)	-	-	
Grade 2 (moderate)	3 (5.6%)	2 (4.5%)	
Grade 3 (severe)	32 (59.3%)	20 (45.5%)	
Grade 4 (life threatening/disabling)	19 (35.2%)	22 (50.0)	
Grade 5 (death)	-	1 (2.3%)	
Any AE leading to death	**-**	**1 (2.3%)**	
Deaths *	**22 (40.7%)**	**20 (45.5%)**	

[#] pre-defined toxicities according to NCI CTC were collected in study APN311-302, not AEs;
* All documented deaths, including deaths during follow-up period
[a] Depending on the study design refers to dinutuximab beta only or to the combination of dinutuximab beta and IL-2 and 13-cis-RA. For APN311-202 refers to dinutuximab beta and IL-2 treatment.
[b] Permanent or temporary discontinuation in studies APN311-303 and -202, permanent discontinuation in study APN311-201.
[c] Referring to SAE grades for APN311-302.
AE=adverse event, N=number of subjects, NA = not applicable, NCI CTC=National Cancer Institute Common Toxicity Criteria, ND = not determined.
Possibly related AEs: AEs with relationship coded as 'Possible', Probable', 'Definite, or with missing relationship

While the number of TEAEs decreased significantly over treatment cycles, the proportion of patients with any TEAE remained high throughout the study (data not shown). The most frequent TEAEs are presented for cycle 1 in studies APN311-202 and -303 below (Table 43). General disorders, namely pyrexia, were the most frequently documented TEAEs, followed by investigation-related TEAEs in study APN311-202 and by gastrointestinal disorders in study APN311-303.

In study APN311-202, the most frequent PTs were pyrexia, pain, vomiting, cough, increased weight, and laboratory abnormalities (increased alanine aminotransferase and gammaglutamyltransferase, anaemia, leukopenia, thrombopenia).

In study APN311-303, the most frequent PTs included also skin reactions, constipation, tachycardia, hypotension, and capillary leak syndrome (only during the first cycle).

Table 43: Most frequent TEAEs reported in cycle 1 (studies APN311-303 and APN311-202)

Cycle	SYSTEM ORGAN CLASS Preferred term	N (%) patients	
		APN311-202 (N=44)	APN311-303 (N=54)
Cycle 1	**Patients with events**	**44 (100.0%)**	**54 (100.0%)**
	GENERAL DISORDERS	**44 (100.0%)**	**54 (100.0%)**
	Pyrexia	44 (100.0%)	36 (66.7%)
	Pain	23 (52.3%)	20 (37.0%)
	Fatigue	12 (27.3%)	18 (33.3%)
	GASTROINTESTINAL DISORDERS	**33 (75.0%)**	**50 (92.6%)**
	INVESTIGATIONS	**36 (81.8%)**	**32 (59.3%)**
	RESPIRATORY DISORDERS	**32 (72.7%)**	**37 (68.5%)**
	Cough	20 (45.5%)	17 (31.5%)
	Hypoxia	14 (31.8%)	15 (27.8%)
	BLOOD AND LYMPHATIC SYSTEM DISORDERS	**28 (63.6%)**	**32 (59.3%)**
	METABOLISM AND NUTRITION DISORDERS	**19 (43.2%)**	**12 (22.2%)**
	SKIN DISORDERS	**26 (59.1%)**	**40 (74.1%)**
	Pruritus	14 (31.8%)	31 (57.4%)
	VASCULAR DISORDERS	**22 (50.0%)**	**45 (83.3%)**
	Hypotension	14 (31.8%)	18 (33.3%)
	Capillary leak syndrome	12 (27.3%)	39 (72.2%)
	MUSCULOSKELETAL DISORDERS	**4 (9.1%)**	**35 (64.8%)**
	INFECTIONS AND INFESTATIONS	**14 (31.8%)**	**15 (27.8%)**
	NERVOUS SYSTEM DISORDERS	**9 (20.5%)**	**19 (35.2%)**
	CARDIAC DISORDERS	**7 (15.9)**	**23 (42.6%)**
	RENAL AND URINARY DISORDERS	**9 (20.5%)**	**14 (25.9%)**

2.10.2.1 Severe (grade 3 & 4) events

The most frequent severe (grade 3/4) AEs were pain, abnormal haematological and liver function tests, pyrexia, infections, allergic reactions and capillary leak syndrome (Table 44).

Table 44: Summary of grade 3 and 4 TEAEs occurring in >1 subject in any study APN311-202 & -303

System Organ Class / PT	APN311-303		APN311-202	
Maximum toxicity grade	**3**	**4**	**3**	**4**
Gastrointestinal disorders				
Abdominal pain upper	6 (11.1%)	3 (5.6%)	-	-
Vomiting	5 (9.3%)	-	3 (6.8%)	-
Diarrhea	3 (5.6%)	1 (1.9%)	1 (2.3%)	-
Nausea	2 (3.7%)	-	3 (6.8%)	-
Abdominal pain	3 (5.6%)	-	2 (4.5%)	-
Abdominal distension	2 (3.7%)	-	-	-
General disorders and administration site conditions				
Pyrexia	5 (9.3%)	-	15 (34.1%)	-
Pain	14 (25.9%)	1 (1.9%)	5 (11.4%)	2 (4.5%)
Inflammation	2 (3.7%)	-	-	-
Skin and subcutaneous tissue disorders				
Pruritis	8 (14.8%)	-	-	-
Urticaria	5 (9.3%)	-	-	-
Rash	3 (5.6%)	-	1 (2.3%)	-
Vascular disorders				
Hypotension	2 (3.7%)	-	9 (20.5%)	-
Capillary leak syndrome	7 (13.0%)	-	2 (4.5%)	1 (2.3%)
Musculoskeletal and connective tissue disorders				
Pain in extremity	11 (20.4%)	4 (7.4%)	-	-
Back pain	6 (11.1%)	-	-	-
Arthralgia	4 (7.4%)	-	-	-
Bone pain	2 (3.7%)	-	-	-
Respiratory, thoracic and connective tissue disorders				
Cough	9 (16.7%)	4 (7.4%)	1 (2.3%)	-
Hypoxia	3 (5.6%)	-	8 (18.2%)	-
Bronchospasm	3 (5.6%)	-	1 (2.3%)	-
Acute respiratory distress syndrome	-	-	1 (2.3%)	1 (2.3%)
Pleural effusion	2 (3.7%)	-	-	-
Blood and lymphatic system disorders				
Anemia	18 (33.3%)	2 (3.7%)	18 (40.9%)	-
Neutropaenia	20 (37.0%)	6 (11.1%)	6 (13.6%)	4 (9.1%)
Febrile neutropaenia	-	-	6 (13.6%)	-
Thrombocytopaenia	9 (16.7%)	7 (13%)	2 (4.5%)	2 (4.5%)
Leukopaenia	7 (13.0%)	-	-	-
Cardiac disorders				
Tachycardia	2 (3.7%)	-	-	-
Pericardial effusion	2 (3.7%)	-	-	-
Infections and infestations				
Device related infection	1 (1.9%)	-	11 (25.0%)	-
Sepsis	-	-	-	5 (11.4%)
Urinary tract infection	1 (1.9%)	-	1 (2.3%)	-
Skin infection	-	-	2 (4.5%)	-
Investigations				
Increased ALT	8 (14.8%)	2 (3.7 %)	13 (29.5%)	2 (4.5%)
Increased GGT	7 (13.0%)	-	14 (31.8%)	1 (2.5%)
Decreased neutrophil count	-	-	17 (38.6%)	3 (6.8%)
Decreased platelet count	-	-	10 (22.7%)	9 (20.5%)

	Increased AST	1 (1.9%)	-	4 (9.1%)	-
	Increased weight	2 (3.7%)	-	1 (2.3%)	2 (4.5%)
	Increased CRP	3 (5.6%)	1 (1.9%)	-	1 (2.3%)
	Decreased white blood cell count	-	-	3 (6.8%)	2 (4.5%)
	Increased blood bilirubin	1 (1.9%)	-	2 (4.5%)	1 (2.3%)
	Decreased urine output	-	-	2 (4.5%)	-
	Decreased haemoglobin	-	-	1 (2.3%)	1 (2.3%)
Nervous system disorders					
	Headache	4 (7.4%)	-	1 (2.3%)	-
Metabolism and nutrition disorders					
	Decreased appetite	1 (1.9%)	-	3 (6.8%)	-
	Hyperkalaemia	1 (1.9%)	2 (3.7%)	-	-
	Hyponatraemia	-	-	1 (2.3%)	1 (2.3%)
	Hypokalaemia	1 (1.9%)	1 (1.9%)	-	-
Haematology investigations					
	Prolonged ATPP	2 (3.7%)	-	1 (2.3%)	-
Immune system disorders					
	Cytokine release syndrome	-	-	2 (4.5%)	-
	Anaphylactic reaction	-	-	2 (4.5%)	-
ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, ATPP: Adenosine tetraphosphate, AST: Aspartate aminotransferase, CRP: C-reactive protein					

2.10.2.2 Serious adverse event (SAE)/deaths/other significant events

2.10.2.2.1 Deaths

Seven patients died for a reason other than disease progression.

For three patients, death occurred several months after the end of treatment: one as a result of an accident and two as the result of an infection. Three deaths could be considered as possibly treatment-related as they occurred as a result of an AE that started under therapy.

- Two deaths occurred in study APN311-302 due to capillary leak syndrome and acute respiratory distress syndrome, which may have been the result of an anaphylactic reaction.
- One death in study APN311-202 was due to septic shock and was attributed to delayed antibiotic treatment in an outpatient who presented with repeated fever episodes and was subsequently hospitalised. It does not seem that, in this case, home treatment could be directly incriminated in the delayed antibiotic therapy, but according to the Applicant, rather the fact that the patient was not followed in a specialised environment.

2.10.2.2.2 SAEs

A summary of SAEs occurring in >1 subject in any study is presented in Table 45. The most frequent SAEs were infections observed in study APN311- 202 were pyrexia, hypotension, and thrombocytopaenia. However, a high occurrence of serious hypoxia/respiratory distress was reported specifically in study APN311-202.

The patient incidence of SAEs decreased significantly over the treatment cycles: from 39% (cycle 1) to 7% (cycle 5) in study APN311-202 and from 15% (cycle 1) to 0% (cycle 5) in study APN311-303.

As for the study APN311-302, it allowed to compare the safety profile of dinutuximab beta (+13-cis RA) alone and combined with IL-2. SAEs were reported more frequently in patients receiving IL-2 compared to patients not receiving IL-2: 46% vs 27%. More patients who received IL-2 experienced at least 1 SAE leading to the discontinuation of dinutuximab beta, 13-cis-RA, and/or IL-2, if applicable: 17% vs 6% of patients (47 vs 16 SAEs).

Table 45: Summary of SAEs occurring in >1 subject in any study

SYSTEM ORGAN CLASS **Preferred term**	**Number (%) Patients**	
	APN311-303 **(N=54)**	**APN311-202** **(N=44)**
OVERALL	**12 (22.2%)**	**25 (56.8%)**
BLOOD AND LYPMPHATIC SYSTEM DISORDERS	**-**	**3 (6.8%)**
Thrombocytopenia	**-**	**-**
Anaemia	**-**	2 (4.5%)
GASTROINTESTINAL DISORDERS	**5 (9.3%)**	**5 (11.4%)**
Vomiting	2 (3.7%)	3 (6.8%)
Diarrhea	1 (1.9%)	3 (6.8%)
GENERAL DISORDERS	**3 (5.6%)**	**7 (15.9%)**
Pain	1 (1.9%)	2 (4.5%)
Pyrexia	1 (1.9%)	6 (13.6%)
IMMUNE SYSTEM DISORDERS	**-**	**2 (4.5%)**
Anaphylactic reaction	-	2 (4.5%)
INFECTIONS AND INFESTATIONS	**3 (5.6%)**	**9 (20.5%)**
Bronchitis	1 (1.9%)	-
Gastroenteritis	-	-
Pneumocystis jirovecii pneumonia	-	-
Device related infection	-	3 (6.8%)
Sepsis	-	4 (9.1%)
INVESTIGATIONS	**-**	**6 (13.6%)**
Platelet count decreased	**-**	2 (4.5%)
METABOLISM AND NUTRITION DIS	**1 (1.9%)**	**3 (6.8%)**
Hyponatremia	-	2 (4.5%)
NERVOUS SYSTEM DISORDERS	**2 (3.7%)**	**1 (2.3%)**
Convulsion	1 (1.9%)	-

SYSTEM ORGAN CLASS Preferred term	Number (%) Patients	
	APN311-303 (N=54)	APN311-202 (N=44)
RESPIRATORY DISORDERS	**1 (1.9%)**	**8 (18.2%)**
Hypoxia	-	5 (11.4%)
Acute respiratory distress syndrome	1 (1.9%)	2 (4.5%)
SKIN DISORDERS	**-**	**-**
VASCULAR DISORDERS	**-**	**5 (11.4%)**
Hypotension	-	3 (6.8%)

2.10.2.3 Treatment-related events

Since most TEAEs documented during the studies were judged to have at least a possible relationship to the study treatment (any of dinutuximab beta, IL-2, 13-cis-RA), treatment-related TEAEs were generally comparable to overall TEAE incidences.

Study APN311-302 allowed to compare the safety profile of dinutuximab beta (+13-cis RA) alone and combined with IL-2. Toxicities were generally more frequent in patients who received IL-2 compared to patients who did not receive IL-2 in particular capillary leak syndrome, platelet abnormalities, hypotension, infections, nausea or vomiting, fever, and pain related to dinutuximab beta. Constipation however was observed less frequently with concomitant IL-2 treatment than without IL-2 treatment (Table 46).

Table 46: Toxicities in study APN311-302 (SAF; N=366)

System Organ Class Toxicities	Number (%) of patients dinutuximab beta + 13-cis-RA (N= 183)	dinutuximab beta + 13-cis-RA + IL-2 (N= 183)	All (N = 366)
ANY	181 (98.9)	181 (98.9)	362 (98.9)
GENERAL CONDITION	140 (76.5)	164 (89.6)	304 (83.1)
GUT TOXICITY	135 (73.8)	145 (79.2)	280 (76.5)
Stomatitis	29 (15.8)	40 (21.9)	69 (18.9)
Nausea or vomiting	99 (54.1)	121 (66.1)	220 (60.1)
Diarrhea	92 (50.3)	114 (62.3)	206 (56.3)
Constipation	76 (41.5)	47 (25.7)	123 (33.6)
SKIN TOXICITY	147 (80.3)	159 (86.9)	306 (83.6)
Skin	124 (67.8)	138 (75.4)	262 (71.6)
Allergy	101 (55.2)	119 (65.0)	220 (60.1)
LIVER TOXICITY	118 (64.5)	126 (68.9)	244 (66.7)
Bilirubine	15 (8.2)	35 (19.1)	50 (13.7)
SGOT et SGPT	118 (64.5)	121 (66.1)	239 (65.3)
CARDIAC TOXICITY	61 (33.3)	88 (48.1)	149 (40.7)
Cardiac function	6 (3.3)	10 (5.5)	16 (4.4)
ECHO:LV-SF	1 (0.5)	8 (4.4)	9 (2.5)
Hypotension	48 (26.2)	78 (42.6)	126 (34.4)
Hypertension	24 (13.1)	11 (6.0)	35 (9.6)
INFECTIONS	147 (80.3)	170 (92.9)	317 (86.6)
Infections	106 (57.9)	132 (72.1)	238 (65.0)
Fever	145 (79.2)	168 (91.8)	313 (85.5)
HEMATOLOGICAL TOXICITY	164 (89.6)	174 (95.1)	338 (92.3)
Hemoglobin	162 (88.5)	174 (95.1)	336 (91.8)
WBC	148 (80.9)	153 (83.6)	301 (82.2)
Granulocytes	140 (76.5)	154 (84.2)	294 (80.3)
Platelets	124 (67.8)	156 (85.2)	280 (76.5)

RENAL TOXICITY	46 (25.1)	56 (30.6)	102 (27.9)
Creatinine	25 (13.7)	35 (19.1)	60 (16.4)
Proteinuria	16 (8.7)	11 (6.0)	27 (7.4)
Hematuria	18 (9.8)	24 (13.1)	42 (11.5)
GFR	14 (7.7)	10 (5.5)	24 (6.6)
Tubular phosphate reabsorption	1 (0.5)	3 (1.6)	4 (1.1)
NEUROLOGICAL TOXICITY	28 (15.3)	44 (24.0)	72 (19.7)
Central neurotoxicity	19 (10.4)	28 (15.3)	47 (12.8)
Peripheral neurotoxicity	13 (7.1)	25 (13.7)	38 (10.4)
VASCULAR TOXICITY	70 (38.3)	116 (63.4)	186 (50.8)
Capillary leak syndrome	45 (24.6)	91 (49.7)	136 (37.2)
Cytokine release syndrome	49 (26.8)	64 (35.0)	113 (30.9)
PAIN	115 (62.8)	138 (75.4)	253 (69.1)
Pain related to dinutuximab beta	115 (62.8)	138 (75.4)	253 (69.1)
OCULAR TOXICITY	33 (18.0)	45 (24.6)	78 (21.3)
Dilated pupils	23 (12.6)	40 (21.9)	63 (17.2)
Accommodation defects	15 (8.2)	23 (12.6)	38 (10.4)
Papilloedema	5 (2.7)	3 (1.6)	8 (2.2)

13-cis-RA = 13-cis retinoic acid, ECHO: LV-SF = echocardiogram: left ventricle – systolic function, GFR = glomerular filtration rate, IL-2 = aldesleukin, N = number of patients, SGOT = serum glutamic-oxaloacetic transaminase (= AST)), SGPT = serum glutamic pyruvic transaminase (= ALT)), WBC = white blood cells

2.10.2.4 Adverse drug reactions

The list of ADRs has been established by the manufacturer (Table 47). Due to different methods of AE collection across studies, ADR frequencies were calculated either on the totality of the safety database (N=514) when possible/relevant or on the subpopulation of studies APN311-101, -201, -202, -303 (N=148).

Table 47: Adverse drug reactions reported in the clinical trials submitted

System organ class	ADR Preferred Term	Frequency
Infections and infestations	infection (including pneumonia, skin infection, herpes virus infection, myelitis, encephalomyelitis)	53.3% (N=274/514)
	device related infection	10.1% (N=15/148)
	Sepsis	1.4% (N=7/514)
Blood and lymphatic system disorders	anaemia	77.4% (N=398/514)
	leucopenia	66.5% (N=342/514)
	neutropenia	10.1% (N=15/148)
	thrombocytopenia	62.3% (N=320/514)
	lymphopenia	2.0% (N=3/148)
	disseminated intravascular coagulation	0.4% (N=2/514)
	eosinophilia	0.7% (N=1/148)
Immune system disorders	hypersensitivity	62.8% (N=323/514)
	cytokine release syndrome	32.1% (N=165/514)
	anaphylactic reaction	5.4% (N=828/514)
	serum sickness	0.7% (N=1/148)
Metabolism and nutrition disorders	fluid retention	20.9% (N=31/148)
	decreased appetite	4.1% (N=21/514)
	hypoalbuminaemia	5.4% (N=8/148)
	hyponatraemia	5.4% (N=8/148)
	hypokalaemia	4.7% (N=7/148)
	hypophosphataemia	4.7% (N=7/148)
	hypomagnesaemia	4.1% (N=6/148)
	hypocalcaemia	3.4% (N=5/148)
	dehydration	1.4% (N=2/148)
Psychiatric disorders	agitation	2.0% (N=3/148)
	anxiety	1.4% (N=2/148)
Nervous system disorders	headache	11.5% (N=17/148)
	peripheral neuropathy	9.5% (N=49/514)
	seizure	2.9% (N=15/514)
	paraesthesia	4.7% (N=7/148)
	dizziness	4.1% (N=6/148)
	tremor	1.4% (N=2/148)
	increased intracranial pressure	0.4% (N=2/514)
	posterior reversible encephalopathy syndrome	0.4% (N=2/514)
	mydriasis	12.5% (N=64/514)

Eye disorders	pupillotonia	10.1% (N=15/148)
	eye oedema (eyelid, periorbital)	11.5% (N=17/148)
	ophthalmoplegia	2.3% (N=12/514)
	papilloedema	1.6% (N=8/514)
	accommodation disorder	7.0% (N=36/514)
	blurred vision	3.4% (N=5/148)
	photophobia	2.7% (N=4/148)
Cardiac disorders	tachycardia	15.8% (N=81/514)
	cardiac failure	1.8% (N=9/514)
	left ventricular dysfunction	1.9% (N=10/514)
	pericardial effusion	1.4% (N=2/148)
Vascular disorders	hypotension	39.1% (N=201/514)
	capillary leak syndrome	40.5% (N=208/514)
	hypertension	8.2% (N=42/514)
	hypovolaemic shock	0.2% (N=1/514)
	venoocclusive disease	0.7% (N=1/148)
Respiratory, thoracic and mediastinal disorders	hypoxia	25.7% (N=38/148
	cough	16.3% (N=84/514)
	bronchospasm	4.1% (N=21/514)
	dyspnoea	7.4% (N=11/148)
	respiratory failure	1.4% (N=7/514)
	lung infiltration	2.0% (N=3/148)
	pulmonary oedema	2.0% (N=3/148)
	pleural effusion	7.4% (N=11/148
	tachypnoea	1.4% (N=2/148)
	laryngospasm	2.0% (N=3/148)
Gastrointestinal disorders	vomiting	57.2% (N=294/514)
	diarrhoea	51.2% (N=263/514)
	constipation	32.5% (N=167/514)
	stomatitis	16.7% (N=86/514)
	nausea	7.2% (N=37/514)
	lip oedema	3.4% (N=5/148)
	ascites	5.4% (N=8/148)
	abdominal distension	2.7% (N=4/148)
	ileus	1.4% (N=7/514)
	dry lips	2.7% (N=4/148)
	enterocolitis	0.8% (N=4/514)
Hepatobiliary disorders	hepatocellular injury	0.4% (N=2/514)
Skin and subcutaneous tissue disorders	urticaria	17.6% (N=26/148)
	pruritus	49.3% (N=73/148)
	rash	22.3% (N=33/148)
	dermatitis (including exfoliative)	2.7% (N=4/148)
	erythema	7.4% (N=11/148)
	dry skin	6.1% (N=9/148)
	hyperhidrosis	2.7% (N=4/148)
	petechiae	2.0% (N=3/148)
	photosensitivity reaction	1.4% (N=2/148)
Musculoskeletal and connective tissue disorders	muscle spasms	1.4% (N=2/148)
Renal and urinary disorders	oliguria	4.1% (N=6/148)
	urinary retention	1.9% (N=10/514)
	hyperphosphaturia	1.0% (N=5/514)
	haematuria	8.6% (N=44/514)
	proteinuria	7.6% (N=39/514)
	renal failure	0.6% (N=3/514)
General disorders and administration site conditions	pyrexia	87.9% (N=452/514)
	chills	19.6% (N=29/148)
	pain*	77.4% (N=398/514)
	peripheral oedema	27.0% (N=40/148)
	face oedema	19.6% (N=29/148)
	injection site reaction	4.7% (N=7/148)
Investigations	increased weight	37.8% (N=56/148)
	increased transaminases	52.9% (N=272/514)
	increased gamma glutamyltransferase	16.2% (N=24/148)
	increased blood bilirubin	13.2% (N=68/514)
	increased blood creatinine	14.2% (N=73/514)
	decreased weight	3.4% (N=5/148)
	decreased glomerular filtration rate	4.5% (N=23/514)
	hypertriglyceridaemia	3.4% (N=5/148)

	prolonged activated partial thromboplastin time prolonged prothrombin time prolonged thrombin time	1.4% (N=2/148) 1.4% (N=2/148) 1.4% (N=2/148)

*includes abdominal pain, pain in extremity, musculoskeletal pain, chest pain, arthralgia

2.10.3 *Safety overview*

2.10.3.1 Pain-related AEs and intravenous morphine use

The main expected toxicity of ch14.18 antibody treatment is related to neuropathic pain symptoms. In studies APN311-303 and -202, pain self-assessment was performed using specific paediatric scales (e.g., Wong-Baker Faces Pain Rating Scale or Faces Pain Scale – Revised).

Pain assessment: The total number of patients with at least one documentation of pain in each treatment cycle is provided for the continuous infusion studies APN311-303 and -202, using a dosage of 10 mg/m^2/day (Table 48). In these studies, around 90% of the patients experienced pain in cycle 1. The percentage of patients with pain decreased in subsequent treatment cycles, to about 60% in cycle 5 (Table 49).

Table 48: Total number of patients with pain at any day of the cycle

Cycle	APN311-303		APN311-202	
	N	Patients with pain n (%)	N [1]	Patients with pain n (%)
Cycle 1	54	49 (90.7%)	24	21 (87.5%)
Cycle 2	53	36 (67.9%)	25	17 (68.0%)
Cycle 3	49	36 (73.5%)	20	9 (45.0%)
Cycle 4	41	29 (70.7%)	18	12 (66.7%)
Cycle 5	38	22 (57.9%)	17	10 (58.8%)

N = number of patients with pain assessment, NA = not applicable

[1] Patients with pain based on parent assessment score

Table 49: Occurrence of pain-related events reported by investigators and parents by cycle

Cycle	Pooled pain events		Parent assessement	
	APN311-202 (N = 44) n/N* (%)	APN311-303 (N = 54) n/N* (%)	APN311-202 (N = 44) n/N# (%)	APN311-303 (N = 54) n/N# (%)
Cycle 1	29/44 (65.9)	51/54 (94.4)	21/24 (87.5)	49/54 (90.7)
Cycle 2	20/40 (50.0)	27/53 (50.9)	17/25 (68.0)	36/53 (67.9)
Cycle 3	10/32 (31.3)	24/51 (47.1)	9/20 (45.0)	36/49 (73.5)
Cycle 4	14/31 (45.2)	14/42 (33.3)	12/18 (66.7)	29/41 (70.7)
Cycle 5	9/29 (31.0)	13/39 (33.3)	10/17 (58.8)	22/38 (57.9)

N= number of patients in category, N*= number of patients exposed to dinutuximab beta, N#= number of patients with assessment

Intravenous morphine use: Intravenous morphine is generally used in ch14.18 treatment to prevent expected severe pain events. The proportion of patients requiring i.v. morphine in the continuous infusion studies decreased over the cycles but much more in study APN311-303 (from 96 to 11%, Figure 11) than in study APN311-202 (from 100 to 72%, Figure 12).

Figure 11: Use of morphine in study APN311-303

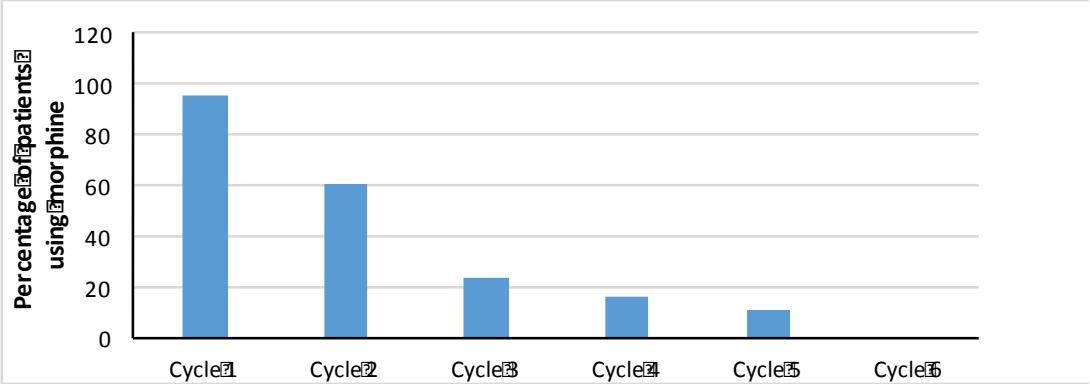
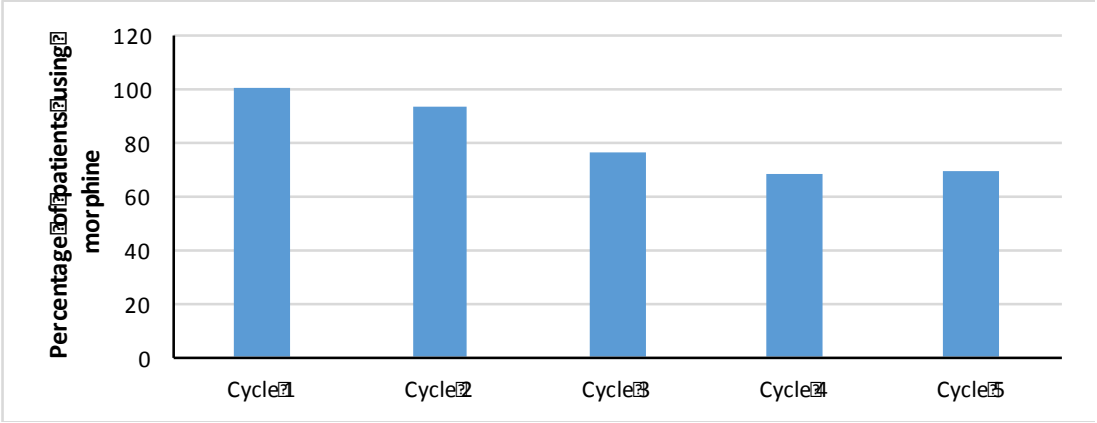


Figure 12: Use of morphine in study APN311-202



The mean morphine dose also declined over cycles, especially in the continuous infusion studies (Table 50).

Table 50: Intravenous morphine use (mean) per cycle in patients receiving morphine

Cycle	APN311-303		APN311-202	
	N	Cumulative morphine dose (mg)	N	Cumulative morphine dose (mg)
Cycle 1	48	54.0	44	41.5
Cycle 2	30	33.2	38	35.5
Cycle 3	11	35.7	26	33.5
Cycle 4	7	17.8	22	30.0
Cycle 5	4	26.9	21	26.7

[1]All patients receiving dinutuximab beta treatment received morphine.

N = number of patients with morphine use, NA = not applicable.

Pain medications other than morphine were allowed in most studies. These included gabapentin, acetaminophen, NSAID, ketamine and fentanyl patches (a morphine analogue). In study APN311-303, several patients (44/54; 81%) received prophylactic naloxone, which is often used to counteract the effects of morphine.

2.10.3.2 Hypersensitivity reactions

In the continuous infusion studies APN311-202 and -303, infusion-associated and allergic reactions were reported in 73% and 89% of the patients, respectively. Most were of mild or moderate severity. Grade 3 reactions were reported in 18% and 17% of the patients, respectively. No grade 4 reaction was reported. Their incidence decreased from cycle 1 (52% and 74%, respectively) to cycle 5 (29% and 41%, respectively).

Manifestations included hypotension (45% and 63%, respectively), facial, periorbital or lip oedema (2% to 44%), bronchospasm (14% and 11%, respectively), urticaria (23% and 24%, respectively) and rashes (20% and 31%, respectively). The rate of

hypotension, however, needs to be interpreted with caution as hypotension is a common complication of iv morphine, non-steroidal anti-inflammatory drugs and antihistamines, which – at least in early treatment cycles- virtually every patient received as concomitant medication.

In study APN311-302, skin allergies were reported in 55% of the patients in the arm without IL-2 and 65% of patients in the arm with IL-2.

Across all studies, 46 serious infusion-associated and allergic reactions were reported in 34 patients (7%). Reactions reported by more than 2 patients included hypersensitivity (18 patients), hypotension (7 patients), anaphylactic reaction (5 patients), and bronchospasm (4 patients). All resolved with the exception of bronchospasm/laryngospasm, and acute respiratory distress syndrome, further complicated by pneumonia and sepsis in one patient (dinutuximab beta alone), who eventually died of multi-organ failure during cycle 3.

In the total safety database, only 6 patients (1.2%) had a coded anaphylactic reaction/shock, definitely diagnosed by the investigator. Following CHMP request, a comprehensive search using PTs terms suggestive of an anaphylactic reaction according to literature consensus, chronology and treatment with adrenaline resulted in 16/148 patients (from studies APN311-101, -201, -202, -303), i.e. 11% overall and 6/148 (4%) with serious reactions. The last figure is consistent with an incidence of 12/366 (3%) in study APN311-303.

2.10.3.3 Hypoxia/respiratory distress

In the continuous infusion studies APN311-202 and -303, hypoxia/respiratory failure were reported in 43% and 44% of the patients, respectively. They were mostly grade 1 or 2. The majority occurred in the first two cycles.

Overall, there were 12 serious hypoxia/respiratory distress events in 11 patients; only 4 cases were reported in study APN311-302 (3/4 without IL-2), one of which was eventually fatal (see **death section**). Most SAEs led to interruption or discontinuation of treatment.

2.10.3.4 Cytokine release syndrome (CRS)

Ten episodes of CRS in 8 patients had been coded by the diagnosis CRS or SIRS and 70 sequences of events were considered as possible episodes of CRS. Therefore, in summary 80 episodes of CRS were identified. The majority of events (95%) were graded as mild to moderate CRS was reported in 36% and 56% of the patients in studies

APN311-202 and -303, respectively. Most episodes occurred during the first treatment cycle of dinutuximab beta. In the following cycles the incidence of CRS gradually decreased. The majority of events (95%) were graded as mild or moderate and no life-threatening event was observed during the episodes of CRS. In study APN311-302, CRS occurrence was only slightly increased by the addition of IL-2: 27% of the patients in the arm without IL-2 and 35% of patients in the arm with IL-2. Their frequency decreased over cycles. Half of CRS events were grade 1 while 10% were severe (grade 3-4).

2.10.3.5 Capillary leak syndrome (CLS)

A specific analysis was conducted to identify patients who experienced the full clinical picture of CLS including the main symptoms of fluid extravasation (oedema), hypoalbuminemia, haemoconcentration, and/or hypotension. Variable rates of CLS were reported across studies reflecting the lack of standardisation in data reporting and emphasis on this particular ADR, e.g. 36% in study APN311-202 and 83% in study -303. More than half of the events occurred in the first cycle and their incidence gradually decreased over cycles; 10% of the events were reported as serious and 18% as severe (grade 3-4) with 2 events being life-threatening.

IL-2 is well known to induce CLS and, in study APN311-302, CLS occurrence was doubled by the addition of IL-2: 25% of the patients in the arm without IL-2 and 50% of patients in the arm with IL-2. Their frequency decreased over cycles and 10% of the events were severe (grade 3-4) overall, but more with IL-2 (12%) than without IL-2 (7%).

2.10.3.6 Neurological disorders

Potentially severe reactions to ch14.18 treatment include neurological disorders of the eye, based on binding of the antibody to optic nerve cells.

In the continuous infusion studies APN311-202 and -303, neurological eye disorders were reported in 23% and 28% of the patients, respectively. These figures are consistent with the eye toxicities reported in study APN311-302: 18% without IL-2 vs 25% with IL-2. Mydriasis and accommodation defects with blurred vision were the most common manifestations. Two grade 4 cases were reported, ophtalmoplegia (which resolved after 10 months) and optic atrophy.

Across all studies, SAEs related to neurological eye disorders were reported in 3% of the patients. They were resolving or resolved, some with sequelae.

In the continuous infusion studies APN311-202 and -303, both motor and sensory neuropathies were reported with an incidence of 9% and 5%, respectively. These figures are consistent with the peripheral neurotoxicities reported in study APN311-201 (9%) and in study APN311-302: 7% without IL-2 vs 14% with IL-2. Most events were of grade 1-2 and resolved; two patients discontinued treatment.

2.10.3.7 Infections

In the continuous infusion studies APN311-202 and -303, infections were reported in 61% and 76% of the patients, respectively. These figures are consistent with the infections reported in study APN311-302: 58% without IL-2 vs 72% with IL-2.

However, severe infections (grade 3-4) were more frequent in study APN311-202 (50% of patients) compared to 15% in study APN311-303. The reason for this finding is unknown. However, study ANP311-202 allowed outpatient treatment with dinutuximab beta if treatment was well tolerated, which may lead to delayed diagnosis and eventually to delayed treatment. The great majority of grade 3 events were device-related infections and more than half of these patients were treated at the same centre. Of note, device-related infections are well-known and frequent complications of central venous catheterization and are thus presumably rather related to the catheter than to dinutuximab beta administration. Nevertheless, one patient died of septic shock, which was attributed to delayed antibiotic treatment; this outpatient presented with repeated fever episodes and was subsequently hospitalised. It does not seem that, in this case, home treatment could be directly incriminated in the delayed antibiotic therapy, but rather the fact that the patient was not followed in a specialised environment.

Of note, IL-2 did not increase the serious infection rate in study APN311-302: 8% without IL-2 vs 10% with IL-2. Overall, three patients died of infectious complications (see **death section**).

2.11 *Ongoing studies*

The ongoing studies are presented in Table 51.

Table 51. Dinutuximab beta Apeiron ongoing studies

Study code	Study title	Patient setting	Design	Co-treatment	Assessment
APN311-201	Haplo study	Relapsed/refractory	Open-label, uncontrolled, multi-centre	IL-2 (cycles 4-9)	Safety, efficacy, pharmacodynamics
APN311-301/302	High-risk study	High-risk naive patients	Open label, randomized, controlled, multi-centre	301: cis-RA 302: cis-RA+IL-2	Safety, efficacy

APN311-304	Single agent study	Relapsed/refractory	Open-label, uncontrolled, single centre	None	Safety, efficacy

In order to further investigate the benefits of Dinutuximab beta Apeiron in the treatment of high-risk neuroblastoma a drug registry (SAFARY) has been proposed by the EUSA Pharma. The objective is to collect more data on pain and its management, effect on peripheral and central nervous system, including visual impairment, long-term safety as well as short- and long-term effectiveness.

2.12 *Innovation*

Until 2010, standard maintenance treatment after consolidation consisted of oral isotretinoin for 6 months, given with the aim of differentiating any remaining neuroblasts (Matthay et al., 1999). Since 2010, with the publication of results from Yu et al. (Yu et al., 2010), some form of anti-GD2 antibody therapy has been included in maintenance therapy, and it is now considered the standard of care in many parts of the world. Indeed, GD2 is highly expressed by neuroblastoma cells, and the tumour-selective expression of this molecule makes GD2 an attractive target for tumour-specific immunotherapy. Dinutuximab beta is a mAb directed against GD2, and compared to other mouse-human chimeric monoclonal IgG1 antibody it is produced in the Chinese hamster ovary (CHO) cells. These cells are virus free and are considered to be an up-to-date standard for the production of recombinant proteins for clinical trials. Furthermore, this production cell line leads to a different glycosylation pattern associated with a reduction in hypersensitivity and allergic reactions compared to other anti-GD2 mAbs expressed in the SP2/0 cell line. Indeed, patients treated with dinutuximab expressed in SP2/0 cells reported allergic/anaphylactic reactions as the most common adverse events: Of the 798 patients treated with dinutuximab, 81.1% reported an allergic reaction-related event. Of these cases, 29% were reported as severe (Grade 3-4) and 18% as anaphylactic reactions. The risk of allergic/anaphylactic reactions as well as prerequisite of pre-/concomitant treatment with anti-histaminic drugs has been extensively outlined also in the summary of product characteristics (SmPC) of dinutuximab. In contrast, safety data of dinutuximab beta demonstrate a clearly reduced potential for allergic reactions when compared with the published data of dinutuximab. Of the 514 patients treated with dinutuximab beta, 20% reported an allergic reaction-related event (including 0.8% with anaphylactic reactions). 6% were reported to have severe (Grade 3-4) allergic reaction-related event.

The majority of clinical data of Dinutuximab beta Apeiron exists for its use in combination with IL-2, 13-cis RA, but studies are ongoing to prove Dinutuximab beta Apeiron's efficacy when used as single agent treatment for neuroblastoma patients.

The biggest difference thus is that even a in case Dinutuximab beta Apeiron will be used in a combination treatment setting, all concomitant medications needed are authorized in the EU unlike in the case of other dinutximab products. Since GM-CSF is not part of the therapeutic regimen with dinutuximab beta and the fact that each additional drug causes more adverse event it can be clearly stated that the prevention of each additional medication is per definition superior regarding safety, especially when considering the fact that one of the concomitant medications is not authorized in the EU. In the first-line setting the Applicant has also demonstrated that co-administration of IL-2 is not superior compared to administration of the antibody alone in terms of efficacy, thus dinutuximab beta without this cytokine or others like the GM-CSF would ameliorate the toxicological profile of the treatment.

Dinutuximab beta Apeiron's main benefit stands in its continuous infusion scheme, which shows major improvements of the safety profile by reducing pain and associated i.v. morphine use. This, together with the possibility of receiving the treatment in outpatient setting, will facilitate patients remaining

on therapy and receiving the full cycle of treatment, thereby optimizing the possibility of long-term benefits.

2.13 *Interpretation of clinical effectiveness and safety evidence*

2.13.1 *Statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

APN311-302: High-risk neuroblastoma patients

The study includes an immunotherapy phase which evaluates if IL-2 given together with dinutuximab beta improves the outcome of high-risk neuroblastoma patients compared to treatment without IL-2. A total of 370 patients were evaluable for the efficacy analysis consisting of 63.8% male and 36.2% female patients with a mean age of 3.7 years (range: 0.6 to 20.0 years). The primary endpoint, the estimated 3-year EFS with and without IL-2 treatment, was 61.2% and 55.4%, respectively, which both represent a marked improvement over differentiation therapy with 13-cis-RA alone (3-year EFS of 46% (Matthay et al., 1999)). Addition of s.c. IL-2 did not significantly improve EFS at 3

years. The results were similar to those found with standard triple therapy i.e. 63% as reported in the pivotal registration study for dinutuximab in neuroblastoma patients treated with ch14.18/SP2/0, GM-CSF, and IL-2 in addition to 13-cis-RA.

Considering only patients without evidence of disease at baseline, the 3-year EFS in the APN311-302 study was 53.8% with and 45.9% without IL-2. Secondary endpoints confirm results seen with the primary outcome. The EFS rate for the FAS population at 2 years was 61.6% and 58.1%, respectively with and without IL-2. Compared with the 2-year EFS of 48% in patients treated with 13-cis-RA alone (CHMP, 2017), this further confirms the clinical benefits of ch14.18 treatment. Overall survival at 3 years was 72.2% with and 71.0% without IL-2 treatment.

Nearly all patients experienced hematological toxicities that often reached severe intensity. These frequent abnormalities may be at least partially related to the preceding myeloablative chemotherapy. Other common toxicities were infections and/or fever, skin toxicities including allergy, and toxicities related to the patients, general condition. Toxicities occurred generally more frequently with IL-2 treatment, in particular capillary leak syndrome was reported markedly more often in patients receiving IL-2 than in patients not receiving IL-2. IL-2 treatment more frequently led to dose reductions and premature discontinuation of treatment. The number of patients who received at least 50% of the planned doses of dinutuximab beta and IL-2 (if applicable) was markedly reduced with IL-2 as compared to no IL-2 treatment (respectively, 39% vs 78% of patients). Also the incidence of treatment-emergent SAEs was considerably increased when patients received IL-2 in addition to treatment with 13-cis-RA and dinutuximab beta. In the groups with and without IL-2 treatment, respectively 46% and 27% of patients had at least 1 SAE reported. Most of the treatment emergent SAEs resolved.

In conclusion, the study showed that treatment with dinutuximab beta in addition to 13-cis-RA has beneficial clinical effects in patients with neuroblastoma when compared with published outcomes of patients receiving 13-cis-RA only. Furthermore, immunotherapy with dinutuximab beta led to similar clinical outcomes than treatment with standard triple therapy i.e. ch14.18/SP2/0, IL-2 and GM-CSF. Addition of IL-2 to dinutuximab beta did not show further substantial clinical improvements in the present study. However, IL-2 treatment increased the occurrence of toxicities and reported SAEs, which negatively affected treatment completion.

<u>APN311-202 & APN311-303 Pooled: Relapsed and refractory patients</u>

Relapsed and refractory patients have historically been treated with a variety of other therapeutic options, including ^{131}I-mIBG radiotherapy, IL-2, and various

chemotherapeutic options, identified through the systematic literature review (**Section 2.8**).

No study has been performed to provide head-to-head data for ^{131}I-mIBG versus Dinutuximab beta Apeiron, but if compared indirectly, the ^{131}I-mIBG EFS outcomes are numerically lower by approximately 24% to 42% when compared to studies of Dinutuximab beta Apeiron effectiveness in relapsed/refractory patients, which have reported 1-year EFS ranges of 42.1-44.8% and 58.2-60.0% (ranges from APN311-202 and 303 clinical results) for relapsed and refractory patients respectively.

Similarly to ^{131}I-mIBG radiotherapy, no study has been performed to provide head-to-head data for various chemotherapy regimens versus dinutuximab beta Aperion, used as second-line treatment in R/R patients. An indirect qualitative comparison of this evidence with EFS outcomes reported for Dinutuximab beta Apeiron in relapsed/refractory patients suggests a higher efficacy of Dinutuximab beta Apeiron, for which numerically higher EFS rates have been observed at any comparable time point (42.1-60% for 1-year EFS, 36.8-55.7% for 2-year EFS, and 36.8-44.6% for 3-year EFS; see detailed results in **section 2.8**)

Finally, no study has been performed to provide head-to-head data for IL-2 administration alone versus Dinutuximab beta Apeiron. A single study (Pession et al., 1998) with 17 patients reported 2-year EFS and OS of 67% and 92%, respectively, for treatment with IL-2 alone as a second-line therapy for R/R neuroblastoma patients. An indirect comparison to APN311-202 and 303, shows that 2-year EFS ranged from 31.0-36.8% and 29.1-55.7% for relapsed and refractory patients, respectively. In this case, treatment with Dinutuximab beta Apeiron did not demonstrate superiority, but this may be due to differences in patient demographics, disease biology, and low patient numbers from the Pession study.

With regards to the historical controls (from (Garaventa et al., 2009) or HRNBL1 R1), Dinutuximab beta Apeiron demonstrated significant improvement in relapsed patient OS compared to the historical treatments (without immunotherapy). 3-year OS was 50% for treatment with Dinutuximab beta Apeiron compared to 24-28% in the historical control populations.

<u>APN311-303:</u>

Immunotherapy with short-term infusion of dinutuximab has been shown to effectively prolong survival in high-risk neuroblastoma patients (Yu et al., 2010). The CU-LTI program introduced a novel treatment approach by administering dinutuximab beta as a

long-term continuous (24 hours) infusion over 10 days instead of short-term infusions given daily for 8 hours, aiming to reduce toxicity and maintain immune modulation. Pain is known to occur with administration of ch14.18 antibodies.

The primary objective of this retrospective data analysis was to evaluate safety, especially reductions in treatment-related pain, in accordance with the novel long-term administration scheme of dinutuximab beta. Further on, efficacy analyses (response evaluation), event-free survival and overall survival were evaluated. A total of 54 patients were treated in the CU-LTI program. Out of these, 30 patients presented with relapsed neuroblastoma and 15 with refractory neuroblastoma. Nine patients had received first-line therapy for high-risk neuroblastoma, out of these, 3 had residual disease prior to immunotherapy and 6 had no evidence of disease.

Treatment-related pain was significantly reduced after the first cycle in this continuous infusion study. In general, the percentage of patients with pain was decreasing across the treatment cycles, in particular from cycle 1 to cycle 2. Mean pain intensity during treatment was also decreasing throughout each cycle. To alleviate treatment-related pain, i.v. morphine is usually required at high doses. In this retrospective analysis it was observed that the number of patients with i.v. morphine use dropped simultaneously with the decrease in pain. From the patients receiving 5-week cycles and receiving i.v. morphine in cycle 1, only about 10% were receiving i.v. morphine in cycle 5. None of these patients received i.v. morphine in cycle 6. In comparison, Yu et al. (2010) reported a rate of 52% for the incidence of neuropathic pain during ch14.18/SP2/0 treatment. Similarly, capillary leak syndrome (13%), fever (9%), hypotension (4%), and diarrhea (8%) of Grade 3 or 4 occurred at lower rates in the CU-LTI program compared to those reported by , Yu et al. (2010) (23%, 39%, 18%, and 13%, respectively).

In accordance with the reduced pain and related morphine use requirements, a high percentage of patients were able to continue dinutuximab beta infusion in an outpatient setting. The most frequent AEs observed in the CU-LTI program were related to pain (pain, abdominal pain, pain in extremity), gastrointestinal disorders (constipation, vomiting, diarrhea), and skin disorders (pruritus, dry skin). Other frequent AEs were pyrexia, capillary leak syndrome, hypotension, and cough.

Capillary leak syndrome is generally known to often occur with IL-2 treatment. In this study, capillary leak syndrome occurred most frequently with onset of dinutuximab beta / IL-2 combination treatment on Day 8 of a cycle, indicating that particularly the interaction of dinutuximab beta treatment with IL-2 treatment promotes capillary leak. Interestingly, capillary leak syndrome tended to resolve shortly after cessation of IL-2 treatment,

despite ongoing dinutuximab beta treatment, often within one day. This result suggests that capillary leak syndrome may not be an adverse reaction to dinutuximab beta treatment itself.

Patients included in the CU-LTI program with relapsed or refractory neuroblastoma had a 2-year OS rate of 69.0% and 69.8%, respectively. One-year OS rates were 89.7% and 92.9%, respectively. In comparison, patients included in the International Neuroblastoma Risk Group (INRG) database, who were diagnosed between 1990 and 2002 and had experienced relapse or progression, had a post-event 2-year OS of about 28% and a 1-year OS of about 40%.

In conclusion, long-term infusion of dinutuximab beta in combination with IL-2 and 13-cis RA treatment was shown to be tolerable with an improved pain-toxicity profile that enabled an outpatient setting. Treatment response in the 37 evaluable patients with evidence of disease who reached end of treatment amounted to 32.5% (8.1% CR, 24.3% PR), indicating antitumour activity. 1- and 2-year OS rates after long-term infusion of dinutuximab beta were higher than those previously reported for these patient populations. Overall, the results indicate a clinically meaningful therapeutic effect for continuous infusion treatment of dinutuximab beta, both based on response rates and OS results.

APN311-202:

This was an interim analysis from data collected in the SIOPEN long-term dinutuximab beta infusion (LTI) study, a phase I/II dose schedule finding study of dinutuximab beta continuous infusion combined with s.c. IL-2 in patients with primary refractory or relapsed neuroblastoma. In this interim analysis, the first 44 patients enrolled in the study were evaluated.

Out of the 44 patients, 25 patients presented with refractory neuroblastoma and 19 with relapsed neuroblastoma. Twelve patients had no evidence of disease at immunotherapy baseline. All 44 patients enrolled were evaluable for efficacy and safety analyses.

In the current study the dose schedule of 100 mg/m^2/cycle, which was already confirmed in previous trials, was used as a starting point. In the dose schedule finding part of this study the 100 mg/m^2/cycle, administered as a 10-day dinutuximab beta infusion schedule of 10 mg/m^2/day was confirmed as safe and efficacious. This was the only dose schedule evaluated in an extended group of 24 patients in the first stage. This dose schedule was used for further evaluation during the second, confirmatory phase of the

study to treat an expansion cohort of 100 patients for 5 treatment cycles, each of 35 days. Twenty patients of the confirmatory cohort were included in this interim analysis.

Overall, 1-year and 2-year EFS rates were 50.9% and 44.9%, respectively. Higher EFS rates were found in patients with refractory neuroblastoma as compared to relapsed neuroblastoma (1-year EFS: 57.8% vs. 42.1% and 2-year EFS: 53.0% vs. 36.1%, refractory vs relapsed, respectively).

In conclusion, a 10-day infusion schedule of 10 mg/m^2 dinutuximab beta (total dose 100 mg/m²) in combination with IL-2 and 13-cis RA treatment was shown to be tolerable with a reduced pain-toxicity profile of dinutuximab beta whilst maintaining immunomodulatory efficacy in patients with either primary refractory or relapsed neuroblastoma. This enabled at least parts of the treatment to be applied in an outpatient setting.

2.13.2 *Discussion of the strengths and limitations of the clinical evidence base for the technology*

The evaluation of safety is hampered by the absence of controlled trials without dinutuximab and by the heterogeneity of data collection across the academic trials. However, the safety profile of anti-GD2 antibodies is already known from the literature. It should be emphasized that the method of AE collection varied across studies. In particular, the largest study (APN311-302) only SAEs were fully reported while for other AEs, a pre-defined list of 31 specific toxicities was used. The SAE incidence in study APN311-303 was much lower than in the other R/R studies. The data set on the clinical safety of Dinutuximab beta Apeiron under normal conditions of use could not be considered comprehensive due to the absence of any randomised head-to-head comparison with a placebo. Furthermore, the method of data collection in the largest data set (study APN311-302) was incomplete as only SAEs were fully reported while for other AEs, a pre-defined list of 31 specific toxicities was used. However, it is not considered feasible to generate a comprehensive data set due to ethical considerations preventing the conduct of a randomised placebo-controlled trial. At the time of this report, dinutuximab is standard of care in the treatment of high-risk neuroblastoma, whereby neither physicians nor patients would be prepared to participate in a placebo-controlled trial.

In the relapsed/refractory setting, 1-year, event-free survival (EFS) was 52% in both studies and overall survival (OS) was 89% and 92%, respectively. At 2-year, EFS was lower in study APN311-303 (35%) than in study APN311-202 (47%) while the opposite trend was observed for OS: 75% and 63%, respectively.

In the first-line setting for high-risk neuroblastoma, APN311-302 provided survival data with and without the addition of IL-2. The 3-year EFS (primary endpoint) showed rates of 55% without IL-2 and 61% with IL-2 while the 3-year OS rates were 64% and 69%, respectively.

For patients categorized as high-risk disease and for those with low or intermediate risk disease that do not respond or have relapsed on appropriate front-line treatment, there is still an unmet medical need. The efficacy of Dinutuximab beta Apeiron is supported by anti-tumour response at the end of the treatment cycles and overall survival compared to historical controls, given that since 2009, it was not possible to conduct randomised studies with a placebo control arm. The studies discussed above represent the population and treatments that are relevant to the NICE decision problem and clinically meaningful outcomes to patients (ie, improvements in survival; Section 3.6.2).

Table 52: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Children diagnosed with high-risk neuroblastoma have a poor prognosis. Based on the historical controls included in this submission (the Italian Neuroblastoma Registry from 1979 to 2006 (Garaventa et al., 2009) and the SIOPEN HRNBL1 in an earlier phase (R1, 2002-2010)), survival in both relapsing and high-risk patients is expected to be shorter than 2 years. Indeed, the median survival for relapsing patients who did not receive immunotherapy (Garaventa control) was 318 days. Similarly, for high-risk patients included in the SIOPEN HRNBL1 study and who did not receive immunotherapy (R1 control), the median survival was 629 days.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Immunotherapy with dinutuximab beta and 13-cis RA with or without IL-2 has shown to provide statistically significantly better OS for patients with high-risk neuroblastoma as compared to patients receiving standard of care treatment without immunotherapy. **Study APN311-303 and -202:** 54.2% of the patients died in the APN311-202 + APN311-303 group compared to 86.2% patients in the historical control group (Garaventa study). Median OS time was longer in APN311-202+ APN311-303 patients compared with the historical control patients (1254 days vs. 318 days, respectively). Most of the relapsed patients of the APN311-202+APN311-303 group survived the first year and 50% of the patients survived until the third year (1-year, 2-year, and 3-year OS rates of 83%, 60% and 50%, respectively). Of the relapsed patients from the Garaventa study included in this analysis, less than 50% survived the first year and only 24% survived the third year (1-year, 2-year, and 3-year OS rates of 45%, 31% and 24%, respectively). The difference in OS was statistically highly significant (p = 0.0031), in favour of dinutuximab beta. The same trend was observed by comparing these two studies vs the historical control R1. The median OS was substantially longer in patients in the combined APN311-202+APN311-303 group (1254 days) than in the historical control R1 (630 days). In addition, yearly OS rates were clearly higher than in the historical control R1 group. OS in the APN311-202 + APN311-303 combined group was 83% at 1 year, 60% at 2 years and 50% at 3 years, compared to 56%, 46% and 28%, respectively, in historical control R1. **Study APN311-302:** A lower percentage of patients died in the MAT+immunotherapy group compared with the historical control who did not receive immunotherapy (31.3% vs 52.9%, respectively). The vast

	majority of the patients in the MAT+immunotherapy group survived the first year and more than 70% of the patients survived the third year (1-year, 2-year, and 3-year OS rates of 89%, 78% and 71%, respectively). Of the MAT patients, the majority survived the first year, but only 59% survived the third year (1-year, 2-year, and 3-year OS rates of 83%, 69% and 59%, respectively). These differences were statistically significant ($p<0.0001$) in favour of dinutuximab beta.

3. Cost effectiveness

3.1 *Published cost-effectiveness studies*

A comprehensive search of the peer-reviewed literature was conducted to identify and select relevant cost-effectiveness studies, however, no pertinent studies relating to cost-effectiveness models assessing the course and treatment of neuroblastoma were identified (Table 53). Full details of the search strategy and results are provided in **Appendix G**.

Table 53: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
No pertinent studies relating to cost-effectiveness models assessing the course and treatment of neuroblastoma were identified via a comprehensive search of peer-reviewed literature.						
Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio						

3.2 *Economic analysis (de novo analysis)*

A de novo economic model is included in the submission because following a systematic literature review, no studies were identified that were related to cost-effectiveness models assessing the course and treatment of neuroblastoma.

3.2.1 *Patient population*

The indication for use of Dinutuximab beta Apeiron within the UK is for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first-line therapy, Dinutuximab beta Apeiron should be combined with interleukin-2 (IL-2).

Two exclusive models have been implemented, one for the high-risk first-line population and one for the patients with history of relapsed or refractory neuroblastoma. They follow the same structure and most of the assumptions are the same. Any difference between the two models will be explicitly mentioned within this document.

Considering the indication, and taking into account the following references in Table 54, we estimated a target patient population for Dinutuximab bet Apeiron of 41 patients.

Table 54: Target treatment population size estimate

UK treatment population calculation				
	#	**Reference**		
Total number of neuroblastoma patients in UK	11,530,789×9.1 cases/10^6 = **105**	1) *(Spix et al., 2006)*: 9.1 cases per million population (1988-1997) 2) *(UK Office for National Statistics)*, 2015 UK population ages 0-14: 11,530,789		
High-risk neuroblastoma				
	%	**#**	**Reference**	**Comments**
High-risk patients	36	38	(Cohn et al., 2009)	INRG task force reporting worldwide neuroblastoma data (n=8,800)
Rate of MRD patients	52	20	(Kushner et al., 2014)	Complete response and very good partial response
Rate of refractory patients	38	14	(Kushner et al., 2014)	Partial response, mixed response and No response
Very low/low-risk neuroblastoma				
	%	**#**	**Reference**	**Comments**
Very low/low-risk patients	55	58	(Cohn et al., 2009)	55% (28.2%+26.8%)
Relapse rate of very low/low-risk patients	10%	6	(Bagatell et al., 2009)	EFS 90% →10% relapse; EFS includes relapse and refractory patients
Intermediate-risk neuroblastoma patients				
	%	**#**	**Reference**	**Comments**
Intermediate-risk patients	9	9	(Cohn et al., 2009)	
Relapse rate of intermediate risk patients	12	1	(Baker et al., 2010)	EFS for all intermediate-risk patients reported is 88.2%
Dinutuximab beta Apeiron Target Population				
	%	**#**		
High-risk MRD patients	18.7	20		
High-risk refractory patients	13.7	14		
Very low/low-risk R/R patients	5.5	6		
Intermediate-risk R/R patients	1.1	1		
Total	**39.0%**	**41**		

3.2.2 *Model structure*

Within the first 5 years after starting treatment the model uses a partitioned survival approach, which is a frequently used analytic framework for evaluating oncology therapies. This approach enables accommodating risks that vary over time, based on survival data in clinical trials.

The model calculates the proportion of patients in different health states using parametric curves fitted to data on OS and EFS curves (Figure 13). Those mutually exclusive health states are: stable, failure and death. The stable state represents patients alive, without occurrence of an event as: relapse, progressive disease, or secondary cancer. The fraction of patients in this health state is calculated at any given time within the first 5

years based on parametric EFS curve. The failure state represents alive patients with occurrence of at least one of the events mentioned above and is calculated as the difference between OS and EFS. The death state is calculated as 1 – OS.

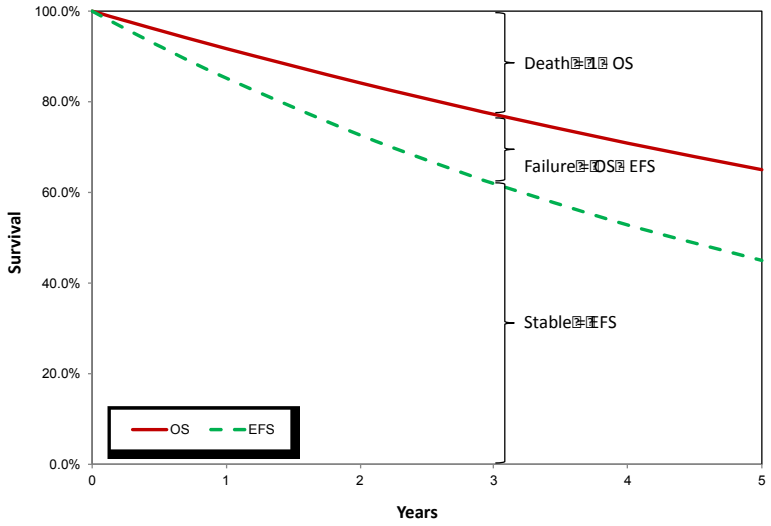


Figure 13: Partitioned survival model- health states with OS and EFS curves.

The three health states, defined in the model by OS and EFS curves, capture main health outcomes in the target population and together with associated costs enable appropriate health economic evaluation.

After 5 first years patients in the stable state are assumed to be neuroblastoma survivors despite the fact that some may relapse (extremely rare according to expert opinion). However, they do not follow the same survival rate as the general population, but suffer from a higher standardised annual mortality ratio of 5.6 (95% CI 4.4 to 6.9), based on a report from the Childhood Cancer Survivor Study (Laverdiere et al., 2009). Patients in this health state continue to use resources specific to neuroblastoma survivors and potential morbidities affecting quality of life are being accounted based on literature (Portwine et al., 2016, Rebholz et al., 2011).

After the 5-year threshold, the model assumes an increased probability of death of 90% in the failure health state (based on expert opinion) and continue with costs and HRQOL associated with the failure state (Barr et al., 1999, Rebholz et al., 2011).

To accurately reflect the treatment algorithms used during the treatment period, the partitioned survival uses cycles that correspond to the different treatment phases, expressed in weeks. These are 5 cycles, 5 weeks (35 days) each. Model cycle lengths correspond to the treatment phase lengths.

Beyond the end of the treatment phase (25 weeks), patients no longer receive Dinutuximab beta Apeiron therapy and the model has a yearly cycle.

Whenever possible, clinical trial data was used to populate the model and this was validated by expert opinion. We sought the advice of clinical experts to assess the applicability of the clinical parameters and to approximate some of the clinical parameters where relevant UK data was lacking.

No previous NICE technology appraisals was accepted for the same indication.

3.2.3 *Key features of the de novo analysis*

Table 55: Features of the de novo economic analysis

Factor	Chosen values	Justification
Time horizon	5-year post treatment initiation	Consistent with the 5-year EFS and OS estimates usually reported in the literature and clinical protocols
	Lifetime	NICE recommendation (National Institute for Health and Clinical Excellence, 2013)
Were health effects measured in QALYs; if not, what was used?	Health effects are measured in QALYs	NICE recommendation (National Institute for Health and Clinical Excellence, 2013)
Discount for utilities and costs	1.5% QALYs and 1.5% Cost	Dinutuximab beta Apeiron has been shown to extend the lives of some children with high-risk neuroblastoma or in patients that are relapsed/refractory.
Perspective (NHS/PSS)	NHS/PSS	NICE recommendation (National Institute for Health and Clinical Excellence, 2013)

Abbreviations: EFS, event-free survival; NHS, National Health Service; OS, overall survival; PSS, Personal Social Services; QALYs, quality-adjusted life years.

3.2.4 *Intervention technology and comparators*

The model evaluates clinical and economic outcomes with the use of immunotherapy (consisting of dinutuximab beta and isotretinoin) compared to standard therapy (isotretinoin) for the 1st line treatment. Historically, isotretinoin has been considered the reference treatment for maintenance therapy of high-risk neuroblastoma after demonstrating improved survival following high dose chemotherapy followed by

autologous bone marrow or stem cell transplantation (Matthay et al., 1999). Therefore, isotretinoin was chosen as the appropriate comparator.

In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first-line therapy, Dinutuximab beta Apeiron should be combined with interleukin 2 (IL-2). This is considered in the model as a 2nd line treatment and compared to a standard therapy in absence of immunotherapy: isotretinoin.

The treatment regimen details implemented in the model over the cycle of 5 courses (each 35 days long) for immunotherapy and standard therapy are consistent with the final scope of the submission. Please refer to Table 16 for regimen details.

Figure 14: Model diagram for the first-line population

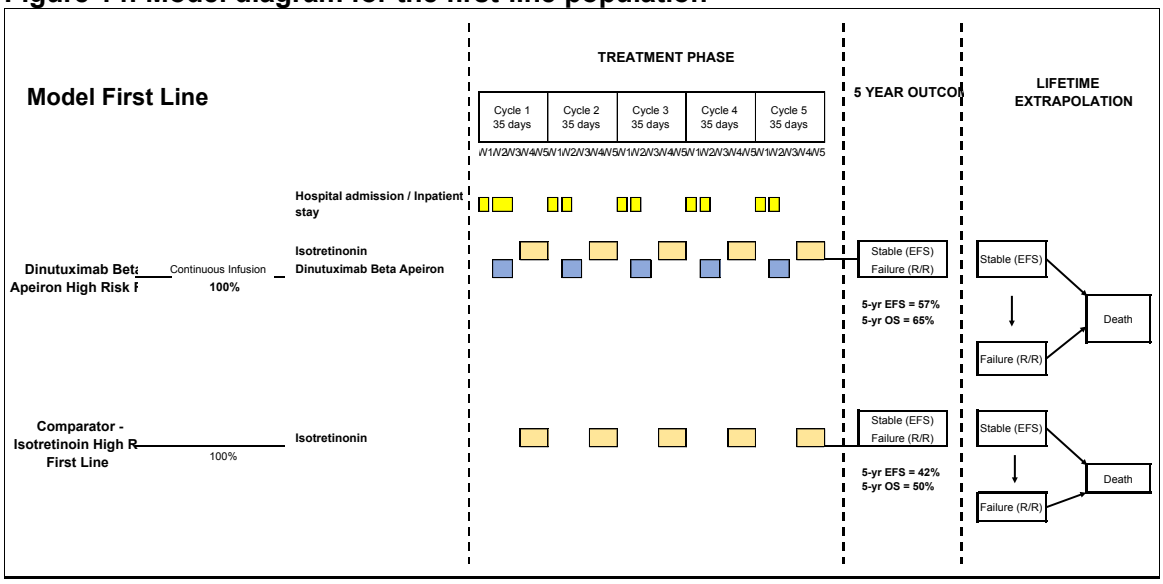
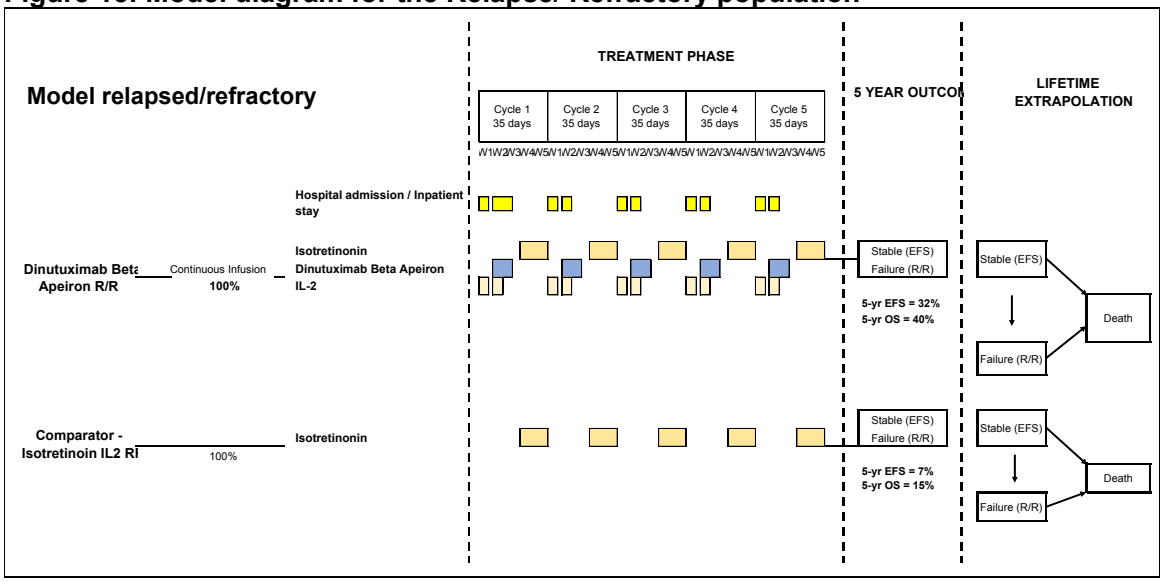


Figure 15: Model diagram for the Relapse/ Refractory population



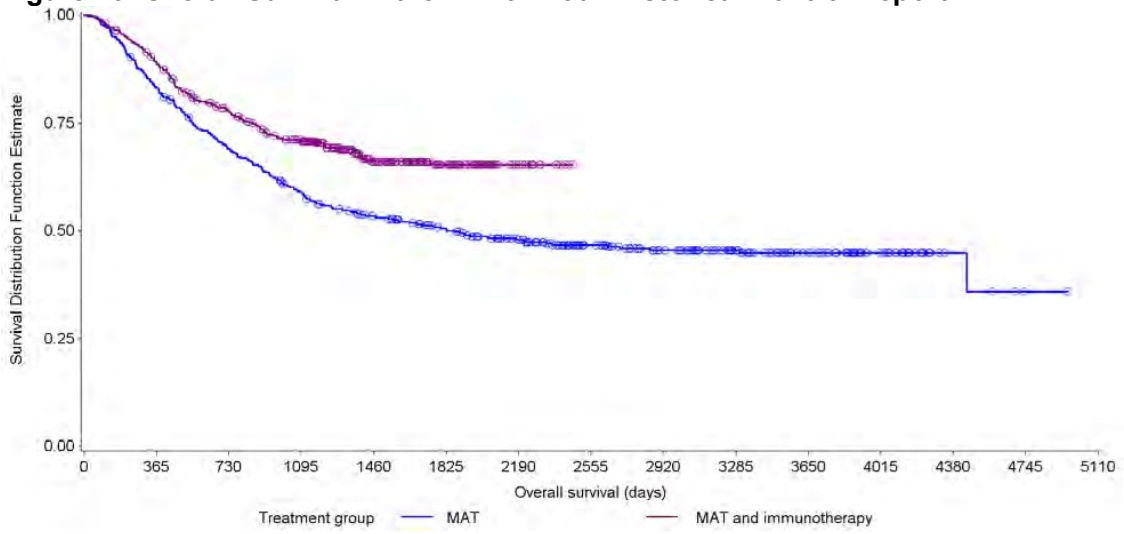
3.3 *Clinical parameters and variables*

3.3.1 *How are clinical data incorporated into the model?*

3.3.1.1 EFS and OS in APN311-302 studies

The 5-year OS estimates for the 1st line treatment was based on the APN311-302 Historical Control Report. In those studies, survival data were compared between patients who were solely part of the consolidation R1 randomisation with myeloablative therapy (MAT) therapy and patients from the R2 randomisation (reported as study APN311-302), who (after MAT) received immunotherapy with dinutuximab beta in addition to differentiation therapy with 13-cis-RA with or without IL-2 as maintenance therapy. The difference in OS between the MAT group and the MAT and immunotherapy group was statistically significant ($p < 0.0001$), in favour of MAT and immunotherapy. The 5 years Kaplan Meier estimate of Overall Survival was 0.5 and 0.65 for the MAT group and the MAT and immunotherapy group respectively (Figure 16).

Figure 16: Overall Survival in the APN311-302 Historical Control Report



EFS estimates in APN311-302 studies are provided up to year 3. Due to lack of clinical data for year 5, it is assumed that the absolute separation (in %) between OS and EFS curve at year 5 is of value of separation at year 3 (8%). This is a conservative assumption, as the separation between OS and EFS curves observed in the studies decreases year by year through available data timeline (expert opinion). This assumption is applied to both groups: the MAT group and the MAT with immunotherapy group.

Exponential regressions were applied to 5 year event free (EFS) and overall survival (OS) data. Therefore, a fixed instantaneous rate of event (transition to death, transition to failed health state) over time was assumed. This instantaneous event rate was computed as follows:

$$Rate = -[\ln(1-x)]/5$$

with x being the 5-year probability of the event (for example 10% for a 5-year EFS of 90%)

When extrapolating to a lifetime time horizon, beyond the 5 years modelled in the partitioned survival approach, stable health state (event-free) patients were considered neuroblastoma survivors despite the fact that some may relapse (extremely rare according to expert opinion) (expert opinion) and were subject to a higher standardised annual mortality ratio of 5.6, based on a report from the Childhood Cancer Survivor Study (Laverdiere et al., 2009) in respect to general mortality risk taken from the Office of National Statistics life table for England weighted by the male/female proportion reported in the APN311-302 study. No further transition to failure state was allowed for these patients in the model. Failure health state patients still alive at 5 years were also subject to elevated mortality risk of neuroblastoma survivors but additionally increased by 90% (i.e. x 1.9 x 5.6 general mortality; expert opinion). These patients could no longer transition to the stable (event-free) health state.

3.3.1.2 OS in APN311-303 Historical Control Report

Patients with a history of relapsed/refractory disease and patients who have not achieved a complete response after first-line therapy, have a lower OS than the 1st line patients. APN311-303 Historical Control Report provides Kaplan Meier curves for treatment and Historical Control by Garaventa et al. At 5 years, OS in the control group is 15% (observed value), while APN311-303 treatment group showed an OS rate of 40% (extrapolated estimate). As no EFS estimates for 5 year outcomes are provided, the same assumptions as described in **section 3.3.1.1** about OS and EFS separation was taken.

3.3.1.3 Dose of Dinutuximab beta Apeiron

Treatment with Dinutuximab beta Apeiron consists of 5 consecutive courses, each course comprising 35 days. The individual dose is determined based on the body surface area and should be a total of 100 mg/m^2 per course.

Two modes of administration are possible:

1. A continuous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m^2
2. or five daily infusions of 20 mg/m^2 administered over 8 hours, on the first 5 days of each course

For the purpose of the cost-effectiveness analysis and based on expert opinion, all UK patients will receive the product with a continuous infusion over the first 10 days to decrease cost for NHS and improve the safety profile (supposed reduced risk of hypersensitivity events).

When IL-2 is combined with Dinutuximab beta Apeiron for the 2nd line treatment, it should be administered as subcutaneous injections of 6×10^6 IU/m^2/day, for 2 periods of 5 consecutive days, resulting in an overall dose of 60×10^6 IU/m^2 per course. The first 5-day course should start 7 days prior to the first infusion of dinutuximab beta and the second 5-day course should start concurrently with dinutuximab beta infusion (days 1 to 5 of each dinutuximab beta course).

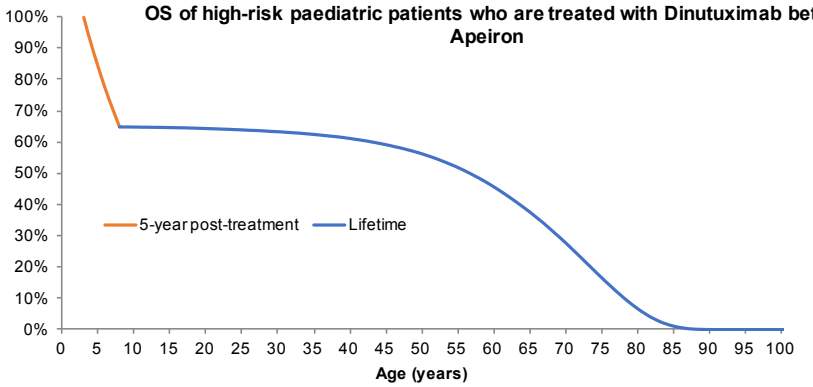
3.3.2 *Transition probabilities*

The partitioned survival approach does not use transition probabilities per se, but uses the survival curves to model the patient population evolution through the stable (EFS), failure (OS – EFS) and death (1 – OS) health states.

Illustrations of the survival functions are provided in

Figure 17 for the OS of high-risk patients (baseline age of 3 years) for the 1st line therapy and 1st line comparator.

Figure 17: Illustrations of survival curves for the first-line Population



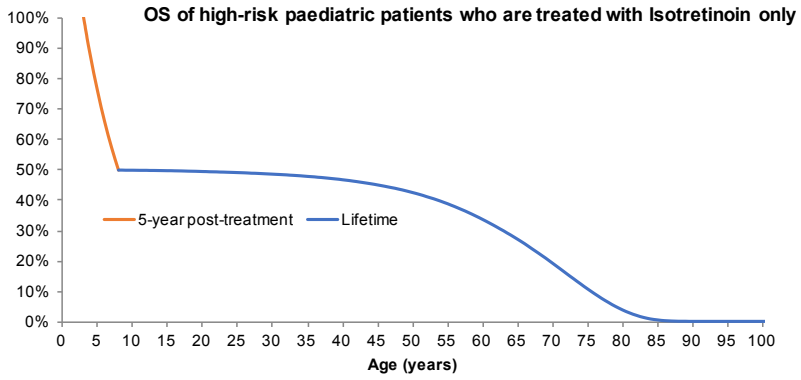
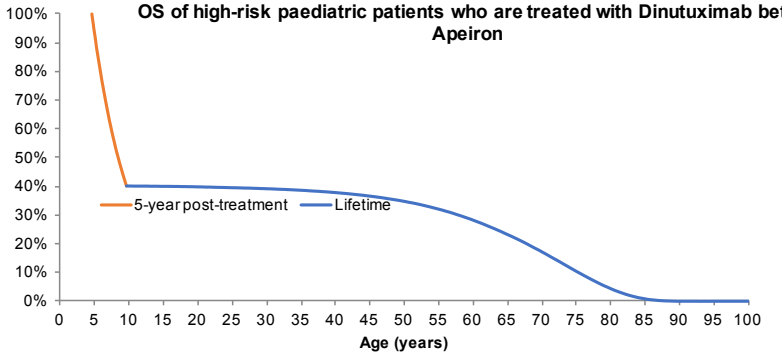
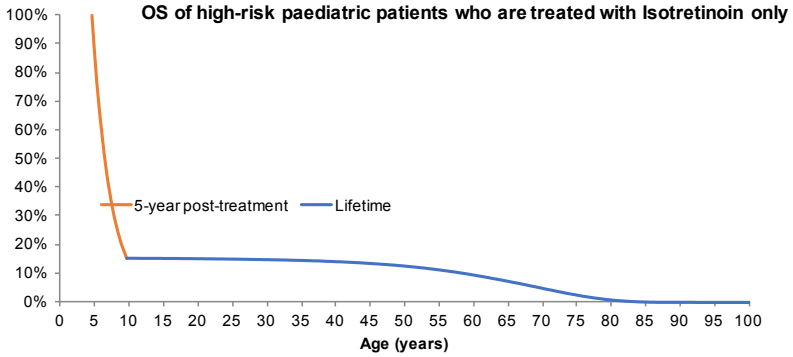


Figure 18: Illustrations of survival curves for the Relapsed/refractory Population





3.3.3 *Adverse reactions*

Due to different methods of AE collection across studies, ADR frequencies were calculated either on the totality of the safety database (N=514) when possible/relevant, or on the subpopulation of studies APN311-101, -201, -202, -303 (N=148). Table with common adverse reactions considered for the cost-effectiveness analysis is presented below and for the active arms are reported as well in the summary of product characteristics of the product.

Table 56: Adverse reactions considered for the cost-effectiveness analysis

Adverse event type	APN-302 – First-line Population	APN-303 – Relapsed/refractory Population	Historical control Group[a]
Pain (including abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia)	77%	77%	6%
Hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release syndrome, serious anaphylactic reactions)	63%	63%	2%
Severe Capillary Leak Syndrome	10%	10%	7%
Eye problems	13%	13%	1%
Peripheral neuropathy	9%	9%	6%
Pyrexia, Infection	88%	88%	22%
Vomiting, Diarrhoea	57%	57%	3%
[a] Derived from Yu et al. (2010)			

3.4 *Measurement and valuation of health effects*

The health effects were expressed in QALYs.

3.4.1 *Health-related quality-of-life data from clinical trials*

There was no health-related quality of life data available from clinical trials, mainly because the majority of children treated in those clinical trials were too young for a proper assessment of quality of life metrics.

3.4.2 *Mapping*

There was no mapping carried out for health-related QoL data. QoL data used in the model were derived from the literature (Barr et al., 1999, Portwine et al., 2016). In addition, patient level data was unavailable to undertake any mapping activity.

3.4.3 *Health-related quality-of-life studies*

A comprehensive search of the peer-reviewed literature was conducted to identify and select relevant health related quality of life studies. Due to the limited health-related quality of life studies in neuroblastoma, searches were undertaken to capture studies that reported health-state specific health utilities of both high-risk and relapsed/refractory neuroblastoma patient populations, as well as for the survivors of neuroblastoma. As for the treatment, we considered any anti-GD2 antibody therapy as intervention or any relevant comparator for each respective population. In addition, a less restrictive systematic search that included studies regardless of intervention or comparator

described, as well as a post-hoc manual search were performed. Full details of the strategy for these literature searches are provided in **Appendix H.**

3.4.3.1 Results of studies identified in the literature review

The main outcomes of the studies identified with both systematic and manual searches are presented in Table 57. Appropiateness of each study for the cost-effectiveness analysis is also discussed

Table 57: Health-related quality of life studies: results of the studies identified in the literature review

Study	Population	Primary outcome measures	Results	Appropiateness of the study for the cost effectiveness analysis
Jubab et al. (2016)	Patients diagnosed with NB, between 2 months and 11 years of age	Wisconsin Quality of Life Questionnaire (WQOLQ)	• Mean QOL score was 1.68 ±0.57 (range -0.27 to 3.0) for neuroblastoma and 1.89 ±0.49 (range -0.24 to 2.73) for comparison group, p=0.863. • QoL scores and SD by managements approach (mean(SD)) --> Chemotherapy: 1.69(0.51); Radiation: 1.59(0.45); Surgery: 1.62(0.57); Combination: 1.53(0.63) • Patients who attended school had higher QOL scores (mean(SD)) than lower-educated patients (2.03(0.33) vs 1.45(0.54), p<0.001). • QoL scores and SD by tumour stage (Mean(SD)) --> Stage 1: 1.54(1.01); Stage 2: 1.43 (0.09); Stage 3: 1.73 (0.477); Stage 4: 1.68; 0.54; p=0.90.	QoL data not deemed appropiate for the CEA (not possible to acurately convert to health utility values). WQOLQ not a QoL measure appropiate for childhood cancer

Study	Population	Primary outcome measures	Results	Appropiateness of the study for the cost effectiveness analysis
Barr et al. (1999)	Children who have completed therapy for tumours of the CNS and who were attending the neuro-oncology follow-up clinic in the children's Hospital at the Chedoke-McMaster (Hamilton, Ontario, Canada) during the interval from February 1993 to February 1995. Mean time from diagnosis to the time of the study was 3.3 years, and from completion of therapy to the time of the study 2.6 years. The tumour types were astrocytoma/glioma (n= 24), primitive neuro-ectodermal tumour/medulloblastoma (n =7), ependymoma (n=3) and others (n= 10)	• **Impact of disease status on global health-related quality of life (utility) expressed as HUI2 and HUI3 scores.** • Impact of site of radiotherapy on global health-related quality of life (utility) expressed as HUI2 and HUI3 scores.	• HUI2 by health state (n, mean, SD, median, minumum, maximum) ・Non-evident (28, 0.89, 0.13, 0.93, 0.46, 1.00) ・Residual (10, 0.81, 0.19, 0.89, 0.38, 0.95) ・Recurrent (3, 0.56, 0.41, 0.65, 0.12, 0.92) • Children with demonstrable disease (residual or recurrent) had a significantly poorer HRQL than those whose disease appeared to be in complete remission (P= 0.027 for HUI2) • HUI2 utility score for patients with non-evident disease was significantly diferent (P <0.001) than that for patients with recurrent disease • HUI3 by health state (n, mean, SD, median, minumum, maximum) ・Non-evident (28, 0.78, 0.26, 0.82, -0.13, 1.00) ・Residual (10, 0.56, 0.26, 0.66, 0.08, 0.89) ・Recurrent (3, 0.32, 0.57, 0.35, -0.27, 0.88)	The population does NOT include neuroblastoma patients but it has several similarities with the population considered in the CEA: ・Paediatric patients had suffered from cancer ・Patients completed therapy ・Similar health states were studied (residual disease and recurrent disease) Given the lack of data specific to the NB population, the findings from this study were deemed appropiate to be used.

Study	Population	Primary outcome measures	Results	Appropiateness of the study for the cost effectiveness analysis
Cai (2012)	Chinese patients, aged between 3 years and 22 years at the time of inclusion into the study with histologically confirmed neuroblastoma, which was refractory to standard treatments.	・Tumour response ・Toxicities ・**QoL as measured by Karnofsky or Lansky performance status and face rating pain scale**	• Only Karnofsky or Lansky PS ≥50 were eligible for this study, almost all the patients got obvious improvement of PS after one course of treatment. The Karnofsky or Lansky PS (% of patients before therapy (BT) and after therapy (AT)) reported were: -Score 50: 28.6% BT, 0% AT -Score 60-70: 42.8% BT, 57.1% AT -Score 80-100: 28.6% BT, 42.8% AT • Alleviation of bone pain was the main cause of improvement of quality of life observed. The face rating pain scale (% of patients before therapy (BT) and after therapy (AT)) reported were: - Score 0-1: 42.8% BT, 71.4% AT - Score 2-5: 28.6% BT, 28.6% AT - Score 6-10: 28.6% BT, 0% AT	QoL data not deemed appropiate for the CEA (not possible to acurately convert to health utility values).

Study	Population	Primary outcome measures	Results	Appropiateness of the study for the cost effectiveness analysis
Hudson et al. (2003)	long-term survivors of childhood cancer who were diagnosed between 1970 and 1986. A randomly selected cohort of the survivors, siblings served as a comparison group	・**Six health status domains were assessed:** general health', mental health'functional status, activity limitations, cancer-related pain, and cancerrelated anxiety/fears. The first 4 domains were assessed in the control group. ・Factors associated with adverse health status in survivors were identified	• Compared with siblings, survivors (total population) were significantly more likely to report: -Adverse general health (odds ratio [OR), 2.5; 95% CI, 2.1-3.0; P<.001) -Mental health (OR, 1.8; 95% CI, 1.6-2.1; P<.001) -Activity limitations (OR, 2.7; 95% CI, 2.3-3.3; P<.001) -Functional impairment (OR, 5.2; 95% CI, 4.1-6.6; P<.001) • 40% of survivors (total population) reported at least 1 adversely affected health status domain. • Compared with siblings, NB survivors were more likely to report: -Adverse general health (odds ratio [OR), 2.1; 95% CI, 1.3-3.2) -Mental health (OR, 1.4; 95% CI, 1.0-2.0) -Activity limitations (OR, 2.7; 95% CI, 1.9-4.0) -Functional impairment (OR, 3.8; 95% CI, 2.3-6.2) • Percentage of NB survivors with adverse health status general health: 8.6%, mental health: 15.6%, functional impairment: 8.3%, activity limitations: 11.7%, pain: 7.6%, anxiety: 10.7%, any domain: 41.2%.	QoL data not deemed appropiate for the CEA (not possible to acurately convert to health utility values).

Study	Population	Primary outcome measures	Results	Appropiateness of the study for the cost effectiveness analysis
Mort et al. (2011)	Young survivors of childhoo cancer aged 11-18 years, who had been treated for extracranial malignancies ≤ 16 years of age, had survived ≥ 4 years after the diagnosis, and were currently free of cancer.	Self-assessment of HRQL was measured using ageappropriate and prevalidated standard measures: ・16D was used for 12- to 18-year-old survivors and their controls ・17D was used only for 11-year-old survivors and their controls. ・Pediatric QoL Inventory (PedsQL)	• Survivors estimated with PedsQLTM instrument their physical health (mean 88.43) as significantly higher (P<0.001) than their psychosocial health (mean 83.74). • They gave total 16D scores and all PedsQL scores higher than their controls, but the only statistically significantly (P<0.05) higher score was the PedsQLTM physical health mean score: - PedsQLTM total score in survivors (n=203), mean 86.08, SD 11.23. - PedsQLTM total score in controls (n=266), mean 85.17, SD 9.77.	QoL data not deemed appropiate for the CEA (not possible to acurately convert to health utility values).
Nathan et al. (2007)	Survivors of Wilms tumour and NB who were participants of the Childhood Cancer Survivor Study (CCSS) aged 18y. or older at the time of the CCSS follow-up questionnaire. They were diagnosed before the age of 21 y. between 1970 and 1986 and were alive at least 5y. from their original diagnosis.	HRQOL assessed with the 36-Item Short Form Health Survey (SF-36).	• <u>Adjusted mean scores on SF-36 subscales for NB survivors (Mean, SE):</u> ・Physical function: 52.02, 1.16 ・Role physical: 52.09, 1.90 ・Bodily pain: 52.84, 1.56 ・General health: 48.99, 1.76 ・Vitality: 39.97, 2.03 ・Social function: 46.30, 1.62 ・Role emotional: 42.41 2.68 ・Mental health: 50.08, 1.69 • <u>NB survivors who scored poor HRQOL (lower than 40, greater than one standard deviation below the mean):</u> ・Physical function: 30 (7.4%) ・Role physical: 53 (13.0%) ・Bodily pain: 45 (11.0%) ・General health: 68 (16.7%) ・Vitality: 159 (39.1%) ・Social function: 87 (21.4%) ・Role emotional: 98 (24.1%) ・Mental health: 35 (8.6%)	QoL data not deemed appropiate for the CEA (not possible to acurately convert to health utility values).

Study	Population	Primary outcome measures	Results	Appropiateness of the study for the cost effectiveness analysis
Portwine et al. (2016)	Survivors of high-risk NBL, diagnosed between 1991 and 2010 and treated with HSCT.	HUI1, HUI2 and HUI3	• On a scale of 0 (being dead) to 1.0 (perfect health), mean HRQL utility scores were 0.89 (SD = 0.11) in HUI2 and 0.84 (SD = 0.18) in HUI3. • Mean HRQL in survivors of high-risk NBL was significantly less than that of the general population (HUI3 mean = 0.96; P < 0.001). • Parents reported morbidity in sensation (52.5%), pain (30.3%), cognition (28.0%), and emotion (24.2%) in HUI2 and in hearing (38.4%), pain (30.3%), cognition (27.3%), and speech (23.2%) in HUI3. • HRQL was not significantly different compared to NBL survivors treated without HSCT, but was less than in nontransplanted survivors of acute lymphoblastic leukemia and Wilms tumour, and children in the general population, yet higher than in survivors of brain tumours.	The study is considered appropiate for the CEA due to: ・The population is the most consistent with one of the DB target population (high-risk NB patients who underwent ASCT) ・Reports Health utility values ・Provides a comparison of HRQOL between NB population and the general population
Wengenroth et al. (2015)	Survivors of childhood cancer. 8% of participants were survivors of NB	Self- and parent-reported HRQoL through the KIDSCREEN-27 instrument and standardized norms in the five dimensions of Physical well-being, Psychological well-being, Autonomy, Peers, and School environment	• Self-reported physical well-being was comparable to norms. Other HRQoL dimensions were higher than norms, with the highest mean = 52.2 ($p<0.001$) for school environment. • Parent-reported HRQoL in survivors was comparable to population norms; physical well-being was lower (mean = 47.1, $p<0.001$), and school environment was higher (mean = 51.1, $p = 0.035$).	QoL data not deemed appropiate for the CEA (not possible to acurately convert to health utility values).

3.4.3.2 Key differences

Not applicable. QoL data was not available from clinical trials or from mapping exercises.

3.4.4 *Adverse reactions*

The Dinutuximab beta Apeiron clinical trials dataset and results from the systematic literature review did not reveal any information in respect to the effect of adverse events on health-related quality of life metrics.

3.4.5 *Health-related quality-of-life data used in the cost-effectiveness analysis*

During the first 5 years, patients in the stable state experience a health utility of 0.840 (derived from Portwine et al. (2016)), which represents a 12,5% utility decrement from age-adjusted UK EQ-5D population norms interpolated with a logistic regression (Figure 19). This decrement is motivated by health utilities reported by Portwine et al. (2016) for survivors of high-risk neuroblastoma after stem cell transplant, while compared with a general population [1-(0.84/0.96) = 0.125].

Patients in the failure health state have a lower health utility of 0.560 (value based on the "recurrent" health state estimates reported by Barr et al. (1999), which represents a 41.7% utility decrement from age-adjusted UK EQ-5D population norms interpolated with a logistic regression. This decrement is motivated by health utilities reported by Barr et al. (1999) for patients with relapsed form of the disease, while compared with a general population [1-(0.56/0.96) = 0.417].

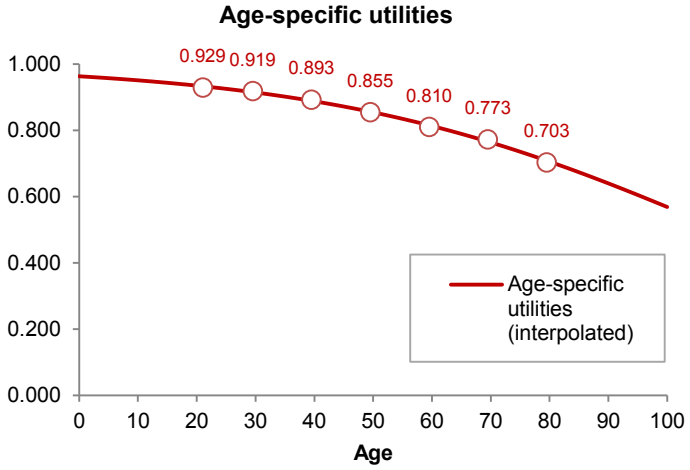
Neuroblastoma survivors (patients in the stable health state after 5 years) still experience a 12.5% utility decrement from age-adjusted UK EQ-5D population norms interpolated with a logistic regression.

Patients that at year 5 are in a failure health state are assumed to continue experiencing a 41.7% utility decrement from age-adjusted UK EQ-5D population norms interpolated with a logistic regression.

For the relapsed/refractory population model, and based on expert opinion, same assumptions were made in regards to the utility values. The population starts with a utility value of 0.84 (derived from Portwine et al. (2016)), which represents a 12,5% utility decrement from age-adjusted UK EQ-5D population norms interpolated with a logistic regression (Figure 19). The stable state R/R is considered as having a utility value of 0.84 (age-adjusted). The failure state population is considered as experiencing a 41.7% utility decrement from age-adjusted UK EQ-5D population norms interpolated with a logistic

regression. A sensitivity analysis decreasing the utility values specific for this patient populations has also been provided.

Figure 19: Interpolated age-specific utilities (EQ-5D population norms)



Interpolated age-specific EQ-5D population norms, $U(age) = \frac{1}{1+e^{(0.030.age+3.259)}}$, with R^2=0.995.

Table 58 shows how the calculated utility decrements were applied in each treatment phase for patients in different health states.

Table 58: Utilities applied in the model

First-line Population	**Stable state**	**Failure state**	**Death**
First 5 years	0.84 (age adjusted)	0.56 (Age adjusted)	0
After 5 years	12.5% decrement[a]	41.7% decrement[a]	0
Relapsed/ Refractory Population	**Stable state**	**Failure state**	**Death**
First 5 years	0.84 (age adjusted)	0.56 (Age adjusted)	0
After 5 years	12.5% decrement[a]	41.7% decrement[a]	0

[a] percent utility decrement in respect to published UK EQ-5D population norms;

Table 59: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section)
1st line population Stable HS	0.84 (0.0181)[a]	0.8364 – 0.8436	**Section 3.4.5**
1st line population Failure HS	0.56 (0.2367)[b]	0.2921 – 0.8279	**Section 3.4.5**
Relapsed/refractory population Stable HS	0.84 (0.0181)[a]	0.8364 – 0.8436	**Section 3.4.5**
Relapsed/refractory population Failure HS	0.56 (0.2367)[b]	0.2921 – 0.8279	**Section 3.4.5**
Death	0	N/A	N/A
% reduction in health utility due to neuroblastoma compared to general population after 5 years[c]	12.5% (0.269%)	0.1255 – 0.1255	**Section 3.4.5**
% reduction in health utility due to Relapsed/refractory neuroblastoma compared to general population after 5 years[d]	41.7% (17.62%)	0.2175 – 0.6165	**Section 3.4.5**

Abbreviations: HS – health state; N/A – Not Applicable
[a] as reported by (Portwine et al., 2016)
[b] Calculated as 0.41/SQRT(3) based on (Barr et al., 1999)
[c] Calculated as (0.96-0.84)/0.96 based on (Portwine et al., 2016). SE is derived from the SE reported by Portwine 2016 for the neuroblastoma patients.
[d] Calculated as (0.96-0.56)/0.96 based on Barr 1999. SE is derived from the SD reported by Barr 1999 for the recurrent neuroblastoma patients.

3.5 *Cost and healthcare resource use identification, measurement and valuation*

3.5.1 *Resource identification, measurement and valuation studies*

Studies reporting costs and resource use, as identified in the literature searches described in **Appendix G**, are summarised in **Appendix I**.

From reported studies, the most relevant data for the model were from Rebholz et al. (2011). Resource utilization reported in those large-scale studies (Table 60), combined with UK-specific costs can be used for estimating costs related to the stable state patients.

Table 60: Resource utilization for neuroblastoma survivors reported in Rebholz 2011

Resource	At Least Once vs Never [% of survivors]	More Than Once Vs Once [% of survivors]
Talked to a doctor in the last 2 weeks	14.2%	24.1%
Attended hospital outpatient department in the last 3 months	24.1%	33.3%
Hospitalized as a day patient (no overnight stay) in the last year	11.8%	38.8%
Hospitalized as an inpatient (overnight stay) in the last year	9.6%	35.0%

3.5.2 *Appropriateness of NHS Ref costs/PbR tariffs*

Immunotherapy forms the backbone of neuroblastoma treatment regimens used in current clinical practice for the patient populations considered within this application. As the remainder of the chemotherapeutic regimen is unaltered, only costs associated with the maintenance phase were modelled, some of which were derived from NHS reference costs or PbR tariffs.

Costs used for administration time required for each injection or infusion were considered to be different between the treatment arms considered and are reported in the treatment regimens table.

The clinical expert stated that most patients are necessitating careful monitoring during the first phase and at least during the first half of the second phase and so require their treatment in hospital, subsequent treatment phases usually occur on an outpatient setting.

Detailed consideration on the costs considered for the cost-effectiveness analysys are detailed in the next chapter. No specific code currently exist within the NHS for the the treatment of neuroblastoma patients.

3.5.3 *Intervention and comparators, costs and resource use*

Patients follow the treatment regimens shown Table 61 during the first 5 cycles of the model.

Table 61: Treatment regimens

	Agent	Route	Dose/Day	Time/ Administration	Number of administration/ Cycle	Duration/ Cycle (days)
Standard Therapy (valid for both population considered)	Isotretinoin	Oral	160mg/m^2	-	14	14
Immunotherapy First-line Population	Isotretinoin	Oral	160mg/m^2	-	14	14
	Dinutuximab beta Apeiron	i.v. infusion	10mg/m^2	120 hours	2	10
Immunotherapy Relapse/ Refractory Population	Isotretinoin	Oral	160mg/m^2	-	14	14
	Dinutuximab beta Apeiron	i.v. infusion	10mg/m^2	120 hours	2	10
	IL-2	s.c. injection	6.106 IU/m^2	-	10	10

Treatment costs for immunotherapy and standard therapy, based on the treatment regimens of the 1st and 2nd line are shown in Tables 62 and 63, respectively. For determining appropriate dosing and amount of vials / tablets needed for each of 5 cycles of treatment, body surface of 0.63m^2 was taken for the first-line population (median BSA reported in the APN311-302 clinical study report and corresponding to the median age of 3 in the same clinical dataset), and a body surface area of 0.73m^2 was taken for the relapsed/refractory

population(median BSA reported in the APN311-303 clinical study report and corresponding to the median age of 6 in the same clinical dataset). Unit drug costs were obtained from the British National Formulary (BNF), except for Dinutuximab beta Apeiron, where cost was taken as £7,610 per 20mg vial.

Total drug costs for the 1st line case in all model cycles were estimated as £152,486 for immunotherapy and £286 for standard therapy. In case of Relapsed/refractory model, which includes IL-2 in combination with Dinutiximab beta Apeiron and isotretinoin, total drug costs were £158,086 and £286 for immunotherapy and standard therapy, respectively.

Table 62: Drug costs 1st line

Model Cycle Number	Agent	Units	Cost/Vial or Tablet (£)	Vials/ Tablets Used	Cost/ Model Cycle (£)	Explanation
Immunotherapy						
1	Dinutuximab beta Apeiron	20 mg vial	£7,610	4	£30,440	0.63 m^2 x 50 mg/m^2/5 days = 31.5 mg x 2 per cycle
	Isotretinoin	20 mg tablet	£0.68 (37.85/56)	84	£57.12	0.63 m^2 x 160 mg/m^2/day = 100.8 mg/day x 14 per cycle
	TOTAL				£30,497.12	
2	TOTAL				£30,497.12	Same as cycle 1
3	TOTAL				£30,497.12	Same as cycle 1
4	TOTAL				£30,497.12	Same as cycle 1
5	TOTAL				£30,497.12	Same as cycle 1
All model cycles	TOTAL				£152,485.6	
Standard therapy						
Each model cycle (1-5)	Isotretinoin	20 mg tablet	0.68 (37.85/56)	84	£57.12	0.63 m^2 x 160 mg/m^2/day = 100.8 mg/day x 14 per cycle
All model cycles	TOTAL				£285.6	

Table 63: Drug costs Relapsed/refractory model

Model Cycle Number	Agent	Units	Cost/Vial or Tablet (£)	Vials/ Tablets Used	Cost/ Model Cycle (£)	Explanation
Immunotherapy						
1	Dinutuximab beta Apeiron	20 mg vial	£7,610	4	£30,440	0.73 m^2 x 50 mg/m^2/5 days = 36.5 mg x 2 per cycle
	IL-2	18x10^6 vial	£112	10	£1,120	0.73 m^2 x 6 MIU/m2/day = 4.38 MIU/ day x 10 per cycle
	Isotretinoin	20 mg tablet	£0.68 (37.85/56)	84	£57.12	0.73 m^2 x 160 mg/m^2/day = 116.8 mg/day x 14 per cycle

	TOTAL				£31,617.12	
2	TOTAL				£31,617.12	Same as cycle 1
3	TOTAL				£31,617.12	Same as cycle 1
4	TOTAL				£31,617.12	Same as cycle 1
5	TOTAL				£31,617.12	Same as cycle 1
All model cycles	TOTAL				£158,085.60	
Standard therapy						
Each model cycle (1-5)	Isotretinoin	20 mg tablet	0.68 (37.85/56)	84	£57.12	0.73 m^2 x 160 mg/m^2/day = 116.8 mg/day x 14 per cycle
All model cycles	TOTAL				£285.6	

Administration costs per cycle assume that a patient starting the treatment will be considered as in-patient at the resuscitation setting during the first-cycle and during the first part of the second-cycle. If no hypersensitivity, nor any serious adverse event is experienced, then the patient is discharged and administration will be continued in the out-patient setting. This assumption is based on current clinical practice in the UK (expert opinion).

For the relapsed/refractory population, during each IL-2 cycle, patients are considered as requiring hospitalisation and careful monitoring.

Table 64: Administration and hospitalisation costs 1st line

Model Cycle Number	Agent	Administration and hospitalisation Costs per cycle (£)	Explanation
Immunotherapy			
1	Dinutuximab beta Apeiron	£407+£273 = £680	1st administration: NHS Reference Costs 2015-2016; Chemotherapy; Service Code: DCRDN; Service Description: Daycase and Reg Day/Night; Currency code: SB14Z; Currency description: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance 2nd administration: NHS Reference Costs 2015-2016; Chemotherapy; Service Code: DCRDN; Service Description: Daycase and Reg Day/Night; Currency code: SB15Z; Currency description: Deliver Subsequent Elements of a Chemotherapy Cycle
	Isotretinoin	£0	Oral
	Pump/Syringe device for infusion	£80*2 = £160	Average cost of providing a syringe or a pump (based on expert opinion)
	Hospital days	10*934 = £9,340	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Service Description: Elective Inpatient Currency code: PM43C; Currency description: Paediatric Other Neoplasms with length of stay 1 day or more, with CC Score 0, National Average Unit Cost / Average length of stay
	TOTAL	£10,180	
2	Dinutuximab beta Apeiron	£273+£212 = £485	1st administration: NHS Reference Costs 2015-2016; Chemotherapy; Service Code: DCRDN; Service Description: Daycase and Reg Day/Night; Currency code: SB15Z; Currency

			description: Deliver Subsequent Elements of a Chemotherapy Cycle 2nd administration: NHS Reference Costs 2015-2016; Service Code: OP; Service Description: Outpatient; Currency code: SB15Z; Currency description: Deliver Subsequent Elements of a Chemotherapy Cycle
	Isotretinoin	£0	Oral
	Pump/Syringe device for infusion	£80*2 = £160	Average cost of providing a syringe or a pump (based on expert opinion)
	Hospital days	5*934 = £4,670	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Service Description: Elective Inpatient Currency code: PM43C; Currency description: Paediatric Other Neoplasms with length of stay 1 day or more, with CC Score 0, National Average Unit Cost / Average length of stay
	TOTAL	£5,315	
3	Dinutuximab beta Apeiron	£212*2 = £424	NHS Reference Costs 2015-2016; Service Code: OP; Service Description: Outpatient; Currency code: SB15Z; Currency description: Deliver Subsequent Elements of a Chemotherapy Cycle
	Isotretinoin	£0	Oral
	Pump/Syringe device for infusion	£80*2 = £160	Average cost of providing a syringe or a pump (based on expert opinion)
	Hospital days	0*934 = £0	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Service Description: Elective Inpatient Currency code: PM43C; Currency description: Paediatric Other Neoplasms with length of stay 1 day or more, with CC Score 0, National Average Unit Cost / Average length of stay
	TOTAL	£584	
4	TOTAL	£584	Same as cycle 3
5	TOTAL	£584	Same as cycle 3
All model cycles	TOTAL	£17,247	
Standard therapy			
Each model cycle (1-5)	Isotretinoin	£0	Oral
All model cycles	TOTAL	£0	

Table 65: Administration costs 2nd line

Model Cycle Number	Agent	Administration Cost per Cycle (£)	Explanation
Immunotherapy			
1	Dinutuximab beta Apeiron	£407+£273 = £680	1st administration: NHS Reference Costs 2015-2016; Chemotherapy; Service Code: DCRDN; Service Description: Daycase and Reg Day/Night; Currency code: SB14Z; Currency description: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance 2nd administration: NHS Reference Costs 2015-2016; Chemotherapy; Service Code: DCRDN; Service Description: Daycase and Reg Day/Night; Currency code: SB15Z; Currency description: Deliver Subsequent Elements of a Chemotherapy Cycle
	IL-2	£346*10 = £3,460	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Service Description: Inpatient Currency code: SB01Z;

			Currency description: Procure Chemotherapy Drugs for Regimens in Band 1
	Isotretinoin	£0	Oral
	Pump/Syringe device for infusion	£80*2 = £160	Average cost of providing a syringe or a pump (based on expert opinion)
	Hospital days	15*934 = £14,010	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Service Description: Elective Inpatient Currency code: PM43C; Currency description: Paediatric Other Neoplasms with length of stay 1 day or more, with CC Score 0, National Average Unit Cost / Average length of stay
	TOTAL	£18,310	
2	Dinutuximab beta Apeiron	£273+£212 = £485	1st administration: NHS Reference Costs 2015-2016; Chemotherapy; Service Code: DCRDN; Service Description: Daycase and Reg Day/Night; Currency code: SB15Z; Currency description: Deliver Subsequent Elements of a Chemotherapy Cycle 2nd administration: NHS Reference Costs 2015-2016; Service Code: OP; Service Description: Outpatient; Currency code: SB15Z; Currency description: Deliver Subsequent Elements of a Chemotherapy Cycle
	IL-2	£346*10 = £3,460	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Service Description: Inpatient Currency code: SB01Z; Currency description: Procure Chemotherapy Drugs for Regimens in Band 1
	Isotretinoin	£0	Oral
	Pump/Syringe device for infusion	£80*2 = £160	Average cost of providing a syringe or a pump (based on expert opinion)
	Hospital days	10*934 = £9,340	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Service Description: Elective Inpatient Currency code: PM43C; Currency description: Paediatric Other Neoplasms with length of stay 1 day or more, with CC Score 0, National Average Unit Cost / Average length of stay
	TOTAL	£13,445	
3	Dinutuximab beta Apeiron	£212*2 = £424	NHS Reference Costs 2015-2016; Service Code: OP; Service Description: Outpatient; Currency code: SB15Z; Currency description: Deliver Subsequent Elements of a Chemotherapy Cycle
	IL-2	£346*10 = £3,460	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Service Description: Inpatient Currency code: SB01Z; Currency description: Procure Chemotherapy Drugs for Regimens in Band 1
	Isotretinoin	£0	Oral
	Pump/Syringe device for infusion	£80*2 = £160	Average cost of providing a syringe or a pump (based on expert opinion)
	Hospital days	10*934 = £9,340	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Service Description: Elective Inpatient Currency code: PM43C; Currency description: Paediatric Other Neoplasms with length of stay 1 day or more, with CC Score 0, National Average Unit Cost / Average length of stay
	TOTAL	£13,384	
4	TOTAL	£13,384	Same as cycle 3
5	TOTAL	£13,384	Same as cycle 3
All model cycles	TOTAL	£71,907	
Standard therapy			
Each model cycle (1-5)	Isotretinoin	£0	Oral

All model cycles	TOTAL	£0	

Table 66: Concomitant medication costs

Concomitant Medication	Cost per continuous infusion (10 days=2x5days)	Unit price	Source
Opioids (morphine)	£57.80	£5.78	BNF (1mg/ml inj, 1x50ml vial = £5.78)
Nonopioid analgesics	£37.92	£3.16	BNF Child 2–4 years 180 mg every 4–6 hours (max. 4 doses in 24 hours) (120mg/5ml solution, 500 ml = £3.16)
Gabapentin	£42.00	£66.13	BNF (Oral solution, gabapentin 50 mg/mL, net price 150-mL pack = £66.13)
Antihistamine premedication	£1.87	£1.87	BNF (cetirizine hydrochloride 5 mg/5 mL, net price 200 mL = £1.87)
Sodium chloride/human albumin for dilution	£60.20	£3.10 £27.00	IHS database (Wholesaler price Fresenius Kabi for 1L solution for infusion in polyethylene bottle) IHS database (Wholesaler price Zenalb Human Albumin solution for infusion 20% 200mg/ml)

Table 67: Monitoring costs

Monitoring costs	Unit price per cycle	Source
Pulse oxymetry	£55.03	NHS Reference Costs 2015-2016; Directly Accessed Diagnostic Services; Currency code: DZ57Z; Currency description: Oximetry or Blood Gas Studies
Full blood count, Liver, and Renal function test	£3.10	NHS Reference Costs 2015-2016; Directly Accessed Pathology Services; Currency code: DAPS05; Currency description: Haematology

3.5.4 *Health-state unit costs and resource use*

The costs and resources related to the Stable state are presented in Table 68. Those costs are based on data of resources used for neuroblastoma survivors in UK (Rebholz et al., 2011) and the NHS Reference Costs. Rebholz et al. (2011) reported percentages of patients using a given resource in the following data format:

- resource used at least once vs none
- resource used more than once vs once

This dichotomization of output was due to the fact that the distribution of frequencies of health care events was highly skewed and comprised a limited number of discrete values. In order to be able to calculate monthly costs based on average amount of resources used, a separate analysis of this dataset was necessary. The following steps and assumptions were made:

- Fraction of resources used was derived for each of the three categories: none, once, more than once.
- Due to a highly skewed distribution of events, it was assumed that an average amount of events in more than once category equals two.
- Average resource usage (per month) was calculated as a weighted average of the three categories.
- Average cost per month was derived by multiplying average resource usage by unit costs of a resource.

Even though assumptions from the second point might seem to be an underestimate, the data from patient's survey reported by Rebholz et al. (2011) included cases when some patients were receiving chemotherapy or radiotherapy or were in a relapse or second neoplasm state. Since such types of events and their corresponding costs are already accounted for in the model separately, the resource use estimates from Rebholz et al. (2011) may be an overestimate for the health state in question. Taking this into account, assumption of taking an average value of two for "more than once" category can be considered a reasonable assumption. With the analysis as detailed above, the average monthly cost of the Stable state is £76.50.

Table 68: Costs and resources associated to Stable state in the economic model

Resource	Average Monthly Units of Resources Consumed	Unit Cost (£)	Monthly Cost (£)	Explanation
Talked to a doctor in the last 2 weeks	0.35	£128.63	£45.02	Source: NHS Reference Costs 2015-2016 Consultant-led outpatient attendances, currency code: WF01C, currency description: non-admitted non-face-to-face attendance follow-up, service code: 300, service description: general medicine
Attended hospital outpatient department in the last 3 months	0.11	£156	£17.99	Source: NHS Reference Costs 2015-2016 Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 300, service description: general medicine
Hospitalized as a day patient (no overnight stay) in the last year	0.01	£733.31	£7.33	National day-case hospital visit average

Hospitalized as an inpatient (overnight stay) in the last year	0.01	£615.83	£6.16	National non-elective inpatient short stay average

Costs determination for Failure state was based on expert opinion, it was assumed that the patients in the failure state followed the treatment regimen used in the phase 2 randomized trial of topotecan/cyclophosphamide (London et al., 2010). Patients assigned to TOPO/CTX received intravenous topotecan 0.75mg/m^2/d and cyclophosphamide 250mg/m^2/d for 5 days. Cycles were 21 days, starting subcutaneous filgrastim 5 µg/kg/d on day 6. The protocol permitted continued treatment until disease progression or up to 1 year without progression.

Table 69: Costs and resources associated to Failure state in the economic model

Items	. Unit Cost (£)	Monthly Cost (£)	Explanation
Topotecan	£261.55	£379.09	Topotecan 4mg/4ml concentrate for solution for infusion vials, BNF price £261.55 (Hospital only). Monthly costs calculated based on one 4 mL vial at 1 mg/mL per 21 days cycle: (261.55/21)*(365.25/12)
Cyclophosphamide	£17.06	£24.73	Cyclophosphamide 1g powder for solution for injection vials), BNF price £17.06 (Hospital only). Monthly costs calculated based on one 1g powder for solution for injection vial per 21 days cycle: (17.06/21)*(365.25/12)
Filgrastim	£30.60	£709.63	Nivestim 12million units/0.2ml solution for injection pre-filled syringes, BNF price £153 for 5 pre-filled syringes (Hospital only). Monthly costs calculated based on one prefilled syringe per day during 16 days per 21 days cycle: (30.60*16/21)*(365.25/12)
Administration costs	£1,808.01	£2,620.54	NHS Reference Costs 2015-2016, Chemotherapy; Service Code: IP; Service Description: Inpatient Currency code: SB10Z; Currency description: procure chemotherapy drugs for regimen in Band 10. Monthly costs calculated based on one overall administration cost per 21 days cycle: (1808.01/21)*(365.25/12)

3.5.5 *Adverse reaction unit costs and resource use*

Table 70: List of adverse reactions and summary of costs in the economic model

Items	. Per event Cost (£)	Explanation
Pain (including abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia)	£288.13	Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 241, service description: paediatric pain management
Hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release	£220.38	Consultant-led outpatient attendances ttendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service

syndrome, serious anaphylactic reactions)		code: 260, service description: Paediatric Clinical Immunology and Allergy Service
Capillary Leak Syndrome	£2,834.88	Non-Elective Long Stay: Currency Code: PX57A; Currency Description: Paediatric, Examination, Follow-Up, Special Screening or Other Admissions, with CC Score 4+
Eye problems	£118.59	Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance first attendance, service code: 216, service description: paediatric ophtalmology
Peripheral neuropathy	£343.79	Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 421, service description: paediatric neurology
Pyrexia, Infection	£358.97	Day cases, currency code: PW20B, currency description: paediatric fever of unknown origin with CC score 2+
Vomiting, Diarrhoea	£547.96	Day cases, currency code: PF26B, currency description: paediatric other gastrointestinal disorders with CC score 1–3

3.5.6 *Miscellaneous unit costs and resource use*

No other costs and resource use in addition to those mentioned in the previous sections were considered.

3.6 *Summary of base-case analysis inputs and assumptions*

3.6.1 *Summary of base-case analysis inputs*

A list of all variables used in the economic model is provided in Table 71.

Table 71: List of all variables used in the economic model

Variables				Base value	One-way Deterministic Sensitivity Analysis			Probabilistic Sensitivity Analysis	
					Range		Assumption	Distribution	Standard Error
					Lower	Upper			
Inputs General	**Administration and hospitalisation costs (per admin)**	inpatient	**Dinutuximab Beta Apeiron**	£407.0	£60.0	£2,500		Gamma	£12.2
		inpatient	**IL-2**	£346.0	£60.0	£2,500	+/-30%	Gamma	£10,0
		outpatient 2nd Admin	**Dinutuximab Beta Apeiron**	£212.0	£148,4	£275.6	+/-30%	Gamma	£6,8
		inpatient 2nd admin	**Dinutuximab Beta Apeiron**	£273.0	£191,1	£354.9	+/-30%	Gamma	£9,1
		inpatient	**Hospital admission costs**	£934.0	£653,8	£1,214.2	+/-30%	Gamma	£30,7
		inpatient outpatient	**Pump/Syringe Device for infusion**	£80.0	£56,0	£104,0	+/-30%	Gamma	£2,6
	Concomitant medication costs	Continuous infusion for 10 days	**Opioids (morphine)**	£57.8	£40,5	£75,1	+/-30%	Gamma	£1,9
			Nonopioid analgesics	£37.9	£26,5	£49,3	+/-30%	Gamma	£1,2
			Gabapentin	£42.0	£29,4	£54,6	+/-30%	Gamma	£1,3
			Antihistamine premedication	£1.9	£1,3	£2,4	+/-30%	Gamma	£0,1

			Sodium Chloride 9mg/ml, Human Albumin 1%	£60,2	£42,1	£78,3	+/-30%	Gamma	£1,9
	Monitoring Cost		**Pulse Oxymetry**	£55,0	£38,5	£71,5	+/-30%	Gamma	£1,7
			Bone Marrow, Liver and Renal function test	£3,1	£2,2	£4,0	+/-30%	Gamma	£0,1
	Adverse events Cost		**Pain (including abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia)**	£288,1	£201,7	£374,6	+/-30%	Gamma	£9,6
			Hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release syndrome, serious anaphylactic reactions)	£220,4	£154,3	£286,5	+/-30%	Gamma	£7,2
			Capillary Leak Syndrome	£2,834,9	£1,984,4	£3,685,3	+/-30%	Gamma	£81,1
			Eye problems	£118,6	£83,0	£154,2	+/-30%	Gamma	£4,0
			Peripheral neuropathy	£343,8	£240,7	£446,9	+/-30%	Gamma	£11,3
			Pyrexia, Infection	£359,0	£251,3	£466,7	+/-30%	Gamma	£11,9
			Vomiting, Diarrhoea	£548,0	£383,6	£712,3	+/-30%	Gamma	£18,2
	Health states associated costs	**Stable State**	**Talk to a doctor**	£540,2	£378,2	£702,3	+/-30%	Gamma	£17,8
			Hospital outpatient visit	£215,9	£151,1	£280,7	+/-30%	Gamma	£7,1
			Hospital as day patient	£88,0	£61,6	£114,4	+/-30%	Gamma	£2,8
			Hospitalized for overnight stay	£73,9	£51,7	£96,1	+/-30%	Gamma	£2,2
		Failure State	**Topotecan**	£4,549,1	£3,184,4	£5,913,8	+/-30%	Gamma	£148,4
			Cyclophosphamide	£296,7	£207,7	£385,7	+/-30%	Gamma	£9,0
			Filgrastim	£8,515,5	£5,960,9	£11,070,2	+/-30%	Gamma	£268,6
			Administration cost	£31,446,5	£22,012,5	£40,880,4	+/-30%	Gamma	£1,011,7
	Morbidity after 5y	1st Line Population	**Utility decrement (%)**	12,5%	8,8%	16,3%	+/-30%	Beta	0,1%
			Standardised Mortality Ratio	5,6	3,92	7,28	+/-30%	Normal	0,018
	Impact of R/R		**Utility decrement (%)**	42%	29%	54%	+/-30%	Beta	0%
			Increased mortality (%)	90%	63%	100%	+/-30%	Beta	0%
	Morbidity after 5y	Relapsed/refractory Population	**Utility decrement (%)**	12,5%	8,8%	16,3%	+/-30%	Beta	0,1%

			Standardised Mortality Ratio	5.6	3,92	7,28	+/-30%	Normal	0,018
	Impact of R/R		**Utility decrement (%)**	42%	29%	54%	+/-30%	Beta	0%
			Increased mortality (%)	90%	63%	100%	+/-30%	Beta	0%
1st Line population (FL)	Age (years)			3	0,6	20	APN311-302 median age	Normal	0,010
	Body Surface Area (m^2)			0.63	0,37	1,66	APN311-302 median BSA	Normal	0,00
	Dosing Distribution		**Daily infusions (5 days)**	0.00%	0,00%	100,00%	+/-30%	None	0,00%
			Continuous infusions (10 days)	100.00%	100,00%	0,00%	+/-30%	None	0,00%
	Health utilities decrement during treatment		**Cycle 1**	125%	8,8%	16,3%	+/-30%	Beta	0,1%
			Cycle 2	12.5%	8,8%	16,3%	+/-30%	Beta	0,1%
			Cycle 3	12.5%	8,8%	16,3%	+/-30%	Beta	0,1%
			Cycle 4	12.5%	8,8%	16,3%	+/-30%	Beta	0,1%
			Cycle 5	12.5%	8,8%	16,3%	+/-30%	Beta	0,1%
	5y outcomes	**Dinutuximab Beta Apeiron**	**OS**	65.0%	45,5%	84,5%	+/-30%	Beta	0,2%
			EFS	57.0%	74,1%	39,9%	+/-30%	Beta	0,2%
		Isotretinonin	**OS**	50.0%	65,0%	35,0%	+/-30%	Beta	0,2%
			EFS	42.0%	29,4%	54,6%	+/-30%	Beta	0,2%
	Discounting	**QALYS**		1.50%	1,50%	5,00%		None	0,00%
		Cost		1.50%	1,50%	5,00%		None	0,00%
Relapsed/refractory population	Age (years)			6	2	26	APN311-303 median age	Normal	0,015
	Body Surface Area (m^2)			0.73	0,53	1,94	APN311-303 median bsa	Normal	0,001
	Dosing Distribution		**Daily infusions (5 days)**	0.00%	0,00%	100,00%		None	0,00%
			Continuous infusions (10 days)	100.00%	100,00%	0,00%		None	0,00%
	Health utilities decrement during treatment		**Cycle 1**	12.5%	8,8%	16,3%	+/-30%	Beta	0,1%
			Cycle 2	12.5%	8,8%	16,3%	+/-30%	Beta	0,1%
			Cycle 3	12.5%	8,8%	16,3%	+/-30%	Beta	0,1%
			Cycle 4	12.5%	8,8%	16,3%	+/-30%	Beta	0,1%
			Cycle 5	12.5%	8,8%	16,3%	+/-30%	Beta	0,1%
	5y outcomes	**Dinutuximab Beta Apeiron**	**OS**	40.0%	28,00%	52,00%	+/-30%	Beta	0,16%
			EFS	32.0%	41,60%	22,40%	+/-30%	Beta	0,15%
		Isotretinonin	**OS**	15.0%	19,50%	10,50%	+/-30%	Beta	0,11%
			EFS	7.0%	4,90%	9,10%	+/-30%	Beta	0,08%
	Discounting	**QALYS**		1.50%	1,50%	5,00%		None	0,00%
		Cost		1.50%	1,50%	5,00%		None	0,00%
1st Line population (FL)	**Risk of Adverse events**	**Pain (including abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia)**	Dinutuximab Beta Apeiron Arm	77.00%	53,90%	100,00%	+/-30%	Beta	0,13%
			Comparator Arm	6.00%	4,20%	7,80%	+/-30%	Beta	0,07%

		Hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release syndrome, serious anaphylactic reactions)	Dinutuximab Beta Apeiron Arm	63,00%	44,10%	81,90%	+/-30%	Beta	0,15%
			Comparator Arm	2,00%	1,40%	2,60%	+/-30%	Beta	0,04%
		Capillary Leak Syndrome	Dinutuximab Beta Apeiron Arm	10,00%	7,00%	13,00%	+/-30%	Beta	0,09%
			Comparator Arm	7,00%	4,90%	9,10%	+/-30%	Beta	0,08%
		Eye problems	Dinutuximab Beta Apeiron Arm	13,00%	9,10%	16,90%	+/-30%	Beta	0,11%
			Comparator Arm	1,00%	0,70%	1,30%	+/-30%	Beta	0,03%
		Peripheral neuropathy	Dinutuximab Beta Apeiron Arm	9,00%	6,30%	11,70%	+/-30%	Beta	0,09%
			Comparator Arm	6,00%	4,20%	7,80%	+/-30%	Beta	0,08%
		Pyrexia, Infection	Dinutuximab Beta Apeiron Arm	88,00%	61,60%	100,00%	+/-30%	Beta	0,11%
			Comparator Arm	22,00%	15,40%	28,60%	+/-30%	Beta	0,13%
		Vomiting, Diarrhoea	Dinutuximab Beta Apeiron Arm	57,00%	39,90%	74,10%	+/-30%	Beta	0,16%
			Comparator Arm	3,00%	2,10%	3,90%	+/-30%	Beta	0,05%
Relapsed/refractory population	**Risk of Adverse events**	**Pain (including abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia)**	Dinutuximab Beta Apeiron Arm	77,00%	53,90%	100,00%	+/-30%	Beta	0,12%
			Comparator Arm	6,00%	4,20%	7,80%	+/-30%	Beta	0,07%
		Hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release syndrome, serious anaphylactic reactions)	Dinutuximab Beta Apeiron Arm	63,00%	44,10%	81,90%	+/-30%	Beta	0,16%
			Comparator Arm	2,00%	1,40%	2,60%	+/-30%	Beta	0,04%
		Capillary Leak Syndrome	Dinutuximab Beta Apeiron Arm	10,00%	7,00%	13,00%	+/-30%	Beta	0,09%
			Comparator Arm	7,00%	4,90%	9,10%	+/-30%	Beta	0,08%
		Eye problems	Dinutuximab Beta Apeiron Arm	13,00%	9,10%	16,90%	+/-30%	Beta	0,11%
			Comparator Arm	1,00%	0,70%	1,30%	+/-30%	Beta	0,03%
		Peripheral neuropathy	Dinutuximab Beta Apeiron Arm	9,00%	6,30%	11,70%	+/-30%	Beta	0,09%
			Comparator Arm	6,00%	4,20%	7,80%	+/-30%	Beta	0,07%
		Pyrexia, Infection	Dinutuximab Beta Apeiron Arm	88,00%	61,60%	100,00%	+/-30%	Beta	0,10%
			Comparator Arm	22.00%	15,40%	28,60%	+/-30%	Beta	0,13%

		Vomiting, Diarrhoea	Dinutuximab Beta Apeiron Arm	57.00%	39,90%	74,10%	+/-30%	Beta	0,16%
			Comparator Arm	3,00%	2,10%	3,90%	+/-30%	Beta	0,06%

3.6.2 *Rationale for inputs chosen in the base-case analysis*

Justification for 1.5% discount rate: Dinutuximab beta Apeiron has been shown to extend the lives of some children with high-risk neuroblastoma or in patients that are relapsed/refractory. Therefore, the base case for cost-effectiveness analysis of dinutuximab beta Aperion uses a 1.5% discount rate for both costs and health benefits.

Additionally, the committee has already set a precedent for deviating from the reference case during the evaluation of Unituxin for high-risk neuroblastoma.

"*The committee was aware that the company's revised base-case ICER includes the lower discount rate of 1.5% for outcomes and costs. The committee concluded that the non-reference case discount rate could apply because the 2014 analysis showed that the dinutuximab regimen could be considered to cure neuroblastoma in a small proportion of patients.*"

A sensitivity analysis using a 3.5% discount rate has also been provided.

3.6.3 *Assumptions*

- Patients start the model in a stable state at the median age of 3 (based on data from APN311-302 Clinical Study Report) for the high-risk population and at the median age of 6 (based on data from APN311-303 Clinical Study Report) for the relapsed/refractory population
- Average body surface area is 0.63 m^2 for the high-risk population and 0.73 m^2 for the relapsed/refractory population
- Patients in a failure state receive topotecan/cyclophosphamide combination treatment on a monthly / cycle basis until death
- 5-year OS for the first-line treatment were assumed to be 65% and 50% for the immunotherapy and comparator arms, respectively. The 5-year EFS are assumed to be 57% and 42% for the immunotherapy and comparator arms, respectively.
- 5-year OS for the 2nd line treatment was assumed to be 40% and 15% for the immunotherapy and comparator arms, respectively. The 5-year EFS are assumed to be 32% and 7% for the immunotherapy and comparator arms, respectively.

- After 5 first years, patients in the stable state are assumed to be neuroblastoma survivors despite the fact that some may relapse (extremely rare according to expert opinions). They suffer from a higher standardised annual mortality ratio of 5.6 in respect to the general population.
- After 5 years, failure health state patients still alive at 5 years were also subject to elevated mortality risk of neuroblastoma survivors but additionally increased by 90%. These patients could no longer transition to the stable (event-free) health state.

3.7 *Base-case results*

3.7.1 *Base-case incremental cost-effectiveness analysis results*

Base case results are presented in Table 72.

Table 72: Base case results

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
Comparator - Isotretinoin 1st Line	£143,868	16,0326	—	—	—
Dinutuximab beta Apeiron 1st Line	**£316,430**	**20,5158**	**£172,562**	**4,4832**	**£38,491**
Comparator - Isotretinoin Relapsed/refractory	£137,134	4,9361	—	—	—
Dinutuximab beta Apeiron Relapsed/Refractory	**£361,654**	**12,4353**	**£224,520**	**7,4992**	**£29,939**

Table 73: Summary of predicted resource use by category of cost

Item	1st Line					Relapsed/refractory				
	Cost (£), Dinutuximab beta Apeiron	Cost (£), Isotretinoin	Increment	Absolute Increment	% Absolute Increment	Cost (£), Dinutuximab beta Apeiron	Cost (£), Isotretinoin	Increment	Absolute Increment	% Absolute Increment
Drug Cost	£148,984	£274	£148,710	£148,710	86.2%	£150,855	£255	£150,600	£150,600	67.1%
Administration cost	£17,247	£0	£17,247	£17,247	10.0%	£71,909	£0	£71,909	£71,909	32.0%
Concomitant medication cost	£999	£0	£999	£999	0.6%	£999	£0	£999	£999	0.4%
Monitoring cost	£568	£0	£568	£568	0.3%	£555	£0	£555	£555	0.2%
Adverse event cost	£1,319	£337	£981	£981	0.6%	£1,319	£337	£981	£981	0.4%

Failure cost	£125,273	£126,457	-£1,183	£1,183	0,7%	£123,091	£132,487	-£9,396	£9,396	4.2%
Ongoing healthcare cost	£22,040	£16,800	£5,240	£5,240	3,0%	£12,927	£4,054	£8,873	£8,873	4.0%
Total	£316,430	£143,868	£172,562	Total absolute increment	100%	£361,654	£137,134	£224,520	Total absolute increment	100%

3.8 *Sensitivity analyses*

3.8.1 *Probabilistic sensitivity analysis*

3.8.1.1 Inputs

Table 71 summarises the parameters included in the PSA and the distributions used to determine their values. These parameters were considered for PSA to investigate their collective impact on the ICER based on their known SE, if and whenever available, around the base case estimate. A SE of 5% of the mean was assumed for the purpose of PSA where the SE is unknown. Discount rates for costs and QALYs and the dosing and treatment regimens were excluded from the PSA.

3.8.1.2 Results

The results of 1,000 simulations were plotted on the cost-effectiveness plane (Figure 20 and Figure 21) and the cost-effectiveness acceptability curve (CEAC) was calculated (Figure 22 and Figure 23). All simulation results lie in the north-east and south-east quadrants of the cost-effectiveness plane, indicating that Dinutuximab beta Apeiron is always more effective than Isotretinoin alone. The CEAC shows that Dinutuximab beta Apeiron in the first-line setting has a 36% probability of being below the £30,000 willingness to pay threshold when compared with isotretinoin alone. Similarly, Dinutuximab beta Apeiron in conjunction with IL-2 and Isotretinoin for relapse/refractory patients has a 49% probability of being below the £30,000 willingness to pay threshold when compared with isotretinoin alone.

Figure 20: Cost-effectiveness plane for Dinutuximab beta Apeiron for the first-line population with a £30,000/QALY threshold

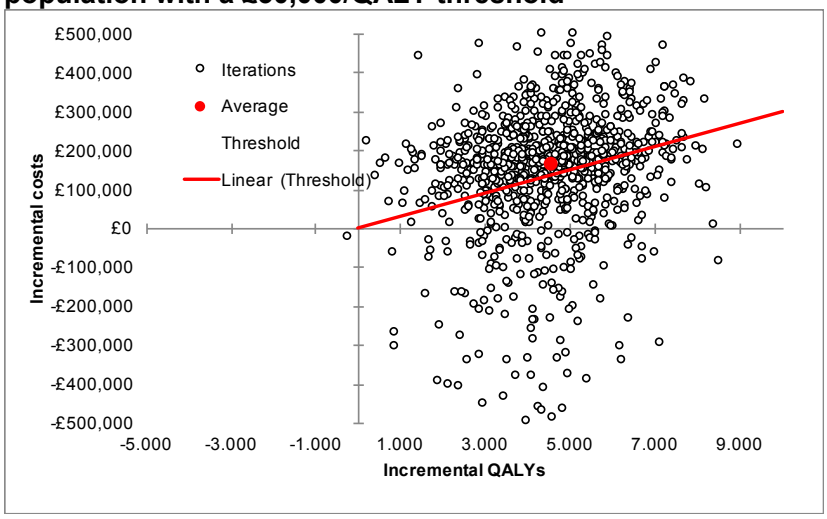


Figure 21: Cost-effectiveness plane for Dinutuximab beta Apeiron for the relapsed/refractory population with a £30,000/QALY threshold

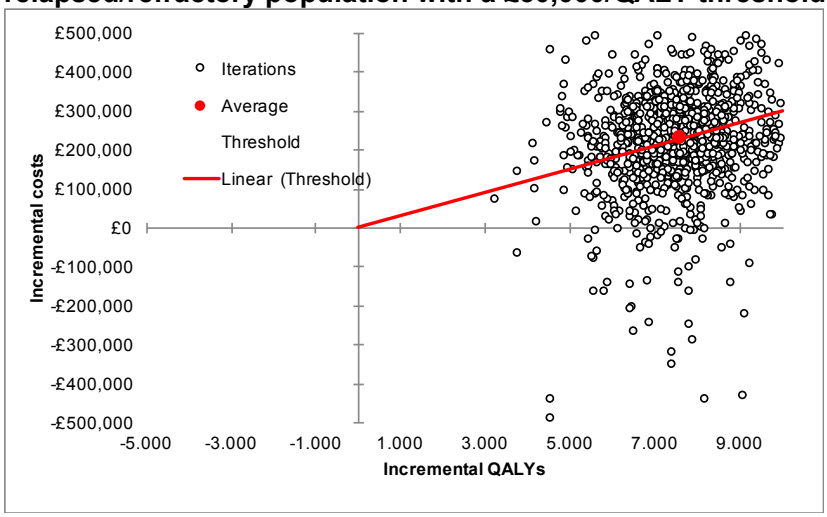


Figure 22: CEAC for Dinutuximab beta Apeiron for the first-line population

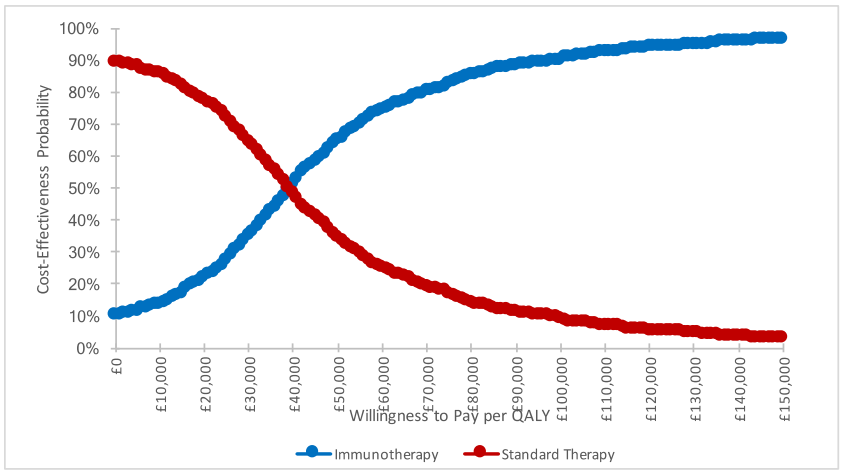


Figure 23: CEAC for Dinutuximab beta Apeiron for the Relapsed/refractory population

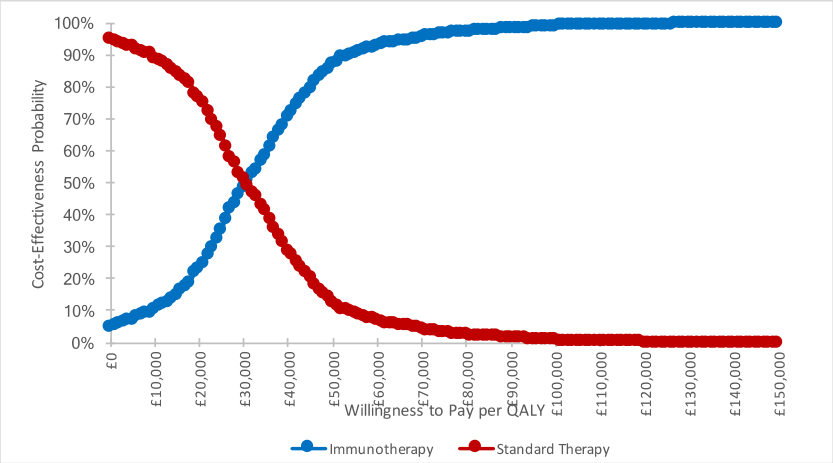


Table 74: PSA results for Dinutuximab beta Apeiron for the first-line population

	Immunotherapy				Standard Therapy			
	Mean	**Median**	**Lower 95% Confidence Interval**	**Upper 95% Confidence Interval**	**Mean**	**Median**	**Lower 95% Confidence Interval**	**Upper 95% Confidence Interval**
Cost (£)	£320,225	£281,477	£310,084	£330,366	£154,800	£107,040	£143,907	£165,692
QALY	20.65	20.60	20.57	20.72	16.14	16.16	16.07	16.21
Mean ICER	£39,184							

Table 75: PSA results for Dinutuximab beta Apeiron for the relapsed/refractory population

	Immunotherapy				Standard Therapy			
	Mean	**Median**	**Lower 95% Confidence Interval**	**Upper 95% Confidence Interval**	**Mean**	**Median**	**Lower 95% Confidence Interval**	**Upper 95% Confidence Interval**
Cost (£)	£369,934	£333,672	£359,754	£380,114	£134,226	£100,349	£126,465	£141,988
QALY	12.50	12.49	12.44	12.57	4.94	4.90	4.89	4.99
Mean ICER	£31,436							

3.8.1.3 Discussion of variation between base case and PSA results

The results from the PSA and base case analysis (**section 3.7.1**) in first-line setting are very similar, the probabilistic mean produced a slightly higher cost for Dinutuximab beta Apeiron

(£3,795) and a better QALY gain (0.1342), producing an ICER of £39,184 (vs £38,491 for the base case).

The results from the PSA and base case analysis in relapsed/refractory patients are very similar, the probabilistic mean produced a slightly higher cost for Dinutuximab beta Apeiron (£8,280) and a marginally better QALY gain (0.0647), producing an ICER of £31,436 (vs £29,939 for the base case).

3.8.2 *Deterministic sensitivity analysis*

Deterministic sensitivity analysis (DSA) was performed on all inputs included in the model, and a tornado diagram was produced. Table 71 summarises the variables included in the tornado diagram and the relative variation used for each. A common variation in parameter inputs (+/-30%) was included in the DSA apart for the patient's age and BSA, to determine the relative sensitivity of model outcomes to different model inputs. For the age and BSA values, clinical trial data of APN311-302 and 303 were used for the high-risk and relapsed/refractory neuroblastoma patients, respectively.

3.8.2.1 Uncertainty about extrapolation

Due to the rarity of the disease, the retrospective nature of the main clinical study and no long-term data, identification of data to inform model inputs was somewhat challenging. Key data constraints were around: 1) the extrapolation of outcomes beyond the trial due to lack of data and to small sample sizes; 2) lack of data for patients not treated with immunotherapy in the maintenance phase; 3) lack of neuroblastoma healthstate-specific HRQOL data. However, the impact of these on model outcomes was tested to the extent possible via DSA.

3.8.2.2 Results of deterministic sensitivity analysis

The results are presented in a Tornado diagram in Figure 24 and Figure 25.These figures show the fourteen parameters to which the ICER is most sensitive. In these diagrams, ICER is stable for the variation of most of the parameters, however it is unstable when survival data and discounting are varied. In the tornado of relapsed/refractory patients, BSA of patients and administration inpatient cost of IL-2 are also driving unstability.

Figure 24: Tornado diagram for DSA results (ICER) for Dinutuximab beta Apeiron for the first-line population

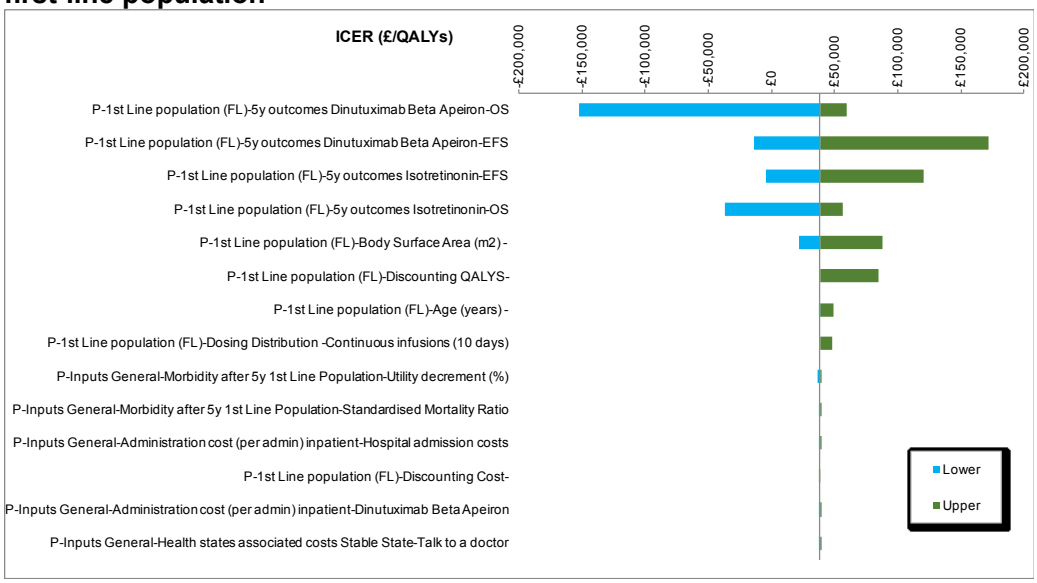
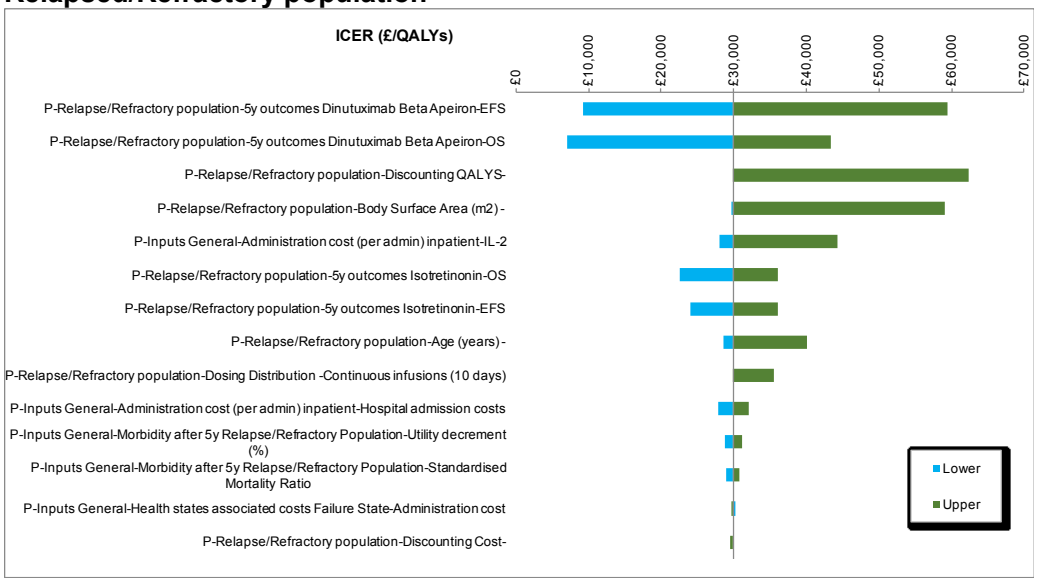


Figure 25: Tornado diagram for DSA results (ICER) for Dinutuximab beta Apeiron for the Relapsed/Refractory population



3.8.3 *Scenario analysis*

A range of scenarios were run to explore the uncertainty in model parameters. Table 78 presents the ICER for each scenario for Dinutuximab beta Apeiron vs the other treatment strategy. The results show that Dinutuximab beta Apeiron ICERs for both populations ranges from £21,906 for the most optimistic scenario considered to £90,086 for the most conservative scenario.

As mentioned previously, a scenario analysis is considering the NICE reference case with a 3.5% discount rate on both costs and QALYs.

A second scenario assumed conservative QALY assumptions with the relapsed/refractory population. Indeed, for the base case results, it was assumed that relapse/ refractory patients will enter the model with the same utility values as for the 1st line high-risk population. A more conservative assumptions would consider that this population could start with a utility value of 0.56 (value based on the "recurrent" health state estimates reported by (Barr et al., 1999) which represents a 41.7% utility decrement from age-adjusted UK EQ-5D population norms interpolated with a logistic regression. The stable state R/R is then considered as having a utility value of 0.56 (age-adjusted). The failure state population is considered as experiencing a 33.3% utility decrement from age-adjusted UK EQ-5D population norms interpolated with a logistic regression. This additional decrement is motivated by the difference in health utilities considered in the model for patients with relapsed form of the disease, while compared with the stable state population [1-(0.56/0.84) = 0.333].

Table 76: Utilities applied in the model for scenario analysis of conservative QALYs

First-line Population	Stable state	Failure state	Death
First 5 years	0.84 (age adjusted)	0.56 (Age adjusted)	0%
After 5 years	12.5% decrement[a]	41.7% decrement[a]	0%
Relapsed/Refractory Population	**Stable state**	**Failure state**	**Death**
First 5 years	0.56 (age adjusted)	0.37 (Age adjusted)	0%
After 5 years	41.7% decrement[a]	33.3% decrement[b]	0%

[a] percent utility decrement in respect to published UK EQ-5D population norms; [b] percent utility decrement in respect to the stable state population

Given that the DSA is showing the widest variabilities with OS and EFS outcomes at 5 years, a third scenario considered is decreasing the difference between active (dinutuximab arm) and comparative arms (isotretinoin arm). A 50% reduction in the difference between OS and EFS values is then considered as shown in Table 77.

Table 77: OS and EFS values applied in the model for scenario analysis of conservative EFS and OS

OS and EFS assumptions for the scenario analysis	OS		EFS	
	High-risk	Relapsed/Refractory	High-risk	Relapsed/Refractory
Dinutuximab beta Apeiron Arm	61.25%	33.75%	53.25%	25.75%
Isotretinoin Arm	53.75%	21.25%	45.75%	13.25%
Delta	7.50%	12.50%	7.50%	12.50%

Given the impact of the BSA assumption on the number of vials to be used, scenario analysis were performed with the minimum and maximum values of BSA coming from clinical trials.

3.8.3.1 Results of Scenario analysis

Table 78: Summary results of scenario analysis

Scenario Analysis	First-line High-risk Neuroblastoma Population (Dinutuximab+Isotretinoin vs. Isotretinoin) ICER	Relapsed/refractory Population (Dinutuximab+IL-2+Isotretinoin vs. Isotretinoin) ICER
Base case	**£38,491**	**£29,939**
3.5% discount rate for costs and QALYs	**£62,221**	**£46,712**
Conservative QALY assumptions[a]	**£38,491**	**£44,997**
Reduced difference in OS and EFS between Dinutuximab beta Apeiron and Isotretinoin (50% delta reduction)[b]	**£75,903**	**£90,086**
Minimum BSA	**£21,906**	**£29,939**
Maximum BSA	**£88,247**	**£58,994**

[a]: As described in Table 76. [b]: as described in Table 77

3.8.3.2 Summary of sensitivity analyses result

Survival parameters and the BSA had the greatest impact on cost-effectiveness.

A conservative reduced difference in OS and EFS resulted in an ICER of £75,903 and £90,086 for first-line high-risk neuroblastoma and replased/refractory patients, respectively. Changing QALY assumptions with a conservative approach for relapsed/refractory patients increased the ICER by £15,058. Using the maximum BSA from the clinical trials had an important impact on ICER, almost double the ICER, mainly due to increase vials.

3.9 *Subgroup analysis*

No subgroup analysis was undertaken for the cost-effectiveness analysis.

3.10 *Validation*

3.10.1 *Validation of cost-effectiveness analysis*

To validate the assumptions used in the model, experts familiar with current and historic protocols were approached to validate inputs and provide expert opinion for inputs that lacked data. The experts consulted agreed with the model structure used as well as inputs, as described. As the experts consulted have extensive experience in treating patients with this disease, they were best-placed to provide insight, which is why this method was undertaken, especially considering the treatment practice in UK and health states.

3.11 *Interpretation and conclusions of economic evidence*

This economic evaluation aimed to evaluate the cost-effectiveness of Dinutuximab beta Apeiron compared to isotretinoin for the treatement of patients with high-risk neuroblastoma, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease.

The base case demonstrated that the incremental cost per QALY gained with Dinutuximab beta Apeiron compared to isotretinoin alone was £38,491 for high-risk neuroblastoma patients and £29,939 for relapsed/refractory patients with a 1.5% discount rate. In order to evaluate the uncertainty, extensive sensitivity analyses was run, per **Section 3.8**. Similar results were observed in probabilistic sensitivity analyses; the CEAC shows that Dinutuximab beta Apeiron for high-risk eurblastoma patients has a 36% probability of being below the £30,000 willingness to pay threshold when compared with isotretinoin alone. Similarly, Dinutuximab beta Apeiron in conjunction with IL-2 and Isotretinoin for relapse/refractory patients has a 49% probability of being below the £30,000 willingness to pay threshold when compared with isotretinoin alone. In deterministic sensitivity analyses, survival parameters and BSA had the greatest impact on cost-effectiveness.

This economical evaluation would be relevant to UK decision-makers as the model reflects the current standard of care for UK patients, and also uses associated UK-specific data, where available. Key inputs were also validated by experts to ensure the values used were reflective of UK experience.

Due to the rarity of the disease, the retrospective nature of the main clinical study and the absence of long-term data, identification of data to inform model inputs was somewhat challenging and it is part of the main limitations (**Section 3.8.2.1**). Survival data of Dinutuximab beta Apeiron were used to inform the model for both population. However, sufficient information regarding patients treated with isotretinoin alone was difficult to collect due to the broad use of immunotherapy as a “standard of care” in the maintenance phase in the current clinical practice since the positive results published by Yu et al (2010). Since then it was deemed unethical to treat patients without immunotherapy. Some uncertainties do exist in the values and data reported, a very conservative approach was therefore used for the cost-effectiveness analysis.

4. References

Ashraf, K., Shaikh, F., Gibson, P., Baruchel, S. & Irwin, M. S. 2013. Treatment with topotecan plus cyclophosphamide in children with first relapse of neuroblastoma. *Pediatric Blood and Cancer,* 60**,** 1636-1641.

Bagatell, R., Beck-Popovic, M., London, W. B., Zhang, Y., Pearson, A. D., Matthay, K. K., Monclair, T., Ambros, P. F., Cohn, S. L. & International Neuroblastoma Risk, G. 2009. Significance of MYCN amplification in international neuroblastoma staging system stage 1 and 2 neuroblastoma: a report from the International Neuroblastoma Risk Group database. *Journal of Clinical Oncology,* 27**,** 365-70.

Bagatell, R. & Cohn, S. L. 2016. Genetic discoveries and treatment advances in neuroblastoma. *Current Opinion in Pediatrics,* 28**,** 19-25.

Baker, D. L., Schmidt, M. L., Cohn, S. L., Maris, J. M., London, W. B., Buxton, A., Stram, D., Castleberry, R. P., Shimada, H., Sandler, A., Shamberger, R. C., Look, A. T., Reynolds, C. P., Seeger, R. C., Matthay, K. K. & Children's Oncology, G. 2010. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. *New England Journal of Medicine,* 363**,** 1313-23.

Barr, R. D., Simpson, T., Whitton, A., Rush, B., Furlong, W. & Feeny, D. H. 1999. Health-related quality of life in survivors of tumours of the central nervous system in childhood--a preference-based approach to measurement in a cross-sectional study. *European Journal of Cancer,* 35**,** 248-55.

Basta, N. O., Halliday, G. C., Makin, G., Birch, J., Feltbower, R., Bown, N., Elliott, M., Moreno, L., Barone, G., Pearson, A. D., James, P. W., Tweddle, D. A. & Mcnally, R. J. 2016. Factors associated with recurrence and survival length following relapse in patients with neuroblastoma. *British Journal of Cancer,* 115**,** 1048-1057.

Cai, W. W., R; Zhao, Hy; Wang, Wl; Wen, Dl; Zhang, Jh; Wang, Y; Tan, Yg; Zou, Hw 2012. Institutional Experience of Five-day Courses of Irinotecan as Palliative Chemotherapy in Chinese Patients with Refractory Neuroblastoma. *Hong Kong Journal of Paediatrics (New Series)***,** 223-229.

Cancer Research Uk. *CancerStats – Childhood Cancer – Great Britain & UK* [Online]. Available: http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@sta/documents/generalcontent/cr_051742.pdf [Accessed 2017].

Chmp, E. M. A. 2017. Unituxin: European Public Assessment Report.

Cohn, S. L., Pearson, A. D., London, W. B., Monclair, T., Ambros, P. F., Brodeur, G. M., Faldum, A., Hero, B., Iehara, T., Machin, D., Mosseri, V., Simon, T., Garaventa, A., Castel, V., Matthay, K. K. & Force, I. T. 2009. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *Journal of Clinical Oncology,* 27**,** 289-97.

Colon, N. C. & Chung, D. H. 2011. Neuroblastoma. *Advances in Pediatrics,* 58**,** 297-311.

Donfrancesco, A., Jenkner, A., Castellano, A., Ilari, I., Milano, G. M., De Sio, L., Cozza, R., Fidani, P., Deb, G., De Laurentis, C., Inserra, A. & Dominici, C. 2004. Ifosfamide/carboplatin/etoposide (ICE) as front-line, topotecan/ cyclophosphamide as second-line and oral temozolomide as third-line treatment for advanced neuroblastoma over

one year of age. *Acta Paediatrica, International Journal of Paediatrics, Supplement,* 93**,** 6-11.

El-Sabban, K., Al Sakhri, H., Alsulaimani, A. & Al Malky, T. 2013. Management of neuroblastoma. Comparative study between first-and second-line radioionated meta-iodobenzylguanidine therapy and chemotherapy alone. *Clinical Cancer Investigation Journal,* 2**,** 41-47.

Garaventa, A., Luksch, R., Biasotti, S., Severi, G., Pizzitola, M. R., Viscardi, E., Prete, A., Mastrangelo, S., Podda, M., Haupt, R. & De Bernardi, B. 2003. A Phase II Study of Topotecan with Vincristine and Doxorubicin in Children with Recurrent/Refractory Neuroblastoma. *Cancer,* 98**,** 2488-2494.

Garaventa, A., Parodi, S., De Bernardi, B., Dau, D., Manzitti, C., Conte, M., Casale, F., Viscardi, E., Bianchi, M., D'angelo, P., Zanazzo, G. A., Luksch, R., Favre, C., Tamburini, A. & Haupt, R. 2009. Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. *European Journal of Cancer,* 45**,** 2835-42.

Gatta, G., Botta, L., Rossi, S., Aareleid, T., Bielska-Lasota, M., Clavel, J., Dimitrova, N., Jakab, Z., Kaatsch, P., Lacour, B., Mallone, S., Marcos-Gragera, R., Minicozzi, P., Sanchez-Perez, M. J., Sant, M., Santaquilani, M., Stiller, C., Tavilla, A., Trama, A., Visser, O., Peris-Bonet, R. & Group, E. W. 2014. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. *Lancet Oncology,* 15**,** 35-47.

George, S. L., Falzone, N., Chittenden, S., Kirk, S. J., Lancaster, D., Vaidya, S. J., Mandeville, H., Saran, F., Pearson, A. D. J., Du, Y., Meller, S. T., Denis-Bacelar, A. M. & Flux, G. D. 2016. Individualized 131I-mIBG therapy in the management of refractory and relapsed neuroblastoma. *Nuclear Medicine Communications,* 37**,** 466-472.

Heck, J. E., Ritz, B., Hung, R. J., Hashibe, M. & Boffetta, P. 2009. The epidemiology of neuroblastoma: a review. *Paediatr Perinat Epidemiol,* 23**,** 125-43.

Hoy, S. M. 2016. Dinutuximab: A Review in High-Risk Neuroblastoma. *Target Oncology,* 11**,** 247-53.

Huang, M. & Weiss, W. A. 2013. Neuroblastoma and MYCN. *Cold Spring Harbor Perspectives in Medicine,* 3**,** a014415.

Hudson, M. M., Mertens, A. C., Yasui, Y., Hobbie, W., Chen, H., Gurney, J. G., Yeazel, M., Recklitis, C. J., Marina, N., Robison, L. R., Oeffinger, K. C. & Childhood Cancer Survivor Study, I. 2003. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA,* 290**,** 1583-92.

Johnson, K., Mcglynn, B., Saggio, J., Baniewicz, D., Zhuang, H., Maris, J. M. & Mosse, Y. P. 2011. Safety and efficacy of tandem 131I-metaiodobenzylguanidine infusions in relapsed/refractory neuroblastoma. *Pediatric Blood and Cancer,* 57**,** 1124-1129.

Jubab, A. A., Alnamshan, M., Alturki, A., Marzogi, M., Faris, A., Harbi, A. & Alansarri, A. 2016. Quality of Life in Children Treated for Neuroblastoma: A Multicenter Study. *International Journal of Advanced Research,* 4**,** 2725-2731.

Kushner, B. H., Modak, S., Kramer, K., Laquaglia, M. P., Yataghene, K., Basu, E. M., Roberts, S. S. & Cheung, N. K. 2014. Striking dichotomy in outcome of MYCN-amplified neuroblastoma in the contemporary era. *Cancer,* 120**,** 2050-9.

Ladenstein, R., Poetschger, U., Luksch, R., Brock, P., Castel, V., Yaniv, I., Papadakis, V., Laureys, G., Malis, J., Balwierz, W., Ruud, E., Kogner, P., Schroeder, H., Popovic, M., Ambros, P., Schreier, G., Lode, H., Loibner, H., Pearson, A. & Couanet, D. 2014. Immunotherapy (IT) with ch14.18/CHO for high-risk neuroblastoma: First results from the randomised HR-NBL1/SIOPEN trial. *Journal of Clinical Oncology* [Online], 32. Available: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/490/CN-01059490/frame.html.

Ladenstein, R., Pötschger, U., Hartman, O., Pearson, A. D. J., Klingebiel, T., Castel, V., Yaniv, I., Demirer, T. & Dini, G. 2008. 28 years of high-dose therapy and SCT for neuroblastoma in Europe: Lessons from more than 4000 procedures. *Bone Marrow Transplantation,* 41**,** S118-S127.

Laverdiere, C., Liu, Q., Yasui, Y., Nathan, P. C., Gurney, J. G., Stovall, M., Diller, L. R., Cheung, N. K., Wolden, S., Robison, L. L. & Sklar, C. A. 2009. Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute,* 101**,** 1131-40.

Lode, H. N., Valteau-Couanet, D., Garaventa, A., Gray, J., Castel, V., Yaniv, I., Siebert, N., Jensen, C., Endres, S., Pill, L., Eger, C., Seidel, D., Juttner, M., Kietz, S., Ehlert, K., Janzek, E., Manzitti, C., Muller, I., Loibner, H. & Ladenstein, R. 2016. Immunotherapy with ch14.18/CHO in combination with IL2 is active and effective in high-risk relapsed/refractory neuroblastoma patients. *Cancer Immunology Research,* 4.

London, W., Frantz, C., Campbell, L., Seeger, R., Brumback, B., Cohn, S., Matthay, K., Castleberry, R. & Diller, L. 2010. Phase II randomized comparison of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a Children's Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* [Online], 28. Available: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/556/CN-00761556/frame.html.

London, W. B., Castel, V., Monclair, T., Ambros, P. F., Pearson, A. D., Cohn, S. L., Berthold, F., Nakagawara, A., Ladenstein, R. L., Iehara, T. & Matthay, K. K. 2011. Clinical and biologic features predictive of survival after relapse of neuroblastoma: a report from the International Neuroblastoma Risk Group project. *Journal of Clinical Oncology,* 29**,** 3286-92.

Maris, J. M. 2010. Recent advances in neuroblastoma. *New England Journal of Medicine,* 362**,** 2202-11.

Maris, J. M., Hogarty, M. D., Bagatell, R. & Cohn, S. L. 2007. Neuroblastoma. *Lancet,* 369**,** 2106-20.

Matthay, K. K., Maris, J. M., Schleiermacher, G., Nakagawara, A., Mackall, C. L., Diller, L. & Weiss, W. A. 2016. Neuroblastoma. *Nature Reviews Disease Primers,* 2**,** 16078.

Matthay, K. K., Reynolds, C. P., Seeger, R. C., Shimada, H., Adkins, E. S., Haas-Kogan, D., Gerbing, R. B., London, W. B. & Villablanca, J. G. 2009. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study.[Erratum appears in J Clin Oncol. 2014 Jun 10;32(17):1862-3]. *Journal of Clinical Oncology,* 27**,** 1007-13.

Matthay, K. K., Villablanca, J. G., Seeger, R. C., Stram, D. O., Harris, R. E., Ramsay, N. K., Swift, P., Shimada, H., Black, C. T., Brodeur, G. M., Gerbing, R. B. & Reynolds, C. P. 1999. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy,

autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. *New England Journal of Medicine,* 341**,** 1165-73.

Matthay, K. K., Yanik, G., Messina, J., Quach, A., Huberty, J., Cheng, S. C., Veatch, J., Goldsby, R., Brophy, P., Kersun, L. S., Hawkins, R. A. & Maris, J. M. 2007. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. *Journal of Clinical Oncology,* 25**,** 1054-60.

Monclair, T., Brodeur, G. M., Ambros, P. F., Brisse, H. J., Cecchetto, G., Holmes, K., Kaneko, M., London, W. B., Matthay, K. K., Nuchtern, J. G., Von Schweinitz, D., Simon, T., Cohn, S. L., Pearson, A. D. & Force, I. T. 2009. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. *Journal of Clinical Oncology,* 27**,** 298-303.

Mort, S., Salantera, S., Matomaki, J., Salmi, T. T. & Lahteenmaki, P. M. 2011. Self-reported health-related quality of life of children and adolescent survivors of extracranial childhood malignancies: a Finnish nationwide survey. *Quality of Life Research,* 20**,** 787-97.

Nathan, P. C., Ness, K. K., Greenberg, M. L., Hudson, M., Wolden, S., Davidoff, A., Laverdiere, C., Mertens, A., Whitton, J., Robison, L. L., Zeltzer, L. & Gurney, J. G. 2007. Health-related quality of life in adult survivors of childhood Wilms tumor or neuroblastoma: A report from the childhood cancer survivor study. *Pediatric Blood Cancer,* 49**,** 704-15.

National Institute for Health and Clinical Excellence 2013. Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/article/pmg9/chapter/foreword (last accessed: 03 Mar 16).

Nice. 2005. *NICE Cancer Service Guideline CSG7: Improving outcomes in children and young people with cancer* [Online]. Available: https://www.nice.org.uk/guidance/csg7 [Accessed June 2017].

Nice. 2014. *NICE Quality Standard QS55: Cancer services for children and young people* [Online]. Available: https://www.nice.org.uk/guidance/qs55 [Accessed June 2017].

Nice. 2015. *NICE Guideline NG12: Suspected cancer: recognition and referral* [Online]. Available: https://www.nice.org.uk/guidance/ng12 [Accessed June 2017].

Orphanet. *Orphanet website UK* [Online]. Available: http://www.orphanet.org.uk/national/GB-EN/index/homepage/ [Accessed 2017].

Park, J. R., Bagatell, R., London, W. B., Maris, J. M., Cohn, S. L., Mattay, K. K., Hogarty, M. & Committee, C. O. G. N. 2012. Children's Oncology Group's 2013 blueprint for research: neuroblastoma. *Pediatric Blood Cancer,* 60**,** 985-93.

Park, J. R., Scott, J. R., Stewart, C. F., London, W. B., Naranjo, A., Santana, V. M., Shaw, P. J., Cohn, S. L. & Matthay, K. K. 2011. Pilot induction regimen incorporating pharmacokinetically guided topotecan for treatment of newly diagnosed high-risk neuroblastoma: a Children's Oncology Group study. *Journal of Clinical Oncology,* 29**,** 4351-7.

Park, J. R., Villablanca, J. G., London, W. B., Gerbing, R. B., Haas-Kogan, D., Adkins, E. S., Attiyeh, E. F., Maris, J. M., Seeger, R. C., Reynolds, C. P. & Matthay, K. K. 2009. Outcome

of high-risk stage 3 neuroblastoma with myeloablative therapy and 13-cis-retinoic acid: A report from the Children's Oncology Group. *Pediatric Blood and Cancer,* 52**,** 44-50.

Pession, A., Prete, A., Locatelli, F., Pierinelli, S., Pession, A. L., Maccario, R., Magrini, E., De Bernardi, B., Paolucci, P. & Paolucci, G. 1998. Immunotherapy with low-dose recombinant interleukin 2 after high-dose chemotherapy and autologous stem cell transplantation in neuroblastoma. *British Journal of Cancer,* 78**,** 528-533.

Polishchuk, A. L., Dubois, S. G., Haas-Kogan, D., Hawkins, R. & Matthay, K. K. 2011. Response, survival, and toxicity after iodine-131-metaiodobenzylguanidine therapy for neuroblastoma in preadolescents, adolescents, and adults. *Cancer,* 117**,** 4286-4293.

Portwine, C., Rae, C., Davis, J., Teira, P., Schechter, T., Lewis, V., Mitchell, D., Wall, D. A., Pullenayegum, E. & Barr, R. D. 2016. Health-Related Quality of Life in Survivors of High-Risk Neuroblastoma After Stem Cell Transplant: A National Population-Based Perspective. *Pediatric Blood Cancer,* 63**,** 1615-21.

Rarecare. *RARECARE database* [Online]. Available: http://dcnapp4.dcn.ed.ac.uk/rcnet/searchpage.aspx [Accessed 2017].

Rebholz, C. E., Reulen, R. C., Toogood, A. A., Frobisher, C., Lancashire, E. R., Winter, D. L., Kuehni, C. E. & Hawkins, M. M. 2011. Health care use of long-term survivors of childhood cancer: the British Childhood Cancer Survivor Study. *Journal of Clinical Oncology,* 29**,** 4181-8.

Simon, T., Berthold, F., Borkhardt, A., Kremens, B., De Carolis, B. & Hero, B. 2011. Treatment and outcomes of patients with relapsed, high-risk neuroblastoma: Results of German trials. *Pediatric Blood and Cancer,* 56**,** 578-583.

Siopen 2014. High-risk Neuroblastoma Study 1.7 of SIOP-Europe (SIOPEN). SIOPEN.

Spix, C., Pastore, G., Sankila, R., Stiller, C. A. & Steliarova-Foucher, E. 2006. Neuroblastoma incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. *European Journal of Cancer,* 42**,** 2081-91.

Tanaka, M., Kigasawa, H., Kato, K., Ijiri, R., Nishihira, H., Aida, N., Ohama, Y. & Tanaka, Y. 2010. A prospective study of a long-term follow-up of an observation program for neuroblastoma detected by mass screening. *Pediatric Blood Cancer,* 54**,** 573-8.

Uk Department of Health. 2010. *National Cancer Patient Experience Survey Programme - 2010 National Survey Report* [Online]. Available: https://www.quality-health.co.uk/resources/surveys/national-cancer-experience-survey/2010-national-cancer-patient-experience-survey/308-2010-national-cancer-patient-experience-survey-programme-national-report/file [Accessed June 2017].

Uk Office for National Statistics. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates [Accessed 2017].

Wengenroth, L., Gianinazzi, M. E., Rueegg, C. S., Luer, S., Bergstraesser, E., Kuehni, C. E. & Michel, G. 2015. Health-related quality of life in young survivors of childhood cancer. *Qualty of Life Research,* 24**,** 2151-61.

Yu, A. L., Gilman, A. L., Ozkaynak, M. F., London, W. B., Kreissman, S. G., Chen, H. X., Smith, M., Anderson, B., Villablanca, J. G., Matthay, K. K., Shimada, H., Grupp, S. A., Seeger, R., Reynolds, C. P., Buxton, A., Reisfeld, R. A., Gillies, S. D., Cohn, S. L., Maris, J. M., Sondel, P. M. & Children's Oncology, G. 2010. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *New England Journal of Medicine,* 363**,** 1324-34.

Zhou, M. J., Doral, M. Y., Dubois, S. G., Villablanca, J. G., Yanik, G. A. & Matthay, K. K. 2015. Different outcomes for relapsed versus refractory neuroblastoma after therapy with 131I-metaiodobenzylguanidine (131I-MIBG). *European Journal of Cancer,* 51**,** 2465-2472.

5. List of appendices

The list of appendices provided as a separate document to the main submission is presented below.

1. **Appendix C:** Summary of product characteristics (SmPC) and European public assessment report (EPAR)
2. **Appendix D:** Identification, selection and synthesis of clinical evidence
3. **Appendix E:** Subgroup analysis
4. **Appendix F:** Adverse reactions
5. **Appendix G:** Published cost-effectiveness studies
6. **Appendix H:** Health-related quality-of-life studies
7. **Appendix I:** Cost and healthcare resource identification, measurement and valuation
8. **Appendix J:** Clinical outcomes and disaggregated results from the model
9. **Appendix K:** Checklist of confidential information

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

APN311 for treating high-risk neuroblastoma [ID910]

Dear [redacted],

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received on 28 June 2017 from EUSAPharma. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Friday 4 August 2017**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Thomas Palmer, Technical Lead (Thomas.Palmer@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

A1. **Priority question.** Please provide individual Kaplan-Meier (KM) curves (unadjusted) for event-free survival (EFS) and overall survival (OS) for the treatment groups listed below. Please provide annual summaries and a summary of the latest cut-off date available, specifying the number of patients at risk as captured through the study and the total number of events at the observed period. Treatment groups of interest (total of 8 curves):

a. APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin;

b. APN311-302: Myeloablative therapy plus isotretinoin;

c. APN311-202;

d. APN311-303.

A2. **Priority question.** Please provide adjusted KM curves for EFS and OS for the four treatment groups requested in A1. Please adjust the KM curves for:

a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS);

b. Age at diagnosis;

c. V-Myc myelocytomatosis viral-related oncogene (MYCN) status;

d. International Neuroblastoma Staging System (INSS) stage.

A3. **Priority question.** Please carry out a matching-adjusted indirect comparison (MAIC) comparing APN311-302 (all people analysed) versus those receiving isotretinoin alone from the study by Yu *et al.* 2010.[1] Please follow methods described in NICE Decision Support Unit Technical Support Document 18.[2] The MAIC could be used to adjust the APN311-302 population using individual patient data to more closely match the population receiving isotretinoin, the comparator of interest to the decision problem. All the important prognostic factors need to be incorporated in the analysis to reduce bias in the indirect comparison. Inclusion of all people in APN311-302 would maximise the number of people available for analysis, and receipt of IL-2 by some people could be accounted for. Please provide:

a. Adjusted KM curves for EFS and OS from APN311-302;

and/or

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

b. Hazard ratios (HRs), with accompanying 95% Confidence Intervals (CIs), for EFS and OS for dinutuximab beta plus combination therapies versus isotretinoin alone.

A4. **Priority question.** If it is not possible to carry out an MAIC as requested in A3, for the comparison listed below, please provide adjusted HRs and accompanying 95% CIs for both EFS and OS:

a. APN311-302: APN311-302 versus historical control R1 (450 people in R1) (myeloablative therapy [MAT] plus immunotherapy versus MAT alone).

Please adjust the KM curves for:

a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS);

b. Age at diagnosis;

c. MYCN status;

d. INSS stage.

A5. **Priority question.** For the comparisons listed below, please provide adjusted HRs and accompanying 95% CIs for both EFS and OS:

a. APN311-202: APN311-202 versus both historical controls, that is, versus R1 (52 people who have relapsed) and Garaventa (immunotherapy versus no immunotherapy in people experiencing relapse).

Please adjust the KM curves for:

a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS);

b. Age at diagnosis;

c. MYCN status;

b. INSS stage.

A6. **Priority question.** For the evaluation of clinical effectiveness of dinutuximab beta in treatment of relapsed neuroblastoma, please clarify why results from APN311-202 and APN311-303 were compared versus the Garaventa historical control rather than versus results from the studies identified for mIBG or for chemotherapy.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A7. For the historical control group referred to as R1 (described in Section 2.9.2.2 of the CS), please clarify:

a. Did all the 450 people in the R1 group forming the control for high-risk neuroblastoma receive isotretinoin as part of maintenance therapy?

b. What maintenance treatments were available to those evaluated in the historical control after high-dose therapy who did not progress to the R2 randomisation phase?

c. The eligibility criteria for inclusion in the historical control R1 for high-risk neuroblastoma against which APN311-302 is compared (i.e., the 450 people without relapse): the discussion in Section 2.9.2.2 describes criteria for relapse but not high-risk;

d. Why so few people randomised in R1 went through to the R2 randomisation phase (seems to be 46 people based on a publication by Ladenstein et al.[3] describing the results of the R1 phase)?

A8. The Evidence Review Group's clinical experts have fed back that the population categorised as "refractory" in the key studies of dinutuximab beta is a clinically distinct population of interest to the decision problem that is the focus of this Single Technology Appraisal. Please provide a clinical and cost effectiveness analysis of dinutuximab beta for the treatment of refractory neuroblastoma, as has been provided for front-line and relapsed disease, using an appropriate control.

A9. Page 65 of the CS states that, "Of the nine studies investigating chemotherapy protocols (with or without stem cell transplantation) in relapsed/refractory NB patients, five studies reported OS data". Please provide reference details for the nine studies.

A10. Please provide definition(s) for relapsed disease as implemented in APN311-202, APN311-302, and APN311-303.

A11. Please provide a list of previous therapies received by people in APN311-202 before their last relapse.

A12. Please provide a list of previous therapies received by people in historical control R1 (52 people who relapsed) before their last relapse.

A13. Please provide a list of previous therapies received by people in the historical control Garaventa before their last relapse.

A14. Page 82 of the CS, states that, "When adding prognostic factors for OS to the model, the treatment difference in OS time was still statistically significant (estimated hazard

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

ratio 0.555 [95% CI 0.32,0.97], p = 0.0376)". Please clarify which prognostic factors have been incorporated into the analysis.

A15. Please clarify how the 5-year OS estimate for APN311-302 has been derived, given that the first person enrolled onto R2 of APN311-302 was recruited on 30 Nov 2009 and the last person on 12 August 2013 (CS pg. 38). Has measurement of 5-year follow-up started at time of randomisation of the first person enrolled? Or is follow-up person-specific and so starts when that person is randomised?

A16. Please provide median (and range) and mean (with accompanying SD or SE) follow-up time at the last cut-off date for analysis for APN311-302 (and the date of analysis) for those receiving dinutuximab beta: (i) at front-line; (ii) at relapse; (iii) for refractory neuroblastoma.

A17. Many thanks for providing the Clinical Study Report (CSR) for APN311-301. Please clarify [redacted].

A18. Page 33 of the CS (Table 11) states, in relation to the randomisation of people in APN311-302, "Randomisation of patients to the different treatment arms was done using a web-based system". Please provide additional information on the method of randomisation and how people accessed the treatment allocation (e.g., centralised access). As part of the response, please give information as to whether the web-based system incorporated a method to conceal allocation sequence from those people assigning participants to intervention groups.

A19. Page 81 of the CS states, in the description of the pooled analysis of APN311-202 and APN311-303 versus historical control R1, that "It cannot be excluded that the Historical Control R1 patients may have been treated with dinutuximab beta within the scope of other relapse studies". Please clarify this statement given the description that the historical control R1 is derived from an earlier stage of the APN311-302 study which included people diagnosed with high-risk neuroblastoma and who had received no previous chemotherapy other than one cycle of etoposide and carboplatin.

A20. The description of the per-protocol-set (PPS) in APN311-302 indicates that people were excluded from the PPS if, "R2 randomisation criteria were not met or missing". Please clarify how people were randomised in R2 and included in the full analysis set if they did not meet R2 randomisation criteria.

A21. Please provide a table of relapse/progression prior to immunotherapy for people in APN311-303 like Table 20 provided for people in APN311-202.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A22. Throughout the reporting of the individual adverse effects associated with dinutuximab beta (Section 2.10.3.2 onwards in the CS), only percentages are reported. For the 98 people who underwent continuous infusion, please provide a table of absolute event numbers, with accompanying denominator, for each adverse effect mentioned in the CS.

A23. Please clarify how EUSAPharma envisages dinutuximab beta being used in the relapsed/refractory setting. Specifically, if people receive dinutuximab beta as a first-line maintenance treatment for high-risk neuroblastoma, would they undergo re-treatment with dinutuximab beta at relapse or non-response to therapy?

A24. Please provide a clinical rationale as to why people would be likely to respond to re-treatment with dinutuximab beta.

A25. Please clarify whether there are any circumstances under which isotretinoin would not be given concomitantly with dinutuximab beta. If so, please give details.

A26. Please give details of any studies, either completed or on-going, that evaluate the use of dinutuximab beta in relapsed or refractory disease in people having received dinutuximab beta as a first-line treatment for high-risk neuroblastoma.

A27. For the evaluation of clinical effectiveness in APN311-302, please clarify why intention-to-treat analyses of the 406 people were not reported.

Section B: Clarification on cost-effectiveness data

Treatment effectiveness

B1. **Priority question**. For both high-risk and relapsed models, please develop a partitioned survival model to estimate the percentage of patients in each state of the economic model during the first 5 years of the analysis (NICE Decision Support Unit's Technical Support Document 19), followed by the long-term survival model already incorporated in the economic models. For the high-risk population, this should encompass the following steps:

a. Please use the 5 years (or longer follow-up if possible) OS and EFS KM data from study 302 (including all patients in the study) to model the percentage of patients in the stable disease, failure and death states of the economic model. If the maximum follow-up period for these outcomes does not reach 5 years, please conduct survival analysis using the KM data (please see question B2 for more details on this).

b. To estimate the percentage of patients in the health states of the comparator model please undertake the following analyses:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

I. As the base case, please use the OS and EFS KM data from the isotretinoin arm in Yu *et al.* 2010,[1] adjusted for prior high-dose therapy (HDT), age at diagnosis, MYCN and INSS stage (requested in A3) to populate the stable disease, failure and death states of the comparator arm of the economic model;

II. If providing adjusted KM curves for both treatment arms is not possible, please use the OS and EFS HRs comparing all patients from study 302 to Yu *et al.* 2010,[1] adjusted for prior HDT, age at diagnosis, MYCN and INSS stage (requested in A3), and apply these to the OS and EFS curves estimated in B1.a), to estimate OS and EFS curves for isotretinoin.

If it is not possible to use study 302 (all patients) and Yu *et al.* 2010[1] (isotretinoin arm) to model the intervention and comparator arms of the model, respectively, please use study 302 (to model dinutuximab beta) and historical control R1 (to model isotretinoin) as explained in A4. If these data sources are used, please follow the requested steps for the modelling approach with the appropriate data.

For the relapsed population, please follow the steps listed above, using the appropriate studies and adjusted data for prognostic factors prior HDT, age at diagnosis, MYCN and INSS stage (requested in A6). Study 202 should be used for modelling the dinutuximab beta arm of the model. To model the comparator arm of the model, please use the Garaventa study and the historical control R1 (relapsed patients) as a scenario analysis.

B2. **Priority question**. For both high-risk and relapsed models, please develop a partitioned survival model to estimate the percentage of patients in each state of the economic model during the first 10 years of the analysis (NICE Decision Support Unit's Technical Support Document 19), followed by the long-term survival model already incorporated in the economic models. For the high-risk population, this should encompass the following steps:

a. Please use the maximum follow-up available to obtain OS and EFS KM data from study 302 (including all patients in the study) to model the percentage of patients in the stable disease, failure and death states of the economic model. Following this step, please fit survival curves and extrapolate the best fitting curve from the last available data point to the 10-year horizon (please undertake the steps reported in the NICE Decision Support Unit's Technical Support Document 14 to carry curve fitting and curve extrapolation).

b. To estimate the percentage of patients in the health states of the comparator model please undertake the following analyses:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

I. As the base case, please use the maximum follow-up available to obtain OS and EFS KM data from the isotretinoin arm in Yu *et al.* 2010,[1] adjusted for prior HDT, age at diagnosis, MYCN and INSS stage (requested in the A3) to model the percentage of patients in the stable disease, failure and death states of the economic model. Following this step, please fit survival curves and extrapolate the best fitting curve from the last available data point to the 10-year horizon (please undertake the steps reported in the NICE Decision Support Unit's Technical Support Document 14 to carry curve fitting and curve extrapolation).

II. If fitting adjusted treatment curves independently is not possible, please use the OS and EFS HRs comparing all patients from study 302 to Yu *et al.* 2010,[1] adjusted for prior HDT, age at diagnosis, MYCN and INSS stage (requested in A3), and apply these to the OS and EFS curves estimated in B2.c), to estimate OS and EFS curves for isotretinoin.

If it is not possible to use study 302 (all patients) and Yu *et al.* 2010[1] (isotretinoin arm) to model the intervention and comparator arms of the model, respectively, please use study 302 (to model dinutuximab beta) and historical control R1 (to model isotretinoin) as explained in A4. If these data sources are used, please follow the requested steps for the modelling approach with the appropriate data.

For the relapsed population, please follow the steps listed above, using the appropriate studies and adjusted data for prognostic factors prior HDT, age at diagnosis, MYCN and INSS stage (requested in A6). Study 202 should be used for modelling the dinutuximab beta arm of the model. To model the comparator arm of the model, please use the Garaventa study and the historical control R1 (relapsed patients) as a scenario analysis.

B3. **Priority question**. Please provide (in an Excel sheet) all the survival curves resulting from the fitting and extrapolation exercise undertaken in B2 extrapolated to a 90-year time horizon (even if only 10 years of the curves are used in the economic model as requested in B2). Please provide two sets of all the survival curves extrapolated – one set based on monthly cycles and the other set of curves based on yearly cycles.

B4. **Priority question**. When modelling both scenarios described above (estimating a 5-year short-term model before patients achieve a potential cure or estimating a 10-year short-term model before patients achieve a potential cure), please:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

a. Set the cycle length in the short-term model to 1 month. This should be consistent throughout the entire short-time model, i.e. all cycles for 5 (or 10) years should have the duration of 1 month;

b. Please discount costs and benefits according to the monthly cycles of the model;

c. Please adjust costs as necessary to reflect monthly costs in the models, for all costs considered. This means estimating monthly costs and attributing the monthly cost to the proportion of patients in the appropriate heath state for each cycle of the economic model. After the 5 (or 10 years) in the short-term model, the costs should be adjusted to reflect annual costs;

d. Please adjust other inputs that depend on cycle length in the model accordingly;

e. After the short-term model (5 or 10 years) please leave the long-term model with yearly cycles, as it is now, and discount costs and QALYs accordingly.

B5. **Priority question**. The ERG's clinical expert stated that once a patient relapses, then it is unlikely that they will be cured from their disease and they will have continual cycles of relapse and remission, shortening in length as time goes on. Please remove the assumption of cure from the relapse model and implement the extrapolated survival curves obtained in B2 to model the long-term portion of the economic model. Because of the change in cycle length to the long-term model from 10 years , the ERG advises using the two sets of curves requested in B3 (i.e. use the monthly fitted curves for the first 10 years and use the annually fitted curves after 10 years). This avoids re-estimating resource use in the model to adjust for cycle length.

Health related quality of life

B6. **Priority question**. The ERG in the suspended single technology appraisal of dinutuximab[4] (ID799) used the mapping algorithm reported in Rowen *et al*. 2009[5] to map the SF-36 quality of life data in Nathan *et al.* 2007[6] into EQ-5D utility data. Please carry out a scenario analysis using the EQ-5D values estimated by the ERG in ID799 .

B7. **Priority question**. After 5 years, any patients in the failure health state are assumed to have a 41.7% decrement to the age adjusted UK EQ-5D population norms. Please provide a scenario where the constant utility value of 0.56 (based on Barr *et al.* 1999[7]) is assumed for the failure health state.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B8. Please provide the clinical rationale for attributing a lower utility value (compared to the general population) to patients in the stable disease state after 5 years, when these patients are assumed to be cured.

B9. Please provide the clinical rationale for attributing the same utility value to patients in the stable disease state in the first-line and in the r/r population. Please provide a similar justification for patients in the failure state.

Adverse events

B10. **Priority question**. Please clarify how the proportions of patients experiencing dinutuximab beta-related adverse events (reported in Table 56 and used in the model) were estimated.

B11. **Priority question**. Please use the appropriate clinical source to model adverse events in the model. For example, if Yu *et al.* 2010[1] is used to model the clinical effectiveness of isotretinoin, please use the adverse events reported in the paper. If the historical control R1 data are used, then please use the adverse events reported in the R1 study or provide a rationale for not doing so. This applies to all treatment arms across both models. When this is not feasible, please provide the rationale for not following this approach.

B12. **Priority question**. Please clarify the criteria used for inclusion of adverse events in the model, and please clarify which proportions/adverse event rates used in the economic model are treatment-related adverse events and which events are treatment-emergent events. Please justify why one or the other was selected.

B13. Please run a scenario analysis using only the rates of adverse events on the subset of patients in the analysis who received dinutuximab beta as a continuous infusion.

Resource use and costs

B14. **Priority question**. Clinical expert opinion sought by the ERG suggested that stable patients are seen every 3 months for the first year, then between 3-6 months between the first and the fifth year with yearly visits after 5 years. Please provide a scenario where costs associated in the stable health state reflect a follow-up of every 3 months for the first 5 years and yearly thereafter.

B15. **Priority question**. In the relapsed model, the weight adjustment is based on the age of the population of the high-risk model. Please correct this.

B16. **Priority question**. As described on page 137 of the CS, patients assigned to TOPO/CTX received intravenous topotecan 0.75mg/m^2/d and cyclophosphamide 250mg/m^2/d for 5 days. Cycles were 21 days, starting subcutaneous filgrastim 5

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

µg/kg/d on day 6. However, in the economic model costs are based on the unit cost of the drug. Please correct the high risk and relapsed models to include body surface area and weight in the cost calculations for the failure health state, taking in to account that the two models have different starting ages (3 years for high risk and 6 years for relapsed) and that weight and surface area change over time.

B17. **Priority question**. Please include the costs IL-2 has in the high-risk model (and associated administration and hospitalisation costs) to accurately reflect the proportion of patients who received IL-2 in the clinical studies used as the source for clinical effectiveness in the economic model. For example, if the entire population from study 302 is used, please use the total number (or percentage) of patients in 302 who received IL-2 to cost the treatment in the economic model.

B18. **Priority question**. Please provide the mean number of hospital days from APN311-302 and APN311-202. If possible, please perform a scenario implementing the mean hospital days into the hospitalisation costs for each arm of the high-risk and relapse model.

B19. Please specify which costs used in the model are from the National tariff or the Payment by Results tariff and why NHS reference costs were not deemed appropriate in these cases.

B20. Please provide the mean treatment duration with dinutuximab beta in APN311-302 and APN311-202.

B21. Please provide the mean treatment duration with isotretinoin in the Yu *et al.* 2010[1] study and in the historical control studies R1 and Garaventa.

B22. Table 65 of the CS reports 15 hospital days in the first cycle. However, dinutuximab beta and IL-2 require 10 days of hospitalisation. Please clarify what the 15-days assumption is based on.

B23. Please include a scenario analysis using the mean weight from the clinical studies used as the source for clinical effectiveness in the economic model. For example, if the entire population from study 302 is used, please use the mean weight of patients in 302 to estimate treatment costs in the economic model. Please do this for all treatments in both economic models.

B24. Please review how weight and body surface area have been implemented in the estimation of treatment costs in both models, ensuring calculations for each model refer to the correct population (high-risk relates to 3-year olds and relapsed relates to 6-year olds) and correct the models if necessary.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B25. Please provide a breakdown of the calculations used to derive the average monthly units of resources consumed based on Rebholz *et al.* 2011[8] presented in Table 68 of the company submission.

B26. In Table 64 and 65 of the CS, for Cycle 2, a second administration inpatient cost is reported instead of a first administration inpatient cost as outlined in the text explanation. Please clarify what was done in the economic model and if necessary, correct the model to reflect the right assumption.

B27. The ERG identified a discrepancy in the outpatient unit cost assumed in the model in Cell I85 of the "InputGeneral" tab and the unit cost reported in Table 68 of the CS. Please clarify which is the correct value.

Literature search & assumptions

B28. Please clarify which assumptions (if any) made in the economic model for this analysis are informed by the modelling approach taken by the company or by the recommendations of the appraisal committee in the suspended single technology appraisal of dinutuximab (ID799)[4]

B29. Please clarify the source used to obtain the standard error estimates (reported in Table 71, page 138), particularly for 5-year OS and EFS outcomes for dinutuximab beta and isotretinoin for the first-line population (SD 0.2%) and the r/r population (0.16%; 0.15%; 0.18% and 0.08%).

Section C: Textual clarifications and additional points

C1. **Priority question**. The ERG encountered errors when running both the deterministic and probabilistic sensitivity analysis in the model. Please ensure that these are running correctly in any model submitted in response to clarification, or the original model if no new models are provided during the clarification stage.

C2. Please report the updated sensitivity analyses results for the updated models together with the updated base case results.

C3. Please clarify which service provider was used to carry out the literature search of EMBASE.

C4. Please clarify whether the data presented in Table 14 of the CS should be marked as AiC: the data are also presented in Table 15 of the CS and are not marked as AiC.

C5. In Table 37 of the CS, please confirm that the unit for data reported in the row labelled, "Time between diagnosis and first relapse" is years. Also, please validate and confirm the data reported for 95% CI, Median, and Min, Max.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

C6. Please provide the footnotes to Table 41 of the CS.

References

1. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *NEJM* 2010;363(14):1324–34.
2. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, NJ W. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016. Last accessed 19th July 2017. Available from: http://www.nicedsu.org.uk/TSD18%20Population%20adjustment%20TSD%20-%20FINAL.pdf.
3. Ladenstein R, Potschger U, Pearson ADJ, Brock P, Luksch R, Castel V, et al. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. *Lancet Oncol* 2017;18(4):500–14.
4. National Institute for Health and Care Excellence (NICE). Dinutuximab for treating high-risk neuroblastoma. 2015. Last accessed 19th July 2017. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag507/documents.
5. Rowen D, Brazier J, Tsuchiya A, Alava MH. Valuing states from multiple measures on the same visual analogue sale: a feasibility study. *Health Econ* 2012;21(6):715–29.
6. Nathan PC, Ness KK, Greenberg ML, Hudson M, Wolden S, Davidoff A, et al. Health-related quality of life in adult survivors of childhood Wilms tumor or neuroblastoma: A report from the childhood cancer survivor study. *Pediatr Blood Cancer* 2007;49(5):704–15.
7. Barr RD, Simpson T, Whitton A, Rush B, Furlong W, Feeny DH. Health-related quality of life in survivors of tumours of the central nervous system in childhood–a preference-based approach to measurement in a cross-sectional study. European journal of cancer (Oxford, England: 1990). 1999;35(2):248–55.
8. Rebholz CE, Reulen RC, Toogood AA, Frobisher C, Lancashire ER, Winter DL, et al. Health care use of long-term survivors of childhood cancer: the British Childhood Cancer Survivor Study. *J Clin Oncol* 2011;29(31):4181–8.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Dinutuximab beta Apeiron [ID910]

Clarification Letter – First part

(Results of the analyses that are possible based on the data immediately available)

[10 August 2017]

Version 2

Date of preparation: 10 August 2017

File name	Version	Contains confidential information	Date
ID910 dinutuximab beta clarification letter–First Part_10th august [noACIC]	**2**	**No [noACIC]**	**10 August 2017**

Table of Contents

Section A: Clarification on effectiveness data 8

A1. Priority question. Please provide individual Kaplan-Meier (KM) curves (unadjusted) for event-free survival (EFS) and overall survival (OS) for the treatment groups listed below..... 8

- **a. APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin; 8**
- **b. APN311-302: Myeloablative therapy plus isotretinoin; 10**
- **c. APN311-202;..... 12**
- **d. APN311-303..... 14**

A2. Priority question. Please provide adjusted KM curves for EFS and OS for the four treatment groups requested in A1 16

- **a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS); 16**
- **b. Age at diagnosis;..... 25**
- **c. V-Myc myelocytomatosis viral-related oncogene (MYCN) status; 33**
- **d. International Neuroblastoma Staging System (INSS) stage. 41**

Table 1 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 8

Table 2 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 8

Table 3 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 9

Table 4 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 9

Table 5 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 10

Table 6 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival..... 10

Table 7 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 11

Table 8 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival..... 11

Table 9 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-202 – Kaplan-Meier plot..... 12

Table 10 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-202 – Table of annual survival 12

Table 11 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-202 – Kaplan-Meier plot..... 13

Table 12 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-202 – Table of annual survival 13

Table 13 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-303 – Kaplan-Meier plot 14

Table 14 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-303 – Table of annual survival 14

Table 15 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-303 – Kaplan-Meier plot 15

Table 16 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-303 – Table of annual survival 15

Table 17 – Survival analysis on overall survival (OS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 16

Table 18 – Survival analysis on overall survival (OS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 17

Table 19 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 17

Table 20 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 18

Table 21 – Survival analysis on overall survival (OS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 18

Table 22 – Survival analysis on overall survival (OS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival 19

Table 23 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 19

Table 24 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival 20

Table 25 – Survival analysis on overall survival (OS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-202 – Kaplan-Meier plot 21

Table 26 – Survival analysis on overall survival (OS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-202 – Table of annual survival 21

Table 27 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-202 – Kaplan-Meier plot 22

Table 28 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-202 – Table of annual survival 22

Table 29 – Survival analysis on overall survival (OS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-303 – Kaplan-Meier plot 23

Table 30 – Survival analysis on overall survival (OS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-303 – Table of annual survival 23

Table 31 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-303 – Kaplan-Meier plot 24

Table 32 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-303 – Table of annual survival 24

Table 33 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 25

Table 34 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 25

Table 35 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 26

Table 36 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 26

Table 37 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 27

Table 38 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival 27

Table 39 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 28

Table 40 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival 28

Table 41 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-202 – Kaplan-Meier plot 29

Table 42 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-202 – Table of annual survival 29

Table 43 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-202 – Kaplan-Meier plot 30

Table 44 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-202 – Table of annual survival 30

Table 45 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-303 – Kaplan-Meier plot 31

Table 46 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-303 – Table of annual survival 31

Table 47 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-303 – Kaplan-Meier plot 32

Table 48 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-303 – Table of annual survival 32

Table 49 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 33

Table 50 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 33

Table 51 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 34

Table 52 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 34

Table 53 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 35

Table 54 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival 35

Table 55 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 36

Table 56 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival 36

Table 57 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-202 – Kaplan-Meier plot 37

Table 58 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-202 – Table of annual survival 37

Table 59 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-202 – Kaplan-Meier plot 38

Table 60 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-202 – Table of annual survival..... 38

Table 61 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-303 – Kaplan-Meier plot 39

Table 62 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-303 – Table of annual survival..... 39

Table 63 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-303 – Kaplan-Meier plot 40

Table 64 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-303 – Table of annual survival..... 40

Table 65 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 41

Table 66 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 41

Table 67 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot 42

Table 68 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival 42

Table 69 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 43

Table 70 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival..... 44

Table 71 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot 45

Table 72 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival..... 45

Table 73 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-202 – Kaplan-Meier plot 46

Table 74 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-202 – Table of annual survival 47

Table 75 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-202 – Kaplan-Meier plot 47

Table 76 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-202 – Table of annual survival 48

Table 77 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-303 – Kaplan-Meier plot 49

Table 78 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-303 – Table of annual survival 49

Table 79 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-303 – Kaplan-Meier plot 50

Table 80 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-303 – Table of annual survival 50

Section A: Clarification on effectiveness data

A1. **Priority question. Please provide individual Kaplan-Meier (KM) curves (unadjusted) for event-free survival (EFS) and overall survival (OS) for the treatment groups listed below.** Please provide annual summaries and a summary of the latest cut-off date available, specifying the number of patients at risk as captured through the study and the total number of events at the observed period. Treatment groups of interest (total of 8 curves):

a. APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin;

Table 1 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

Table 2 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

					95% confidence interval	
Year	Number of subjects at risk	Cumulated number of events	Survivor function estimate	Survival standard error	Lower limit	Upper limit
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 3 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

[redacted]

Table 4 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

					95% confidence interval	
Year	**Number of subjects at risk**	**Cumulated number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

b. APN311-302: Myeloablative therapy plus isotretinoin;

Table 5 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

Table 6 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

					95% confidence interval	
Year	**Number of subjects at risk**	**Cumulated number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Four years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 7 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

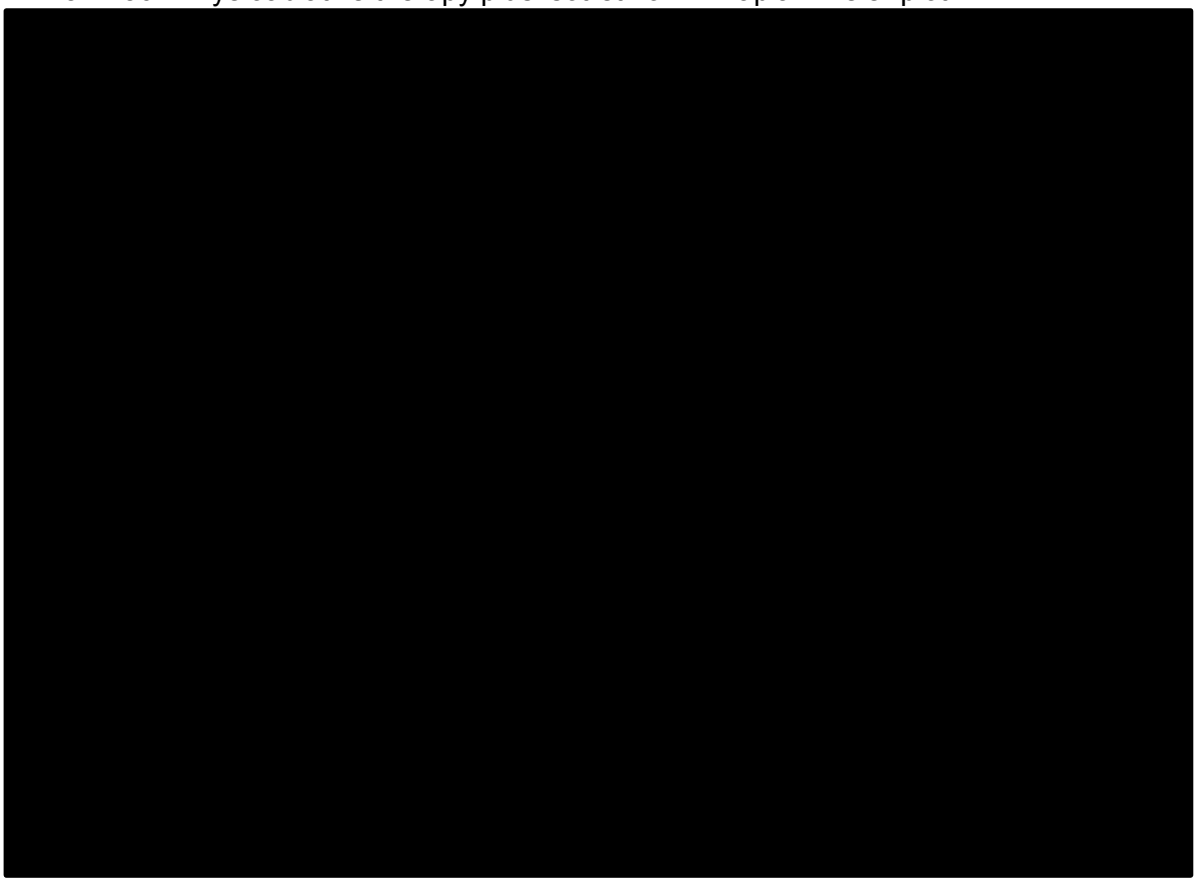


Table 8 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

					95% confidence interval	
Year	**Number of subjects at risk**	**Cumulated number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Four years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

c. APN311-202;

Table 9 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-202 – Kaplan-Meier plot

Table 10 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-202 – Table of annual survival

					95% confidence interval	
Year	Number of subjects at risk	Cumulated number of events	Survivor function estimate	Survival standard error	Lower limit	Upper limit
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-202 – Kaplan-Meier plot

Table 12 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-202 – Table of annual survival

					95% confidence interval	
Year	**Number of subjects at risk**	**Cumulated number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

d. APN311-303.

Table 13 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-303 – Kaplan-Meier plot

Table 14 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-303 – Table of annual survival

					95% confidence interval	
Year	Number of subjects at risk	Cumulated number of events	Survivor function estimate	Survival standard error	Lower limit	Upper limit
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-303 – Kaplan-Meier plot

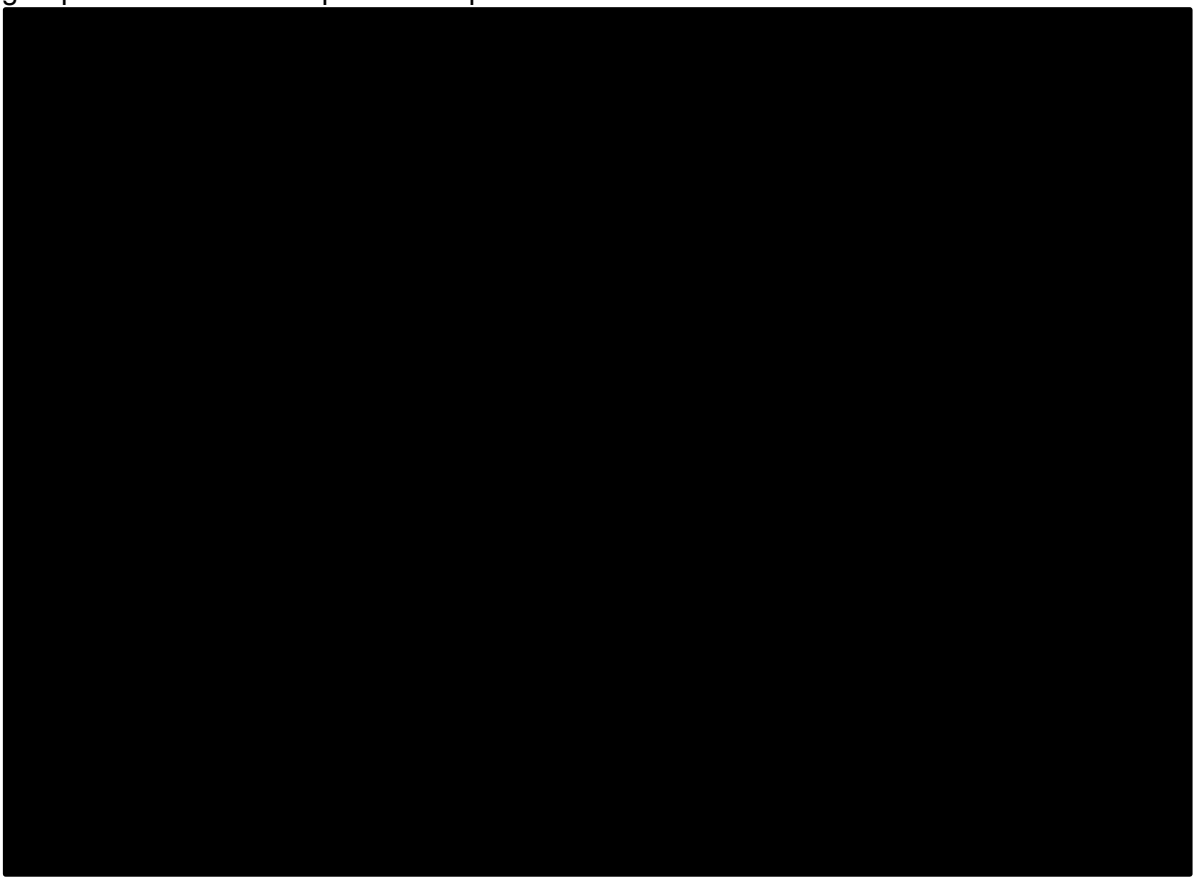


Table 16 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-303 – Table of annual survival

					95% confidence interval	
Year	**Number of subjects at risk**	**Cumulated number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A2. **Priority question. Please provide adjusted KM curves for EFS and OS for the four treatment groups requested in A1**. Please adjust the KM curves for:

a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS);

i. APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin;

Table 17 – Survival analysis on overall survival (OS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

Table 18 – Survival analysis on overall survival (OS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
BuMel+ASCT = yes and CEM+ASCT = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
BuMel+ASCT = no and CEM+ASCT = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 19 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

Table 20 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
BuMel+ASCT = yes and CEM+ASCT = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
BuMel+ASCT = no and CEM+ASCT = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

ii. APN311-302: Myeloablative therapy plus isotretinoin;

Table 21 – Survival analysis on overall survival (OS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

Table 22 – Survival analysis on overall survival (OS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
BuMel+ASCT = yes and CEM+ASCT = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
BuMel+ASCT = no and CEM+ASCT = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 23 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

Table 24 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
BuMel+ASCT = yes and CEM+ASCT = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
BuMel+ASCT = no and CEM+ASCT = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

iii. APN311-202;

Table 25 – Survival analysis on overall survival (OS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-202 – Kaplan-Meier plot

Table 26 – Survival analysis on overall survival (OS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-202 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
BuMel+ASCT = yes and CEM+ASCT = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
BuMel+ASCT = no and CEM+ASCT = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Table 27 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-202 – Kaplan-Meier plot

Table 28 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-202 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
BuMel+ASCT = yes and CEM+ASCT = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
BuMel+ASCT = no and CEM+ASCT = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

iv. APN311-303.

Table 29 – Survival analysis on overall survival (OS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-303 – Kaplan-Meier plot

Table 30 – Survival analysis on overall survival (OS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-303 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
BuMel+ASCT = yes and CEM+ASCT = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
BuMel+ASCT = no and CEM+ASCT = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Table 31 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-303 – Kaplan-Meier plot

Table 32 – Survival analysis on Event Free Survival (EFS), adjusted for prior treatment treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT) for treatment group APN311-303 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
BuMel+ASCT = yes and CEM+ASCT = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
BuMel+ASCT = no and CEM+ASCT = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

b. Age at diagnosis;

i. APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin;

Table 33 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

Table 34 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
Mean age (y) at initial diagnosis = 3.49	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 35 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

Table 36 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
Mean age (y) at initial diagnosis = 3.50	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

ii. APN311-302: Myeloablative therapy plus isotretinoin;

Table 37 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

Table 38 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
Mean age (y) at initial diagnosis = 3.35	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 39 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

Table 40 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
Mean age (y) at initial diagnosis = 3.35	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

iii. APN311-202;

Table 41 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-202 – Kaplan-Meier plot

Table 42 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-202 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
Age (y) at initial diagnosis = 3.70	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Table 43 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-202 – Kaplan-Meier plot

Table 44 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-202 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
Mean age (y) at initial diagnosis = 3.70	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

iv. APN311-303.

Table 45 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-303 – Kaplan-Meier plot

Table 46 – Survival analysis on overall survival (OS), adjusted for Age at diagnosis for treatment group APN311-303 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
Mean age (y) at initial diagnosis = 4.54	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Table 47 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-303 – Kaplan-Meier plot

Table 48 – Survival analysis on Event Free Survival (EFS), adjusted for Age at diagnosis for treatment group APN311-303 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
Mean age (y) at initial diagnosis = 4.54	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

c. V-Myc myelocytomatosis viral-related oncogene (MYCN) status;

i. APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin;

Table 49 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

Table 50 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
MYCN = No	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
MYCN = Yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 51 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

Table 52 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
MYCN = No	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
MYCN = Yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

ii. APN311-302: Myeloablative therapy plus isotretinoin;

Table 53 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

Table 54 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
MYCN = No	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
MYCN = Yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 55 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

Table 56 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
MYCN = No	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
MYCN = Yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

iii. APN311-202;

Table 57 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-202 – Kaplan-Meier plot

Table 58 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-202 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
MYCN = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
MYCN = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Table 59 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-202 – Kaplan-Meier plot

Table 60 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-202 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
MYCN = no	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
MYCN = yes	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

iv. APN311-303.

Table 61 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-303 – Kaplan-Meier plot

Table 62 – Survival analysis on overall survival (OS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-303 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
MYCN = Nonamplified	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
MYCN = Amplified	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Table 63 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-303 – Kaplan-Meier plot

Table 64 – Survival analysis on Event Free Survival (EFS), adjusted for V-Myc myelocytomatosis viral-related oncogene (MYCN) status for treatment group APN311-303 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
MYCN = Nonamplified	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
MYCN = Amplified	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

d. International Neuroblastoma Staging System (INSS) stage.

i. APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin;

Table 65 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

Table 66 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
INSS = 3	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

INSS = 4S	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 67 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Kaplan-Meier plot

[redacted]

Table 68 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
INSS = 3	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]

	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4S	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

ii. APN311-302: Myeloablative therapy plus isotretinoin;

Table 69 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

[redacted]

Table 70 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
INSS = 2	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 3	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4S	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4S	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 71 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Kaplan-Meier plot

Table 72 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
INSS = 2	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 3	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]

	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4S	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Four years	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4S	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

iii. APN311-202;

Table 73 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-202 – Kaplan-Meier plot

Table 74 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-202 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
INSS = 1	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4s	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Table 75 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-202 – Kaplan-Meier plot

Table 76 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-202 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
INSS = 1	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4s	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

iv. APN311-303.

Table 77 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-303 – Kaplan-Meier plot

Table 78 – Survival analysis on overall survival (OS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-303 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
INSS = 1	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 2A	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 3	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

INSS = 4	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Three years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

Table 79 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-303 – Kaplan-Meier plot

[redacted]

Table 80 – Survival analysis on Event Free Survival (EFS), adjusted for International Neuroblastoma Staging System (INSS) stage for treatment group APN311-303 – Table of annual survival

				95% confidence interval	
Adjustment condition	**Year**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
INSS = 1	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 2A	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

INSS = 3	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]
INSS = 4	One year	[redacted]	[redacted]	[redacted]	[redacted]
	Two years	[redacted]	[redacted]	[redacted]	[redacted]
	Last cut-off	[redacted]	[redacted]	[redacted]	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Dinutuximab beta Apeiron [ID910]

Clarification Letter – First part

(Results of the analyses that are possible based on the data immediately available)

[16 August 2017]

Version 2

Date of preparation: 16 August 2017

File name	Version	Contains confidential information	Date
ID910 dinutuximab beta clarification letter–First Part_AdditionalQuestions_16th august [noACIC]	**2**	**No [noACIC]**	**16 August 2017**

Table of Contents

Section A: Clarification on effectiveness data 5

A1. Priority question. Please provide individual Kaplan-Meier (KM) curves (unadjusted) for event-free survival (EFS) and overall survival (OS) for the treatment groups listed below. 5

a. In response to A1, the company has provided the number of patients at risk at annual cut off dates, rather than at various time points throughout the analysis. Are these numbers available? 5

a. APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin; 5

b. APN311-302: Myeloablative therapy plus isotretinoin; 8

c. APN311-202; 12

d. APN311-303. 15

b. In response to A2, absolute numbers of people analysed at the various time points are not reported. Are these available? 17

c. In A1 and A2, the company has provided information at the last cut-off date for all analyses but the dates of cut off/length of follow-up at the time points are not clear. Would it be possible to obtain this information as requested in the original clarification document? 17

d. In A2, the company has kindly gone to a lot of effort to supply the KM curves adjusted for each individual prognostic factor specified in the question (providing 32 figures and accompanying tables). I'm afraid there has been a misunderstanding. A2 is intending to ask for the KM curves adjusted simultaneously for all the listed factors, so a total of 8 curves. On re-reading the question, we can understand how the company has interpreted the question and the confusion has arisen. We apologise for any inconvenience caused on our part. Would it be possible to obtain KM curves adjusted for all factors? 17

1 Overall Survival 18

1.1 Treatment group isotretinoin+Dinutuximab beta EUSA 18

1.2 Treatment group isotretinoin+Dinutuximab beta EUSA+IL2 23

1.3 Treatment group APN311-202 27

1.4 Treatment group APN311-303 30

2 Event-free Survival 33

2.1 Treatment group isotretinoin+Dinutuximab beta EUSA 33

2.2 Treatment group isotretinoin+Dinutuximab beta EUSA+IL2 38

2.3 Treatment group APN311-202 42

2.4 Treatment group APN311-303 45

Table 1 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of survival time estimates . 5

Table 2 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of survival time estimates 7

Table 3 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of survival time estimates 8

Table 4 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of survival time estimates 10

Table 5 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-202 – Table of survival time estimates 12

Table 6 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-202 – Table of survival time estimates 13

Table 7 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-303 – Table of survival time estimates 15

Table 8 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-303 – Table of survival time estimates 15

Table 9 - Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Kaplan-Meier plots 18

Table 10 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of survival time estimates 19

Table 11Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of survival time estimates 20

Table 12 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of annual survival information 22

Table 13 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Kaplan-Meier plots 23

Table 14 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Table of survival time estimates 24

Table 15 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Table of annual survival information 26

Table 16 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Kaplan-Meier plots 27

Table 17 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of survival time estimates 28

Table 18 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of annual survival information 29

Table 19 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Kaplan-Meier plots 30

Table 20 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of survival time estimates 30

Table 21 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of annual survival information 32

Table 22 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Kaplan-Meier plots 33

Table 23 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of survival time estimates 34

Table 24 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of annual survival information 37

Table 25 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Kaplan-Meier plots 38

Table 26 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Table of survival time estimates 39

Table 27 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Table of annual survival information 41

Table 28 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Kaplan-Meier plots 42

Table 29 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of survival time estimates 42

Table 30 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of annual survival information 44

Table 31 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Kaplan-Meier plots 45

Table 32 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of survival time estimates 46

Table 33 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of annual survival information 47

Section A: Clarification on effectiveness data

A1. **Priority question. Please provide individual Kaplan-Meier (KM) curves (unadjusted) for event-free survival (EFS) and overall survival (OS) for the treatment groups listed below.** Please provide **<u>annual summaries</u>** and a summary of the latest cut-off date available, specifying the number of patients at risk as captured through the study and the total number of events at the observed period. Treatment groups of interest (total of 8 curves):

a. **In response to A1, the company has provided the number of patients at risk at annual cut off dates, rather than at various time points throughout the analysis. Are these numbers available?**

   a. **APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin;**

Table 1 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of survival time estimates

			95% confidence interval	
Number of days of survivals	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin – Table of survival time estimates

			95% confidence interval	
Number of days of survivals	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b. APN311-302: Myeloablative therapy plus isotretinoin;

Table 3 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of survival time estimates

			95% confidence interval	
Number of days of survivals	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-302: Myeloablative therapy plus isotretinoin – Table of survival time estimates

			95% confidence interval	
Number of days of survivals	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

c. APN311-202;

Table 5 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-202 – Table of survival time estimates

			95% confidence interval	
Number of days of survivals	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-202 – Table of survival time estimates

			95% confidence interval	
Number of days of survivals	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

d. APN311-303.

Table 7 – Unadjusted survival analysis on overall survival (OS) for treatment group APN311-303 – Table of survival time estimates

			95% confidence interval	
Number of days of survivals	Survivor function estimate	Survival standard error	Lower limit	Upper limit
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8 – Unadjusted survival analysis on Event Free Survival (EFS) for treatment group APN311-303 – Table of survival time estimates

			95% confidence interval	
Number of days of survivals	Survivor function estimate	Survival standard error	Lower limit	Upper limit
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b. **In response to A2, absolute numbers of people analysed at the various time points are not reported. Are these available?**

Please find below, the information requested.

c. **In A1 and A2, the company has provided information at the last cut-off date for all analyses but the dates of cut off/length of follow-up at the time points are not clear. Would it be possible to obtain this information as requested in the original clarification document?**

Please find below, the information requested.

d. **In A2, the company has kindly gone to a lot of effort to supply the KM curves adjusted for each individual prognostic factor specified in the question (providing 32 figures and accompanying tables). I'm afraid there has been a misunderstanding. A2 is intending to ask for the KM curves adjusted simultaneously for all the listed factors, so a total of 8 curves. On re-reading the question, we can understand how the company has interpreted the question and the confusion has arisen. We apologise for any inconvenience caused on our part. Would it be possible to obtain KM curves adjusted for all factors?**

Please find below, the information requested.

1 Overall Survival

1.1 Treatment group isotretinoin+Dinutuximab beta EUSA

Table 9 - Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Kaplan-Meier plots

Patients [redacted] with missing date of death were excluded from the analysis

Table 10 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of survival time estimates

					95% confidence interval	
Number of days of survivals	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]						

(continued)

Patients [redacted] with missing date of death were excluded from the analysis

Table 11Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of survival time estimates

					95% confidence interval	
Number of days of survivals	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]						

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 12 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of annual survival information

					95% confidence interval	
Year (Last Year=Cut-off)	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Four years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

1.2 Treatment group isotretinoin+Dinutuximab beta EUSA+IL2

Table 13 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Kaplan-Meier plots

Patients [redacted] with missing date of death were excluded from the analysis

Table 14 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Table of survival time estimates

					95% confidence interval	
Number of days of survivals	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]						

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

Table 15 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Table of annual survival information

					95% confidence interval	
Year (Last Year=Cut-off)	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing date of death were excluded from the analysis

1.3 Treatment group APN311-202

Table 16 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Kaplan-Meier plots

Table 17 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of survival time estimates

					95% confidence interval	
Number of days of survivals	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]						

Table 18 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of annual survival information

					95% confidence interval	
Year (Last Year=Cut-off)	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.4 Treatment group APN311-303

Table 19 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Kaplan-Meier plots

Table 20 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of survival time estimates

					95% confidence interval	
Number of days of survivals	Number of patients at risk	Cumulative number of events	Survivor function estimate	Survival standard error	Lower limit	Upper limit
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 21 Survival analysis on overall survival (OS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of annual survival information

					95% confidence interval	
Year (Last Year=Cut-off)	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2 Event-free Survival

2.1 Treatment group isotretinoin+Dinutuximab beta EUSA

Table 22 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Kaplan-Meier plots

Patients [redacted] with missing information on event free survival were excluded from the analysis

Table 23 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of survival time estimates

					95% confidence interval	
Number of days of survivals	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]						

[redacted]						

Patients [redacted] with missing information on event free survival were excluded from the analysis

Table 24 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA - Table of annual survival information

					95% confidence interval	
Year (Last Year=Cut-off)	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Four years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

2.2 Treatment group isotretinoin+Dinutuximab beta EUSA+IL2

Table 25 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Kaplan-Meier plots

Patients [redacted] with missing information on event free survival were excluded from the analysis

Table 26 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Table of survival time estimates

					95% confidence interval	
Number of days of survivals	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

Table 27 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage for treatment group isotretinoin+Dinutuximab beta EUSA+IL2 - Table of annual survival information

					95% confidence interval	
Year (Last Year=Cut-off)	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients [redacted] with missing information on event free survival were excluded from the analysis

2.3 Treatment group APN311-202

Table 28 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Kaplan-Meier plots

Table 29 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of survival time estimates

					95% confidence interval	
Number of days of survivals	Number of patients at risk	Cumulative number of events	Survivor function estimate	Survival standard error	Lower limit	Upper limit
[redacted]						

[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Table 30 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of annual survival information

					95% confidence interval	
Year (Last Year=Cut-off)	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Three years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.4 Treatment group APN311-303

Table 31 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Kaplan-Meier plots

Table 32 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of survival time estimates

					95% confidence interval	
Number of days of survivals	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
[redacted]						

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 33 Survival analysis on event-free survival (EFS), adjusted for prior treatment, age at diagnosis, MYCN status, INSS stage - Table of annual survival information

					95% confidence interval	
Year (Last Year=Cut-off)	**Number of patients at risk**	**Cumulative number of events**	**Survivor function estimate**	**Survival standard error**	**Lower limit**	**Upper limit**
One year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Dinutuximab beta EUSA [ID910]

Clarification Letter – Second part

[24 August 2017]

Version 2

Date of preparation: 24 August 2017

File name	Version	Contains confidential information	Date
ID910 dinutuximab beta clarification letter–Second Part_24th august [noACIC]	**2**	**No [noACIC]**	**24 August 2017**

Section A: Clarification on effectiveness data

A1. **Priority question.** Please provide individual Kaplan-Meier (KM) curves (unadjusted) for event-free survival (EFS) and overall survival (OS) for the treatment groups listed below. Please provide annual summaries and a summary of the latest cut-off date available, specifying the number of patients at risk as captured through the study and the total number of events at the observed period. Treatment groups of interest (total of 8 curves):

a. APN311-302: Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin;

b. APN311-302: Myeloablative therapy plus isotretinoin;

c. APN311-202;

d. APN311-303.

The answer was submitted on the 10th August and responses to additional questions were submitted on the 16th August.

A2. **Priority question.** Please provide adjusted KM curves for EFS and OS for the four treatment groups requested in A1. Please adjust the KM curves for:

a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS);

b. Age at diagnosis;

c. V-Myc myelocytomatosis viral-related oncogene (MYCN) status;

d. International Neuroblastoma Staging System (INSS) stage.

The answer was submitted on the 10th August and responses to additional questions were submitted on the 16th August.

A3. **Priority question.** Please carry out a matching-adjusted indirect comparison (MAIC) comparing APN311-302 (all people analysed) versus those receiving isotretinoin alone from the study by Yu *et al.* 2010 (1). Please follow methods described in NICE Decision Support Unit Technical Support Document 18. The MAIC could be used to adjust the APN311-302 population using individual patient data to more closely match the population receiving isotretinoin, the comparator of interest to the decision problem. All the important prognostic factors need to be incorporated in the analysis to reduce bias in the indirect comparison. Inclusion of all people in APN311-302 would maximise the number of people available for analysis, and receipt of IL-2 by some people could be accounted for. Please provide:

a. Adjusted KM curves for EFS and OS from APN311-302;

and/or

b. Hazard ratios (HRs), with accompanying 95% Confidence Intervals (CIs), for EFS and OS for dinutuximab beta plus combination therapies versus isotretinoin alone.

We went through the methods of MAIC in the NICE Decision Support Unit Technical Support Document 18. This comparison does not seem an appropriate analysis to run due to the following limitations:

1) Like all post hoc analyses, there is the potential for bias, as the comparison does not benefit from the effect of randomisation.

2) It assumes that the study designs, procedures, treatment pathways and outcome definitions are sufficiently similar to allow rational comparison. Whilst the broad approach to treatment in study 302 and Yu et al (1) are similar, there are areas of uncertainty around post-progression treatment that may impact the reliability of the OS comparisons.

3) The selection of prognostic variables is fundamentally dependent on the availability of data from both studies. It is to be expected that there will be undocumented confounders which, were they known, would have a potential impact on the results. As an example, recent work has identified a number of cellular markers that may indicate a greater likelihood of response to dinutuximab beta (2). As these markers had not been identified at the time study 302 and Yu et al (1)were designed, no information is available as to whether the patient groups are well matched for this variable.

Thus, we have addressed question A4.

A4. **Priority question.** If it is not possible to carry out a MAIC as requested in A3, for the comparison listed below, please provide adjusted HRs and accompanying 95% CIs for both EFS and OS:

   a. APN311-302: APN311-302 versus historical control R1 (450 people in R1) (myeloablative therapy [MAT] plus immunotherapy versus MAT alone).

   Please adjust the KM curves for:

   a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS);

   b. Age at diagnosis;

   c. MYCN status;

   d. INSS stage.

During the clarification letter call on 1 August 2017, the Company emphasized the fact that during the historical control R1 study EFS was not documented.

Please find below the table for the OS adjusted in Cox model for study 302.

Table 1: Cox proportional hazard model: Overall survival adjusted for MAT

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group	1	[redacted]	[redacted]
MAT	1	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group	MAT vs MAT and immunotherapy	[redacted]	[redacted]
MAT	Bumel vs Cem	[redacted]	[redacted]

Table 2: Cox proportional hazard model: Overall survival adjusted for age at diagnosis

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group	1	[redacted]	[redacted]
Age (categories)	3	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group	MAT vs MAT and immunotherapy	[redacted]	[redacted]
Age (categories)	< 1 yrs vs > 5 yrs	[redacted]	[redacted]
Age (categories)	< 1 yrs vs > 1.5 - <= 5 yrs	[redacted]	[redacted]
Age (categories)	< 1 yrs vs >= 1 - <= 1.5 yrs	[redacted]	[redacted]
Age (categories)	> 5 yrs vs > 1.5 - <= 5 yrs	[redacted]	[redacted]
Age (categories)	> 5 yrs vs >= 1 - <= 1.5 yrs	[redacted]	[redacted]
Age (categories)	> 1.5 - <= 5 yrs vs >= 1 - <= 1.5 yrs	[redacted]	[redacted]

Table 3: Cox proportional hazard model: Overall survival adjusted for MYCN status

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group	1	[redacted]	[redacted]
MYCN status	1	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group	MAT vs MAT and immunotherapy	[redacted]	[redacted]
MYCN status	amplified vs not amplified	[redacted]	[redacted]

Table 4: Cox proportional hazard model: Overall survival adjusted for INSS stage at initial diagnosis

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group	1	[redacted]	[redacted]
INSS stage at initial diagnosis (2 combined)	3	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group	MAT vs MAT and immunotherapy	[redacted]	[redacted]
INSS stage at initial diagnosis (2 combined)	2 comb. vs 4S	[redacted]	[redacted]
INSS stage at initial diagnosis (2 combined)	3 vs 4S	[redacted]	[redacted]
INSS stage at initial diagnosis (2 combined)	4 vs 4S	[redacted]	[redacted]

Regarding KM curves, unfortunately, we consider that it is not reasonable to perform adjusted KM analyses. The reason for this is that one would have to build subgroups defined by the single categories of all the factors to be considered. These subgroups would be too small to conduct a KM analysis within them (very small frequencies result for the single factor combinations even though we have a large number of patients overall, see Table 5.

Table 5: Frequency of subgroups

Treatment Group	Age at diagnosis	MYCN	INSS comb	MAT	Frequency	%	Cumulative Frequency	Cumulative Percent
MAT	< 1 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	< 1 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	< 1 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment Group	Age at diagnosis	MYCN	INSS comb	MAT	Frequency	%	Cumulative Frequency	Cumulative Percent
MAT	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	< 1 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	< 1 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	< 1 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	< 1 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	< 1 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	>= 1 - <= 1.5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment Group	Age at diagnosis	MYCN	INSS comb	MAT	Frequency	%	Cumulative Frequency	Cumulative Percent
MAT and immunotherapy	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 1.5 - <= 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAT and immunotherapy	> 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A5. **Priority question.** For the comparisons listed below, please provide adjusted HRs and accompanying 95% CIs for both EFS and OS:

a. APN311-202: APN311-202 versus both historical controls, that is, versus R1 (52 people who have relapsed) and Garaventa (immunotherapy versus no immunotherapy in people experiencing relapse).

Please adjust the KM curves for:

a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS);

b. Age at diagnosis;

c. MYCN status;

b. INSS stage.

During the clarification letter call on 1 August 2017, the Company emphasized the fact that during the historical control R1 study EFS was not documented, nor was it examined during the Garaventa study.

Please find below the table for the OS adjusted in Cox model for study 202. There were no records of “prior treatment” in APN311-202, thus it was not included in this analysis.

Table 6: Cox proportional hazard model: Overall survival adjusted for age at diagnosis

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group	1	[redacted]	[redacted]
Age (categories)	1	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group	APN311-202 vs Historical controls	[redacted]	[redacted]
Age (categories)	<= 5 yrs vs > 5 yrs	[redacted]	[redacted]

Table 7: Cox proportional hazard model: Overall survival adjusted for MYCN status

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group	1	[redacted]	[redacted]
MYCN status	1	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group	APN311-202 vs Historical controls	[redacted]	[redacted]
MYCN status	amplified vs not amplified	[redacted]	[redacted]

Table 8: Cox proportional hazard model: Overall survival adjusted for INSS stage at initial diagnosis

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group	1	[redacted]	[redacted]
INSS stage at initial diagnosis	2	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group	APN311-202 vs Historical controls	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
INSS stage at initial diagnosis	1 vs 4	[redacted]	[redacted]
INSS stage at initial diagnosis	3 vs 4	[redacted]	[redacted]

Regarding KM curves, unfortunately, we consider that it is not reasonable to perform adjusted KM analyses. The reason for this is that one would have to build subgroups defined by the single categories of all the factors to be considered. These subgroups would be too small to conduct a KM analysis within them (very small frequencies result for the single factor combinations even though we have a large number of patients overall).

A6. **Priority question.** For the evaluation of clinical effectiveness of dinutuximab beta in treatment of relapsed neuroblastoma, please clarify why results from APN311-202 and APN311-303 were compared versus the Garaventa historical control rather than versus results from the studies identified for mIBG or for chemotherapy.

Garaventa historical control was the preferred historical control because it provided a large amount of individual patient level data available through the SIOPEN network (i.e. 781 children with neuroblastoma who experienced tumour recurrence [424 progressions and 357 relapses] at the time of collection) and has the most comparable patients to APN311-202 and APN311-303. The studies identified through SLR for mIBG and for chemotherapy present aggregated data.
A possible source for additional historic data was the International Neuroblastoma Risk Group (INRG), which has established a database containing information from over 11,500 children with neuroblastoma around the world (http://inrgdb.org). However, the INRG does not provide patient level data for analyses outside of the INRG system. Similar issues were encountered with a German patient database established by groups of specialists at neuroblastoma treatment sites. Other registries, like the Deutsche Kinderkrebsregister (German Child Cancer Registry) collect information on a variety of cancers in children, but do not collect the information on neuroblastoma cases which would be necessary for a historic control comparison to patients treated with dinutuximab beta.

A7. For the historical control group referred to as R1 (described in Section 2.9.2.2 of the CS), please clarify:

a. Did all the 450 people in the R1 group forming the control for high-risk neuroblastoma receive isotretinoin as part of maintenance therapy?

Yes, all 450 people in the R1 group (i.e. MAT) have received isotretinoin as part of maintenance therapy. R1 randomisation (BuMel vs.CEM) was activated 02/2002, in the high-risk neuroblastoma study 1 of SIOPEN (HR-NBL-1/SIOPEN). Standard treatment was induction treatment without GM-CSF, surgery (non-randomised treatment element), MAT treatment with busulfan and melphalan (BuMel) followed by stem cell reinfusion, local radiotherapy (non-randomised treatment element) and differentiation treatment with isotretinoin without additional immunotherapy (see HR-NBL-1/SIOPEN protocol v1 and v1.7). As described in the section 2.9.2.2 in CS, patients included in the R1 randomization phase who received standard of care neuroblastoma treatment, including MAT but no immunotherapy, form a valid historical control group to patients receiving immunotherapy in addition to standard of care neuroblastoma treatment.

b. What maintenance treatments were available to those evaluated in the historical control after high-dose therapy who did not progress to the R2 randomisation phase?

As described above in point a, the maintenance therapy available was only isotretinoin.

c. The eligibility criteria for inclusion in the historical control R1 for high-risk neuroblastoma against which APN311-302 is compared (i.e., the 450 people without relapse): the discussion in Section 2.9.2.2 describes criteria for relapse but not high-risk;

This information could be found in the Appendix L 1.8 of the company evidence submission (APN311-302 – Historic control report):

APN311-302 R1 Randomization (no ch14.18/CHO treatment)
The HR-NBL-1.5/SIOPEN study is an open, multicenter randomized phase III therapy optimization study. Within this study, the R1 randomization compared two different regimens for MAT (BuMel vs. CEM) in the consolidation part of first-line treatment. For details refer to the study protocol (HR-NBL-1 v1 and v1.7). The historic control group consisted of the patients who were solely part of the R1 randomization. Patients were eligible if they had received first-line treatment, ie, had completed the induction phase, and received treatment with BuMel or CEM MAT chemotherapy and had no disease progression after MAT nor after radiotherapy (ie, the overall response or metaiodobenzylguanidine [mIBG] response shouldn't be Progressive Disease). In summary, the patients should have met the inclusion criteria for randomization to immunotherapy (R2), though should not have received treatment with ch14.18/CHO.

d. Why so few people randomised in R1 went through to the R2 randomisation phase (seems to be 46 people based on a publication by Ladenstein et al.[3] describing the results of the R1 phase)?

As per the protocols of HR-NBL-1 (v1 and 1.7, attached), R1 randomisation was part of the HR-NBL-1 clinical study protocol started in 2001/2002 and was closed in 2010 when the recruitment target was reached. R2 randomisation wasn't activated before 2006 and was only implemented in very few countries until 2009. Thus, only a few patients having participated in R1 (one of the inclusion criteria of R2) could have been randomised to R2.

A8. The Evidence Review Group's clinical experts have fed back that the population categorised as "refractory" in the key studies of dinutuximab beta is a clinically distinct population of interest to the decision problem that is the focus of this Single Technology Appraisal. Please provide a clinical and cost effectiveness analysis of dinutuximab beta for the treatment of refractory neuroblastoma, as has been provided for front-line and relapsed disease, using an appropriate control.

We agree that from a diagnosis standpoint the refractory and relapsed patients are not the same, however we could not disentangle any difference in background risk in the refractory subgroup in terms of clinical outcomes with the data we have due to the following reasons:

- The treatment algorithm is the same for both refractory (i.e. refractory patients receiving induction therapy, high-dose chemotherapy and reinjection of hematopoietic stem cells) and relapsed neuroblastoma patients (expert opinion, SIOPEN clinical guidelines to be published soon)

- Most of the literature already reported in the SLR are combining the relapsed and refractory patients when they report their clinical outcomes. In the 17 articles reported in the SLR having OS outcomes (attached a revised Appendix D, 1.3.1), only 2 were reporting the OS data separated for relapsed and refractory patients (Zhou et al, 2015 (3) and Moreno et al, 2017 (4)) and the other articles were always pooling the R/R patient data together. Zhou et al (3) reported significantly higher 24-month OS for refractory patients was significantly higher at 65.3% (95% CI 51.8%–75.9%), compared to 38.7% (95% CI 30.4%–46.8%) for relapsed patients ($p < 0.001$). However, this difference could be due to the different background risk of relapsed or refractory patients **or** if it is due to the differential treatment effects due to mIBG treatment in these patients. Neither study had an adequate control arm that would be needed to unconfound the two potential hypotheses. That is, the data limitation due to non-controlled studies does not allow us to answer that the ERG posed.

- In the clinical data of Dinutuximab beta EUSA, all patients received dinutuximab beta, since a control arm without immunotherapy was excluded due to ethical reasons. Thus, the requested analysis of the hypothesis test for testing whether there are differences in the two patient subgroups is confounded. I.e. We don't know if it is a differential effect on dinutuximab beta in the two patient sets **or** a difference in background risk of dying. As requested, by using APN311-202 and APN311-303 clinical data, we have run a Cox proportional hazards regression model adjusting for baseline disease status, prior treatment, age at diagnosis, MYCN status and INSS stage. We have analysed the effect of baseline disease status on overall survival and event-free survival in the patients treated with Dinutuximab beta EUSA. In the primary study APN311-202, a significant difference was observed between the two DB arms at the level of OS ([redacted]) but not EFS ([redacted]), as described in the results below (Table 9). These should be interpreted with caution since there is no control arm. Meaning that differences do not necessarily mean that there is a difference in risk in the two subsets of patients. In study APN311-303, no differences were observed however these results should be taken cautiously due to a heterogeneous population (Table 10). **However, we do not know if the difference in OS observed for relapsed and refractory patients (Table 9A) is due to the different background risk of R/R patients or due to dinutuximab beta working differently in these populations.** We do not have a control arm in maintenance treatment to clarify whether the difference is due to dinutuximab beta (since a control arm without immunotherapy is currently considered unethical).

Table 9: Effect of baseline disease status on overall survival (OS) (A) or event-free survival (EFS) (B) in patients receiving dinutuximab beta in Study APN311-202. Results derived from proportional hazards regression analysis (Cox model). Analysis is based on estimation and testing in the context of a proportional hazards model including the following factors: baseline disease status, prior treatment, age at diagnosis, MYCN status, INSS Stage.

A.

Least square means on difference refractory-relapsed disease				Hazard ratio		
		95% confidence interval			95% Wald confidence interval	
Estimate	p-value	Lower limit	Upper limit	Estimate	Lower limit	Upper limit
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.

Least square means on difference refractory-relapsed disease			Hazard ratio	
		95% confidence interval		95% Wald confidence interval

Estimate	p-value	Lower limit	Upper limit	Estimate	Lower limit	Upper limit
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10: Effect of baseline disease status on overall survival (OS) (A) or event-free survival (EFS) (B) in patients receiving dinutuximab beta in Study APN311-303. Results derived from proportional hazards regression analysis (Cox model). Analysis is based on estimation and testing in the context of a proportional hazards model including the following factors: baseline disease status, prior treatment, age at diagnosis, MYCN status, INSS Stage.

A.

Least square means on difference refractory-relapsed disease				Hazard ratio		
		95% confidence interval			95% Wald confidence interval	
Estimate	p-value	Lower limit	Upper limit	Estimate	Lower limit	Upper limit
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.

Least square means on difference refractory-relapsed disease				Hazard ratio		
		95% confidence interval			95% Wald confidence interval	
Estimate	p-value	Lower limit	Upper limit	Estimate	Lower limit	Upper limit
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For those reasons, the base case for the cost-effectiveness analysis is considering both populations together.

A9. Page 65 of the CS states that, “Of the nine studies investigating chemotherapy protocols (with or without stem cell transplantation) in relapsed/refractory NB patients, five studies reported OS data”. Please provide reference details for the nine studies.

We thank the ERG and the technical team at NICE for pointing out the missing references. Reference details for the nine studies were presented in section 1.2 (pages 14-16) and section 2 (references) of Appendix D. However, to clarify Document B, we will add the reference to the Appendix D where the reader could find all the information. The sentence should read: “Of the nine studies investigating chemotherapy protocols (with or without stem cell transplantation) in relapsed/refractory NB patients (see Appendix D, section 1.2), five studies reported OS data (see Appendix D, section 1.3.1).” In the same section 2.8.4.2, we would like to also clarify the following numbers and update the sentences: “Of the 10 studies investigating mIBG therapy in relapsed/refractory NB patients (see Appendix D, section 1.2), nine studies provide OS data for time points ranging from less than 1 year to 5 years (see Appendix D, section 1.3.1). Of these, it was possible to pool the outcomes of six studies that reported OS rates for 1, 2 and 3 years.”

A10. Please provide definition(s) for relapsed disease as implemented in APN311-202, APN311-302, and APN311-303.

The APN311-302 trial did not not include any relapsed patients since it examined only first-line use of anti-GD2 therapy, therefore no definition of relapsed disease is expected.

In study APN311-202 and -303, relapse was defined as appearance of any new lesion(s) or deterioration of previous lesion(s) after previous antitumour therapy. At the start of

immunotherapy, patients could present with and without evidence of disease (Appendix L, 1.10 APN311-202+APN311-303- Historic control report (Garaventa)). There was additional information in the inclusion criteria relevant to relapsed disease (Dinutuximab beta EPAR document):

- In study APN311-202, patients should fulfil one of the following criteria:
  - Primary refractory patients with stage 4 disease with at least 2 lines of treatment prior to high-dose therapy/autologous stem cell transplantation (ASCT), causing a delay from diagnosis to ASCT of over 9 months
  - Treated and responding relapse after primary stage 4 disease
  - Treated and responding disseminated relapsed neuroblastoma having received ASCT

- In study APN311-303, patients should fulfil these following criteria:
  - Diagnosis of high risk neuroblastoma according to the INSS criteria, i.e. INSS stage 2, 3, 4, or 4s with MYCN amplification, or INSS stage 4 without MYCN amplification or relapsed or refractory neuroblastoma **of any stage**

A11. Please provide a list of previous therapies received by people in APN311-202 before their last relapse.

The therapies received by patients in APN311-202 before their last relapse are given in the table below (see also Appendix L, 1.7 APN311-202 – CSR, 11.2.3 *Prior and concomitant medication*, page 6610/8255). First-line treatment consisted of single courses or combinations of the following treatments: surgery, radiotherapy, chemotherapy, high-dose therapy and maintenance therapy with 13-cis-RA. Most frequently patients received rapid COJEC followed by high-dose BuMel treatment. About [redacted] of the patients received radiotherapy and [redacted] received 13-cis-RA maintenance therapy prior to immunotherapy.

Table 11: Treatment history first line for patients in APN311-202

Category	Therapy	Number of Patients (n=44) N (%)
Chemotherapy	CADO (cyclophosphamide/Adriamycin/Vincristine)	[redacted]
	Etoposide/Carboplatin (VP/Carbo)	[redacted]
	Etoposide/Cisplatin (P/E)	
	High-dose CAV	
	Rapid COJEC	
High-dose therapy	BuMel+ASCT	[redacted]
	CEM+ASCT	[redacted]
	MIBG treatment	
	Other+ASCT:fludara, Thitepa, Okt-3, Haplo, DLO, Melphalan	
	Other+ASCT:iflosphamideCarboplatinEtoposide	
	Other+ASCT: Thiotepa	
	Other+ASCT: Thiotepa 300mg/m^2 3 days	
Local therapy	Radiotherapy	[redacted]
	Surgery	[redacted]
Maintenance therapy	Isotretinoin (13-cis-RA)	[redacted]
Any other therapy	1 Ex1 Ex + VP161 Ex – Carbo – VP16	[redacted]
	1 cycle ICE	[redacted]
	ANBL02P1	[redacted]

Category	Therapy	Number of Patients (n=44) N (%)
	Endoxan 4 g/m^2 N5/N6 according NB2004 Vinblastin, Cisplatin, EtoposinJuly 2011 Frontline chemotherapy according NB2004 (GPOH) 3 N5; 3N6 (10/2006 – 03/2007) 2 cycles ICE	[redacted]

A12. Please provide a list of previous therapies received by people in historical control R1 (52 people who relapsed) before their last relapse.

The previous therapies received by patients in historical control R1 before their last relapse could not be found though the per-patient data. However, we could refer to the R1 protocol where patients received the standard treatment: induction treatment without GM-CSF, surgery, MAT treatment with Busulphan and Melphalan (BUMEL) followed by stem cell reinfusion, local radiotherapy and isotretinoin (HR-NBL-1 v1 protocol). Patients should not have received any other therapy other than those specified in the clinical study report before they relapsed.

A13. Please provide a list of previous therapies received by people in the historical control Garaventa before their last relapse.

The previous therapies of most recent relapse received by patients in the historical control Garaventa are listed below:

Table 12: Treatment of most recent relapse prior to Dinutuximab beta EUSA or auxiliary staring point (APN311-303 vs Historic Control Garaventa)

Treatment regimen	Historic Control Garaventa (N=29) 303	APN311-303 (N=30)
Chemotherapy, n (%)		
Carboplatin, Cisplatin, Cyclophosphamide, Vincristine, Etoposide (COJEC)	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Cyclophosphamide, celecoxib	[redacted]	[redacted]
Etoposide, carboplatin	[redacted]	[redacted]
Fludarabina Tiothepa-Melphalan	[redacted]	[redacted]
Gemcitabine-Oxaliplatin	[redacted]	[redacted]
ICE - ifosfamide, carboplain, etoposide	[redacted]	[redacted]
Irinotecan/Temozolomide	[redacted]	[redacted]
Irinotecan/Temozolomide/celeloxib	[redacted]	[redacted]
N4 - doxorubicin, vincristin, cyclophosphamide	[redacted]	[redacted]
N5 - cisplatin, etoposide, vindesine	[redacted]	[redacted]
N6 - vincristin, decarbazine, iphosphamid, doxorubicin	[redacted]	[redacted]

N8 - topotecan, cyclophosphamide, etoposide	[redacted]	[redacted]
Oral etoposide	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]
Rapid COJEC	[redacted]	[redacted]
RIST (rudamicin, irinotecan, temozolomide, dasatinib)	[redacted]	[redacted]
TCE	[redacted]	[redacted]
Temiri	[redacted]	[redacted]
Topotecan, cyclophosphamide	[redacted]	[redacted]
Topotecan/Etoposide	[redacted]	[redacted]
Topotecan/temozolomide	[redacted]	[redacted]
Topotecan-Vincristine-Doxorubicin (TVD)	[redacted]	[redacted]
Vincristine-Doxorubicin-Cyclophosphamide	[redacted]	[redacted]
High-dose therapy, n (%)		
Allogenic SCT	[redacted]	[redacted]
Allogenic SCT, thiotepa, melphalan	[redacted]	[redacted]
allogenic HSCT with non-myeloablative regimen	[redacted]	[redacted]
Antilymphocyte serum (ATG) with allogeneic SCT	[redacted]	[redacted]
Bone marrow transplant	[redacted]	[redacted]
BuMel + ASCT	[redacted]	[redacted]
CEM+ASCT	[redacted]	[redacted]
Cyclophosphamide, etoposide, carboplatin + ASCT	[redacted]	[redacted]
Haplotransplantation	[redacted]	[redacted]
MATIN (mIBG, topotecan, ASCT)	[redacted]	[redacted]
mIBG	[redacted]	[redacted]
Other + ASCT	[redacted]	[redacted]
Local therapy, n (%)		
Radiotherapy	[redacted]	[redacted]
Surgery	[redacted]	[redacted]
Maintenance therapy, n (%)		
13-cis-RA	[redacted]	[redacted]
Other, n (%)		
Lutetium octreotate-177	[redacted]	[redacted]
interleukin-2	[redacted]	[redacted]

Lymphocyte Infusion (DLI) AntiGD2	[redacted] [redacted]	[redacted] [redacted]
No therapy, n (%)	[redacted]	[redacted]
Missing, n (%)	[redacted]	-

A14. Page 82 of the CS, states that, "When adding prognostic factors for OS to the model, the treatment difference in OS time was still statistically significant (estimated hazard ratio 0.555 [95% CI 0.32,0.97], p = 0.0376)". Please clarify which prognostic factors have been incorporated into the analysis.

The following prognostic factors were added to the Cox model with treatment group as the basic factor using forward selection at a significance level of 0.05 (reference: Appendix L, 1.11 APN311-202 &/+ APN311-303 – Historic control report (R1), 3.3.3 Statistical Evaluation, page 7739):

- Categorized age at diagnosis
- Gender
- MYCN amplification
- INSS stage - All INSS stages but 4 will be combined for this analysis.

A15. Please clarify how the 5-year OS estimate for APN311-302 has been derived, given that the first person enrolled into R2 of APN311-302 was recruited on 30 Nov 2009 and the last person on 12 August 2013 (CS pg. 38). Has measurement of 5-year follow-up started at time of randomisation of the first person enrolled? Or is follow-up person-specific and so starts when that person is randomised?

Randomization was done from the year 2009 until 2013. For some patients, there is information that patient is alive longer than 4 year after randomization. Since there is no definition in the protocol that follow-up information of more than 4 years cannot be used, they were included in the calculations (Appendix L, 1.2 APN311-302 CSR Addendum, page 1453).

A16. Please provide median (and range) and mean (with accompanying SD or SE) follow-up time at the last cut-off date for analysis for APN311-302 (and the date of analysis) for those receiving dinutuximab beta: (i) at front-line; (ii) at relapse; (iii) for refractory neuroblastoma.

Study 302 only included first-line patients, therefore there are no patients with relapsed or refractory neuroblastoma.

In the table below, the results on "time of follow-up" for those receiving dinutuximab beta at front-line in APN311-302 are presented:

Table 13: Statistics on time of follow up (days) after last treatment in study APN311-302

Treatment group	Time of follow up (days)							
	N	Mean	Std	Min	Q1	Median	Q3	Max
13-cis-RA+ch14.18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13-cis-RA+ch14.18+IL2	[redacted]							
Total	[redacted]							

A17. Many thanks for providing the Clinical Study Report (CSR) for APN311-301. Please clarify

[redacted]

The longest follow-up was about [redacted] days which is approximately [redacted] years ([redacted]). From the distribution of censors, there are just a few patients with such long follow-up. Most censors and almost all events (death or progressions) are until time 4 years*365.25=1'461 days. Thus, the reporting of EFS and OS results is limited to 4 years' follow-up.

A18. Page 33 of the CS (Table 11) states, in relation to the randomisation of people in APN311-302, "Randomisation of patients to the different treatment arms was done using a web-based system". Please provide additional information on the method of randomisation and how people accessed the treatment allocation (e.g., centralised access). As part of the response, please give information as to whether the web-based system incorporated a method to conceal allocation sequence from those people assigning participants to intervention groups.

The HRNBL1/SIOPEN study (Appendix L, page 7023) uses a web-based centralized communication system allowing clinical trial management with remote randomisation and image transfer. The master protocol version in English is held at the International Main Data Center of Studies and Statistics for Integrated Research and Projects department (S²IRP) of the CCRI. National groups were responsible for producing a literal translation into their own language if required according to national rules. National co-ordinators were responsible for the distribution of protocols to centers within their national group. There is no information as to whether or not the web-based system incorporated a method to conceal allocation sequence from those people assigning participants to intervention groups, however the study design was open-label, so perhaps there was no need for concealing allocation.

A19. Page 81 of the CS states, in the description of the pooled analysis of APN311-202 and APN311-303 versus historical control R1, that "It cannot be excluded that the Historical Control R1 patients may have been treated with dinutuximab beta within the scope of other relapse studies". Please clarify this statement given the description that the historical control R1 is derived from an earlier stage of the APN311-302 study which included people diagnosed with high-risk neuroblastoma and who had received no previous chemotherapy other than one cycle of etoposide and carboplatin.

R1 patients from study APN311-302 did receive chemotherapy and high-dose chemotherapy/MAT according to the study protocol and only patients with complete response after MAT were included in the R1 control group. It cannot be entirely excluded that R1 patients, who have been refractory or relapsed, might have received dinutuximab beta in another SIOPEN study than 302 (e.g. in the Phase I study, 2005 – 2006), although it is very unlikely and, if so, might have affected only a few patients.

A20. The description of the per-protocol-set (PPS) in APN311-302 indicates that people were excluded from the PPS if, “R2 randomisation criteria were not met or missing”. Please clarify how people were randomised in R2 and included in the full analysis set if they did not meet R2 randomisation criteria.

As with any other study, it might turn out retrospectively (e.g. during monitoring) that a randomized patient did not meet inclusion/exclusion criteria, and thus did not meet randomisation criteria. In that case, these patients were excluded from the PPS, but included in the full analysis set.

A21. Please provide a table of relapse/progression prior to immunotherapy for people in APN311-303 like Table 20 provided for people in APN311-202.

Please find below a table of relapse/progression prior to immunotherapy for patients in APN311-303.

Table 14: Relapse/Progression prior to immunotherapy in APN311-303

Parameter		Number of Patients
Number of relapses/progressions	n Mean (SD) Median Min, Max	31 [redacted]
Number of relapses/progressions	1 2 5 8	[redacted]
Time from initial diagnosis to most recent relapse/progression (days)	n Mean (SD) Median Min, Max	31 [redacted]
Most recent relapse/progression type	primary tumour site alone bone marrow alone skeleton alone other metastatic sites alone combined	[redacted]
Abbreviations: Max = maximum, Min = minimum, SD = standard deviation		

A22. Throughout the reporting of the individual adverse effects associated with dinutuximab beta (Section 2.10.3.2 onwards in the CS), only percentages are reported. For the 98 people who underwent continuous infusion, please provide a table of absolute event numbers, with accompanying denominator, for each adverse effect mentioned in the CS.

Please find below the tables requested:

Table 15: Overall Summary of Treatment Emergent Adverse Events

Patients with	APN311-303	APN311-202
	N (%) patients (N=54)	N (%) patients (N=44)
Any AE	54 (100.0%)	44 (100.0%)
Any AE possibly related to study drug [a]	54 (100.0%)	44 (100.0%)
Any AE possibly related to IL-2	54 (100.0%)	44 (100.0%)
Any AE possibly related to ch14.18/CHO	54 (100.0%)	44 (100.0%)
Any AE possibly related to 13-cis-RA	27 (50.0%)	ND
Any serious AE	12 (22.2%)	26 (59.1%)
Any serious AE possibly related to study drug [a]	6 (11.1%)	22 (50.0%)
Any serious AE possibly related to IL-2	4 (7.4%)	18 (40.9%)
Any serious AE possibly related to ch14.18/CHO	6 (11.1%)	20 (45.5%)
Any serious AE possibly related to 13-cis-RA	-	ND
Any AE leading to discontinuation of study drugs[b]	5 (9.3%)	10 (22.7%)
Maximal NCI CTCAE Grade[c]		
Grade 1 (mild)	-	-
Grade 2 (moderate)	3 (5.6%)	2 (4.5%)
Grade 3 (severe)	32 (59.3%)	20 (45.5%)
Grade 4 (life threatening/disabling)	19 (35.2%)	22 (50.0)
Grade 5 (death)	-	1 (2.3%)
Any AE leading to death	-	1 (2.3%)
Deaths *	22 (40.7%)	20 (45.5%)

[#] pre-defined toxicities according to NCI CTC were collected in study APN311-302, not AEs;
* All documented deaths, including deaths during follow-up period
[a] Depending on the study design refers to ch14.18/CHO only or to the combination of ch14.18/CHO and IL-2 and 13-cis-RA. For APN311-202 refers to ch14.18/CHO and IL-2 treatment.
[b] Permanent or temporary discontinuation in studies APN311-303 and -202, permanent discontinuation in study APN311-201.
[c] Referring to SAE grades for APN311-302.
AE=adverse event, N=number of subjects, NA = not applicable, NCI CTC=National Cancer Institute Common Toxicity Criteria, ND = not determined.
Possibly related AEs: AEs with relationship coded as 'Possible', Probable', 'Definite' or with missing relationship

Table 16: Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term Experienced by ≥20% Patients

SYSTEM ORGAN CLASS Preferred term	N (%) patients	
	APN311-303 (N=54)	APN311-202 (N=44)
Overall	54 (100.0%)	44 (100.0%)
GASTROINTESTINAL DISORDERS	**54 (100.0%)**	**36 (81.8%)**
Constipation	45 (83.3%)	16 (36.4%)
Vomiting	40 (74.1%)	25 (56.8%)
Abdominal pain upper	33 (61.1%)	-

Diarrhea	32 (59.3%)	26 (59.1%)
Nausea	23 (42.6%)	17 (38.6%)
Cheilitis	18 (33.3%)	-
Lip dry	18 (33.3%)	-
Abdominal pain	11 (20.4%)	19 (43.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**54 (100.0%)**	**44 (100.0%)**
Pyrexia	53 (98.1%)	44 (100.0%)
Pain	40 (74.1%)	29 (65.9%)
Fatigue	28 (51.9%)	13 (29.5%)
Face edema	21 (38.9%)	5 (11.4%)
Injection site inflammation	19 (35.2%)	-
Chills	16 (29.6%)	19 (43.2%))
Injection site erythema	16 (29.6%)	-
Asthenia	13 (24.1%)	5 (11.4%)
Edema	12 (22.2%)	5 (11.4%)
Edema peripheral	13 (24.1%)	-
Injection site pain	12 (22.2%)	-
Malaise	3 (5.6%)	11 (25.0%)
Influenza like illness	3 (5.6%)	10 (22.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**54 (100.0%)**	**35 (79.5%)**
Pruritus	50 (92.6%)	21 (47.7%)
Dry skin	41 (75.9%)	16 (36.4%)
Rash	21 (38.9%)	8 (18.2%)
Erythema	19 (35.2%)	-
Urticaria	13 (24.1%)	13 (29.5%)
VASCULAR DISORDERS	**51 (94.4%)**	**29 (65.9%)**
Capillary leak syndrome	45 (83.3%)	16 (36.4%)
Hypotension	34 (63.0%)	22 (50.0 %)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**49 (90.7%)**	**10 (22.7%)**
Pain in extremity	46 (85.2%)	7 (15.9%)
Back pain	18 (33.3%)	-
Arthralgia	13 (24.1%)	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**49 (90.7%)**	**36 (81.8%)**
Cough	43 (79.6%)	29 (65.9%)
Hypoxia	24 (44.4%)	18 (40.9%)
Oropharyngeal pain	16 (29.6%)	-
Pleural effusion	11 (20.4%)	-
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**45 (83.3%)**	**31 (70.5%)**
Anemia	26 (48.1%)	29 (65.9%)
Neutropenia	26 (48.1%)	9 (20.5%)
Thrombocytopenia	16 (29.6%)	6 (13.6%)
CARDIAC DISORDERS	**40 (74.1%)**	**10 (22.7%)**
Tachycardia	40 (74.1%)	7 (15.9%)[a]
INFECTIONS AND INFESTATIONS	**39 (72.2%)**	**29 (65.9%)**
Device related infections	1 (1.9%)	13 (29.5%)
INVESTIGATIONS	**39 (72.2%)**	**40 (90.9%)**
Weight increased	24 (44.4%)	25 (56.8%)
C-reactive protein increased	12 (22.2%)	-
Alanine aminotransferase increased	10 (18.5%)	30 (68.2%)
Gamma-glutamyltransferase increased	7 (13.0%)	28 (63.6%)
Transaminases increased	-	-

Aspartate aminotransferase increased	1 (1.9%)	13 (29.5%)
Neutrophil count decreased	-	22 (50.0%)
White blood cell count decreased	-	17 (38.6%)
Blood bilirubin increased	1 (1.9%)	11 (25.0%)
Platelet count decreased	-	23 (52.3%)
NERVOUS SYSTEM DISORDERS	**26 (48.1%)**	**17 (38.6%)**
Headache	18 (33.3%)	5 (11.4%)
RENAL AND URINARY DISORDERS	**24 (44.4%)**	**6 (36.4%)**
Urinary retention	13 (24.1%)	12 (27.3%)
EYE DISORDERS	**21 (38.9%)**	**11 (25.0%)**
Eyelid edema	11 (20.4%)	-
METABOLISM AND NUTRITION DISORDERS	**22 (40.7%)**	**24 (54.5%)**
Fluid retention	-	-
Hypertriglyceridemia	-	14 (31.8%)
Decreased appetite	16 (29.6%)	7 (15.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**14 (25.9%)**	**-**
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**11 (20.4%)**	**-**
IMMUNE SYSEM DISORDERS	**2 (3.7%)**	**11 (25.0%)**

[a] Sinus tachycardia MedDRA=Medical Dictionary of Regulatory Activities, N=number of subjects, TEAE=treatment-emergent adverse event.

Table 17: Summary of Treatment Emergent Adverse Events Possibly Related to Study Medication (any of ch14.18/CHO, IL-2, 13-cis-RA) Experienced by ≥ 20% Patients

SYSTEM ORGAN CLASS Preferred term	APN311-303 N (%) patients (N=54)	APN311-202 N (%) patients (N=44)
Overall	54 (100.0%)	44 (100.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**54 (100.0%)**	**43 (97.7%)**
Pyrexia	53 (98.1%)	43 (97.7%)
Pain	35 (64.8%)	28 (63.6%)
Fatigue	24 (44.4%)	11 (25.0%)
Injection site inflammation	19 (35.2%)	-
Face edema	19 (35.2%)	5 (11.4%)
Injection site erythema	16 (29.6%)	1 (2.3%)
Chills	15 (27.8%)	19 (43.2%)
Edema	12 (22.2%)	5 (11.4%)
Asthenia	11 (20.4%)	5 (11.4%)
Injection site pain	12 (22.2%)	2 (4.5%)
Edema peripheral	11 (20.4%)	-
Malaise	3 (5.6%)	11 (25.0%)
Influenza like illness	3 (5.6%)	10 (22.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**52 (96.3%)**	**29 (65.9%)**
Pruritus	48 (88.9%)	19 (43.2%)
Dry skin	24 (44.4%)	5 (11.4%)
Rash	18 (33.3%)	8 (18.2%)
Urticaria	12 (22.2%)	12 (27.3%)
GASTROINTESTINAL DISORDERS	**51 (94.4%)**	**34 (77.3%)**
Abdominal pain upper	30 (55.6%)	1 (2.3%)
Vomiting	27 (50.0%)	24 (54.5%)

SYSTEM ORGAN CLASS Preferred term	APN311-303 N (%) patients (N=54)	APN311-202 N (%) patients (N=44)
Diarrhea	18 (33.3%)	24 (54.5%)
Nausea	15 (27.8%)	16 (36.4%)
Cheilitis	12 (22.2%)	-
Lip dry	10 (18.5%)	1 (2.3%)
Abdominal pain	9 (16.7%)	18 (40.9%)
Constipation	4 (7.4%)	8 (18.2%)
VASCULAR DISORDERS	**49 (90.7%)**	**29 (65.9%)**
Capillary leak syndrome	45 (83.3%)	16 (36.4%)
Hypotension	32 (59.3%)	22 (50.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**46 (85.2%)**	**9 (20.5%)**
Pain in extremity	43 (79.6%)	7 (15.9%)
Back pain	16 (29.6%)	1 (2.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**46 (85.2%)**	**34 (77.3%)**
Cough	41 (75.9%)	29 (65.9%)
Hypoxia	18 (33.3%)	17 (38.6%)
Pleural effusion	11 (20.4%)	-
CARDIAC DISORDERS	**40 (74.1%)**	**10 (22.7%)**
Tachycardia	40 (74.1%)	3 (6.8%)
INVESTIGATIONS	**35 (64.8%)**	**39 (88.6%)**
Weight increased	24 (44.4%)	25 (56.8%)
Alanine aminotransferase increased	8 (14.8%)	27 (61.4%)
Transaminases increased	-	-
Aspartate aminotransferase increased	-	13 (29.5%)
Gamma-glutamyltransferase increased	4 (7.4%)	26 (59.1%)
Platelet count decreased	-	21 (47.7%)
Neutrophil count decreased	-	18 (40.9%)
Blood bilirubin increased	-	11 (25.0%)
White blood cell count increased	-	11 (25.0%)
Blood alkaline phosphatase increased	-	12 (27.3%)
NERVOUS SYSTEM DISORDERS	**18 (33.3%)**	**17 (38.6%)**
Headache	14 (25.9%)	4 (9.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**16 (29.6%)**	**29 (65.0%)**
Anemia	6 (11.1%)	27 (61.4%)
EYE DISORDERS	**13 (24.1%)**	**10 (22.7%)**
METABOLISM AND NUTRITION DISORDERS	**11 (20.4%)**	**20 (45.5%)**
Hypoalbuminemia	-	10 (22.7%)
INFECTIONS AND INFESTATIONS	**6 (11.1%)**	**14 (31.8%)**
IMMUNE SYSTEM DISORDERS	**2 (3.7%)**	**11 (25.0%)**
RENAL AND URINARY DISORDERS	**4 (7.4%)**	**12 (27.3%)**

[a] Depending on the study design refers to ch14.18/CHO only or to the combination of ch14.18/CHO and IL-2 and 13-cis-RA. In APN311-101 patients only received ch14.18/CHO. N=number of subjects.

Table 18: Summary of Treatment Emergent Adverse Events Possibly Related to ch14.18/CHO Experienced by ≥ 20% Patients

SYSTEM ORGAN CLASS Preferred term	APN311-303 N (%) patients (N=54)	APN311-202 N (%) patients (N=44)
Overall	54 (100.0%)	44 (100.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**54 (100.0%)**	**43 (97.7%)**
Pyrexia	53 (98.1%)	42 (95.5%)
Pain	35 (64.8%)	28 (63.6%)
Fatigue	22 (40.7%)	11 (25.0%)
Face edema	19 (35.2%)	5 (11.4%)
Chills	9 (16.7%)	17 (38.6%)
Edema	12 (22.2%)	4 (9.1%)
Asthenia	11 (20.4%)	5 (11.4%)
Malaise	3 (5.6%)	11 (25.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**50 (92.6%)**	**26 (59.1%)**
Pruritus	46 (85.2%)	16 (36.4%)
Rash	16 (29.6%)	7 (15.9%)
Urticaria	12 (22.2%)	12 (27.3%)
GASTROINTESTINAL DISORDERS	**49 (90.7%)**	**33 (75.0%)**
Abdominal pain upper	30 (55.6%)	1 (2.3%)
Vomiting	24 (44.4%)	23 (52.3%)
Diarrhea	14 (25.9%)	19 (43.2%)
Nausea	15 (27.8%)	16 (36.4%)
Abdominal pain	9 (16.7%)	18 (40.9%)
Constipation	3 (5.6%)	8 (18.2%)
VASCULAR DISORDERS	**49 (90.7%)**	**27 (61.4%)**
Capillary leak syndrome	45 (83.3%)	15 (34.1%)
Hypotension	32 (59.3%)	20 (45.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**46 (85.2%)**	**8 (18.2%)**
Pain in extremity	42 (77.8%)	7 15.9%)
Back pain	16 (29.6%)	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**45 (83.3%)**	**33 (75.0%)**
Cough	39 (72.2%)	27 (61.4%)
Hypoxia	18 (33.3%)	17 (38.6%)
Pleural effusion	11 (20.4%)	-
CARDIAC DISORDERS	**39 (72.2%)**	**9 (20.5%)**
Tachycardia	39 (72.2%)	3 (6.8%)
INVESTIGATIONS	**32 (59.3%)**	**39 (88.6%)**
Weight increased	24 (44.4%)	25 (56.8%)
Alanine aminotransferase increased	4 (7.4%)	25 (56.8%)
Transaminases increased	-	-
Aspartate aminotransferase increased	-	13 (29.5%)
Gamma glutamyl transferase increased	1 (1.9%)	23 (52.30%)
Platelet count decreased	-	19 (43.2%)
Neutrophil count decreased	-	14 (31.8%)
Blood bilirubin increased	-	10 (22.7%)
Blood alkaline phosphatase increased	-	9 (20.5%)
NERVOUS SYSTEM DISORDERS	**15 (27.8%)**	**16 (36.4%)**

SYSTEM ORGAN CLASS Preferred term	APN311-303 N (%) patients (N=54)	APN311-202 N (%) patients (N=44)
Headache	11 (20.4%)	3 (6.8%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**11 (20.4%)**	**27 (61.4%)**
Anemia	5 (9.3%)	24 (54.5%)
EYE DISORDERS	**13 (24.1%)**	**10 (22.7%)**
METABOLISM AND NUTRITION DISORDERS	**9 (16.7%)**	**19 (43.2%)**
IMMUNE SYSTEM DISORDERS	**2 (3.7%)**	**11 (25.0%)**
RENAL AND URINARY DISORDERS	**4 (7.4%)**	**12 (27.3%)**
INFECTIONS AND INFESTATIONS	**3 (5.6%)**	**13 (29.5%)**

N=number of subjects.

Table 19: Summary of Serious Treatment Emergent Adverse Events reported by at least 1% of Patients

SYSTEM ORGAN CLASS Preferred term	Number (%) Patients	
	APN311-303 (N=54)	APN311-202 (N=44)
Overall	12 (22.2%)	26 (59.1%)
BLOOD AND LYPMPHATIC	**-**	**3 (6.8%)**
SYSTEM DISORDER	-	1 (2.3%)
Febrile neutropenia	-	1 (2.3%)
Neutropenia	-	-
Thrombocytopenia	-	-
Autoimmune hemolytic anemia	-	-
Disseminated intravascular	-	2 (4.5%)
coagulation	**-**	**2 (4.5%)**
Anemia	-	1 (2.3%)
EYE DISORDERS	-	1 (2.3%)
Photophobia	-	-
Vision blurred	-	1 (2.3%)
Iridoplegia	**5 (9.3%)**	**6 (13.6%)**
Mydriasis	2 (3.7%)	3 (6.8%)
GASTROINTESTINAL DISORDERS	1 (1.9%)	3 (6.8%)
Vomiting	1 (1.9%)	-
Diarrhea	1 (1.9%)	-
Enteritis	1 (1.9%)	-
Mechanical ileus	-	-
Subileus	-	-
Pancreatitis	-	-
Proctalgia	-	1 (2.3%)
Constipation	-	-
Nausea	-	2 (4.5%)
Abdominal pain	**3 (5.6%)**	**7 (15.9%)**
Ileus	1 (1.9%)	-

SYSTEM ORGAN CLASS Preferred term	Number (%) Patients	
	APN311-303 (N=54)	APN311-202 (N=44)
GENERAL DISORDERS AND	1 (1.9%)	2 (4.5%)
ADMINISTRATION SITE	1 (1.9%)	6 (13.6%)
CONDITIONS	-	1 (2.3%)
General physical health	-	1 (2.3%)
deterioration	-	-
Pain	-	**-**
Pyrexia	-	-
Edema	**-**	**2 (4.5%)**
Edema nec	-	2 (4.5%)
Systemic inflammatory response	-	1 (2.3%)
syndrome	-	1 (2.3%)
HEPATOBILIARY DISORDERS	**3 (5.6%)**	**11 (25.0%)**
Gallbladder obstruction	1 (1.9%)	-
IMMUNE SYSTEM DISORDERS	-	-
Anaphylactic reaction	1 (1.9%)	-
Cytokine release syndrome	-	-
Hypersensitivity	1 (1.9%)	4 (9.1%)
INFECTIONS AND INFESTATIONS	-	-
Bronchitis	-	-
Gastroenteritis	-	-
Streptococcal sepsis	-	-
Pneumocystis jirovecii pneumonia	-	-
Device related infection	-	-
Encephalitis	-	-
Gastroenteritis rotavirus	-	-
Herpes zoster	-	4 (9.1%)
Human herpesvirus 6 infection	-	1 (2.3%)
Infection	-	-
Meningitis aseptic	-	-
Pneumonia	-	-
Respiratory syncytial virus infection	-	1 (2.3%)
Sepsis	-	1 (2.3%)
Influenza	-	1 (2.3%)
Urosepsis	-	1 (2.3%)
Viral diarrhea	-	1 (2.3%)
Viral infection	-	-
Urinary tract infection	-	1 (2.3%)
Varicella	**-**	**-**
Osteomyelitis	-	-
Respiratory tract infection	**-**	**6 (13.6%)**
Skin infection	**-**	1 (2.3%)
Bactereamia	**-**	1 (2.3%)
Cystitis	**-**	1 (2.3%)
INJURY, POISONING AND	**-**	1 (2.3%)
PROCEDURAL COMPLICATIONS	**-**	3 (6.8%)
Femur fracture	**-**	-
INVESTIGATIONS	**-**	-
Alanine aminotransferase increased	**-**	1 (2.3%)

SYSTEM ORGAN CLASS Preferred term	Number (%) Patients	
	APN311-303 (N=54)	APN311-202 (N=44)
Aspartate aminotransferase increased	-	1 (2.3%)
	1 (1.9%)	**3 (6.8%)**
Blood culture positive	1 (1.9%)	-
Gamma glutamyltransferase increased	-	-
	-	2 (4.5%)
Platelet count decreased	-	1 (2.3%)
Liver function test abnormal	**2 (3.7%)**	**1 (2.3%)**
Transaminases increased	1 (1.9%)	-
Weight decreased	1 (1.9%)	-
Hemoglobin decreased	1 (1.9%)	-
METABOLISM AND NUTRITION DISORDERS	-	1 (2.3%)
	-	-
Hyperkalemia	**-**	**-**
Hypokalemia	**1 (1.9%)**	**8 (18.2%)**
Hyponatremia	1 (1.9%)	1 (2.3%)
Dehydration	-	-
NERVOUS SYSTEM DISORDERS	-	4 (9.1%)
Convulsion (Seizure)	-	2 (4.5%)
Neuropathy peripheral	-	1 (2.3%)
Peripheral motor neuropathy	-	1 (2.3%)
Somnolence	-	1 (2.3%)
PSYCHIATRIC DISORDERS	-	1 (2.3%)
Psychotic disorder	-	1 (2.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	-	1 (2.3%)
	-	-
Respiratory distress	**-**	**-**
Respiratory depression	**-**	-
Hypoxia	**-**	-
Acute respiratory distress syndrome	**-**	**-**
Dyspnea	**-**	**-**
Lung infiltration	**-**	**6 (13.6%)**
Pneumonitis	**-**	3 (6.8%)
Pulmonary edema	-	2 (4.5%)
Respiratory disorder	**-**	**-**
Cough	**-**	**-**
Bronchospasm	**-**	1 (2.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Pruritus		
Rash generalized		
SURGICAL AND MEDICAL PROCEDURES		
Tooth repair		
VASCULAR DISORDERS		
Hypotension		
Capillary leak syndrome		
Embolism arterial		
Venous thrombosis		
Venoocclusive disease		

N=number of subjects.

A23. Please clarify how EUSA Pharma envisages dinutuximab beta being used in the relapsed/refractory setting. Specifically, if people receive dinutuximab beta as a first-line maintenance treatment for high-risk neuroblastoma, would they undergo re-treatment with dinutuximab beta at relapse or non-response to therapy?

Given the lack of data for the use of Dinutuximab beta EUSA in patients that may have already failed (relapsed) or those that are refractory to Dinutuximab beta EUSA, EUSA Pharma do not support a re-treatment with the drug.

A24. Please provide a clinical rationale as to why people would be likely to respond to re-treatment with dinutuximab beta.

EUSA Pharma does not support re-treatment with Dinutuximab beta EUSA in patients that may have already failed (relapsed) or those that are refractory after treatment with Dinutuximab beta EUSA.

A25. Please clarify whether there are any circumstances under which isotretinoin would not be given concomitantly with dinutuximab beta. If so, please give details.

According to the clinical guidelines and clinical practice (expert opinions), isotretinoin is always part of the maintenance regimen and always used concomitantly with dinutuximab beta.

A26. Please give details of any studies, either completed or on-going, that evaluate the use of dinutuximab beta in relapsed or refractory disease in people having received dinutuximab beta as a first-line treatment for high-risk neuroblastoma.

There are no studies on-going that evaluate the use of dinutuximab beta in relapsed or refractory disease in people having received dinutuximab beta as a first-line treatment for high-risk neuroblastoma.

A27. For the evaluation of clinical effectiveness in APN311-302, please clarify why intention-to-treat analyses of the 406 people were not reported.

Information relevant to this question could be found in the Appendix L (1.1 APN311-302 – CSR):

Four hundred patients were planned to enter modified R2. 406 patients were enrolled and randomised for modified R2 in APN311-302 between November 2009 and August 2013. A confirmation CRF was available from 385 patients (ALL). Analysis sets included in this analysis are summarized in Table 11-1 (reported below). For a summary of protocol deviations leading to the exclusion from the various data sets see Table 21 (reported below). Fifteen of 385 randomized patients received no 13-cis-RA, ch14.18/CHO, and IL-2 (if applicable) leading to the exclusion from the Full Analysis Set (i.e. FAS or Intention to Treat population). Data from these patients (i.e. 385-15=370) was used in the analysis described in the CS.

Table 20: Data Sets Analysed in APN311-302

	Number of Patients		
	ch14.18/CHO + 13-cis-RA	ch14.18/CHO + 13-cis-RA + IL-2	All
Randomized	187	198	385
FAS (as randomized)	180	190	370
SAF (as treated)	183	183	366
PPS (as treated)	167	166	333

13-cis-RA = 13-cis retinoic acid, FAS = full analysis set, IL-2 = aldesleukin, PPS = per-protocol set, SAF = safety set.

Table 21: Patients with protocol deviations in APN311-302

Deviation	Number of Patients		
	Ch14.18/CHO + 13-cis-RA as randomized (N=187)	Ch14.18/CHO+ 13-cis-RA+IL-2 as randomized (N=198)	All (N=385)
Leading to exclusion from FAS			
No treatment with 13-cis-RA, ch14.18/CHO and IL-2 (if applicable)	[redacted]	[redacted]	[redacted]
Leading to exclusion from SAF			
No treatment with ch14.18/CHO	[redacted]	[redacted]	[redacted]
Leading to exclusion from PPS			
PD at Baseline	[redacted]	[redacted]	[redacted]
Baseline disease status missing			
Baseline disease status not evaluable			
Rand. Criteria not met or missing			
MAT no or missing			
Not treated as randomized			

13-cis-RA=13-cis retinoic acid, FAS=full analysis set, IL-2=aldesleukine, N=number of patients, MAT=myeoloablative therapy, PD=progressive disease, PPS=per-protocol set, rand.=randomized, SAF=safety set.

Section B: Clarification on cost-effectiveness data

Treatment effectiveness

B1. **Priority question**. For both high-risk and relapsed models, please develop a partitioned survival model to estimate the percentage of patients in each state of the economic model during the first 5 years of the analysis (NICE Decision Support Unit's Technical Support Document 19), followed by the long-term survival model already incorporated in the economic models. For the high-risk population, this should encompass the following steps:

a. Please use the 5 years (or longer follow-up if possible) OS and EFS KM data from study 302 (including all patients in the study) to model the percentage of patients in the stable disease, failure and death states of the economic model. If the maximum follow-up period for these outcomes does not reach 5 years, please conduct survival analysis using the KM data (please see question B2 for more details on this).

b. To estimate the percentage of patients in the health states of the comparator model please undertake the following analyses:

I. As the base case, please use the OS and EFS KM data from the isotretinoin arm in Yu *et al.* 2010,[1] adjusted for prior high-dose therapy (HDT), age at diagnosis, MYCN and INSS stage (requested in A3) to populate the stable disease, failure and death states of the comparator arm of the economic model;

II. If providing adjusted KM curves for both treatment arms is not possible, please use the OS and EFS HRs comparing all patients from study 302 to Yu *et al.* 2010,[1] adjusted for prior HDT, age at diagnosis, MYCN and INSS stage (requested in A3), and apply these to the OS and EFS curves estimated in B1.a), to estimate OS and EFS curves for isotretinoin.

If it is not possible to use study 302 (all patients) and Yu *et al.* 2010[1] (isotretinoin arm) to model the intervention and comparator arms of the model, respectively, please use study 302 (to model dinutuximab beta) and historical control R1 (to model isotretinoin) as explained in A4. If these data sources are used, please follow the requested steps for the modelling approach with the appropriate data.

For the relapsed population, please follow the steps listed above, using the appropriate studies and adjusted data for prognostic factors prior HDT, age at diagnosis, MYCN and INSS stage (requested in A6). Study 202 should be used for modelling the dinutuximab beta arm of the model. To model the comparator arm of the model, please use the Garaventa study and the historical control R1 (relapsed patients) as a scenario analysis.

A partitioned survival model to estimate the percentage of patients in each state of the economic model during the first 5 years of the analysis was developed, followed by the long-term survival model already incorporated in the previous version of the economic model.

For the high-risk population, we use the 5 years OS and EFS KM data from study 302 (including all patients in the study) to model the percentage of patients in the stable disease,

failure and death states of the economic model. Those input values can be found in the "ObservedSurvivalFunctions" worksheet of the model.
As mentioned in A3, it was not deemed appropriate to use study 302 (all patients) and Yu *et al.* 2010 (isotretinoin arm) to model the intervention and comparator arms of the model, respectively.
To estimate the percentage of patients in the health states of the comparator model, we used 5 years OS KM data from the historical control R1 study. As mentioned previously, analyses were restricted to overall survival, so no EFS data was available to populate the model for the comparator arm. Thus, it was assumed in the model that the absolute separation (in %) between OS and EFS observed in the active arm will be the same for the comparator arm over time.

As mentioned previously, the model considers both populations (relapsed & refractory) together (and relapsed or refractory only as potential scenarios).
For the relapsed/refractory population, the maximum follow-up period for OS and EFS outcomes from APN311-202 were used and fit of the survival curves was performed to extrapolate the best fitting curve from the last available data point to the 5-year horizon. To model the comparator arm of the model, we used the Garaventa study and the historical control R1 (relapsed patients).

B2. **Priority question**. For both high-risk and relapsed models, please develop a partitioned survival model to estimate the percentage of patients in each state of the economic model during the first 10 years of the analysis (NICE Decision Support Unit's Technical Support Document 19), followed by the long-term survival model already incorporated in the economic models. For the high-risk population, this should encompass the following steps:

a. Please use the maximum follow-up available to obtain OS and EFS KM data from study 302 (including all patients in the study) to model the percentage of patients in the stable disease, failure and death states of the economic model. Following this step, please fit survival curves and extrapolate the best fitting curve from the last available data point to the 10-year horizon (please undertake the steps reported in the NICE Decision Support Unit's Technical Support Document 14 to carry curve fitting and curve extrapolation).

b. To estimate the percentage of patients in the health states of the comparator model please undertake the following analyses:

I. As the base case, please use the maximum follow-up available to obtain OS and EFS KM data from the isotretinoin arm in Yu *et al.* 2010,[1] adjusted for prior HDT, age at diagnosis, MYCN and INSS stage (requested in the A3) to model the percentage of patients in the stable disease, failure and death states of the economic model. Following this step, please fit survival curves and extrapolate the best fitting curve from the last available data point to the 10-year horizon (please undertake the steps reported in the NICE Decision Support Unit's Technical Support Document 14 to carry curve fitting and curve extrapolation).

II. If fitting adjusted treatment curves independently is not possible, please use the OS and EFS HRs comparing all patients from study 302 to Yu *et al.* 2010,[1] adjusted for prior HDT, age at diagnosis,

MYCN and INSS stage (requested in A3), and apply these to the OS and EFS curves estimated in B2.c), to estimate OS and EFS curves for isotretinoin.

If it is not possible to use study 302 (all patients) and Yu *et al.* 2010[1] (isotretinoin arm) to model the intervention and comparator arms of the model, respectively, please use study 302 (to model dinutuximab beta) and historical control R1 (to model isotretinoin) as explained in A4. If these data sources are used, please follow the requested steps for the modelling approach with the appropriate data.

For the relapsed population, please follow the steps listed above, using the appropriate studies and adjusted data for prognostic factors prior HDT, age at diagnosis, MYCN and INSS stage (requested in A6). Study 202 should be used for modelling the dinutuximab beta arm of the model. To model the comparator arm of the model, please use the Garaventa study and the historical control R1 (relapsed patients) as a scenario analysis.

A partitioned survival model to estimate the percentage of patients in each state of the economic model during the first 10 years of the analysis was developed as described in B1, followed by the long-term survival model already incorporated in the previous version of the economic model.

B3. **Priority question**. Please provide (in an Excel sheet) all the survival curves resulting from the fitting and extrapolation exercise undertaken in B2 extrapolated to a 90-year time horizon (even if only 10 years of the curves are used in the economic model as requested in B2). Please provide two sets of all the survival curves extrapolated – one set based on monthly cycles and the other set of curves based on yearly cycles.

All the survival curves resulting from the fitting and extrapolation exercise undertaken in B2 extrapolated to a 90-year time horizon are provided in the current version of the model in the following worksheets and includes the full set of parametric estimates (Non-Linear, Exponential, Weibull, Gompertz, Log-Logistic and Lognormal):

- "FLSurvivalCurveExtrapolation" for monthly cycles for the high risk population
- "FLSurvivalCurveExtrapol(annual)" for annual cycles
- "RRSurvivalCurveExtrapolation" for monthly cycles
- "RRSurvivalCurveExtrapol(annual)" for monthly cycles

B4. **Priority question**. When modelling both scenarios described above (estimating a 5-year short-term model before patients achieve a potential cure or estimating a 10-year short-term model before patients achieve a potential cure), please:

a. Set the cycle length in the short-term model to 1 month. This should be consistent throughout the entire short-time model, i.e. all cycles for 5 (or 10) years should have the duration of 1 month;

b. Please discount costs and benefits according to the monthly cycles of the model;

c. Please adjust costs as necessary to reflect monthly costs in the models, for all costs considered. This means estimating monthly costs and attributing the monthly cost to the proportion of patients in the appropriate heath state for

each cycle of the economic model. After the 5 (or 10 years) in the short-term model, the costs should be adjusted to reflect annual costs;

d. Please adjust other inputs that depend on cycle length in the model accordingly;

e. After the short-term model (5 or 10 years) please leave the long-term model with yearly cycles, as it is now, and discount costs and QALYs accordingly.

The revised model is incorporating all the above requests.

B5. **Priority question**. The ERG's clinical expert stated that once a patient relapses, then it is unlikely that they will be cured from their disease and they will have continual cycles of relapse and remission, shortening in length as time goes on. Please remove the assumption of cure from the relapse model and implement the extrapolated survival curves obtained in B2 to model the long-term portion of the economic model. Because of the change in cycle length to the long-term model from 10 years , the ERG advises using the two sets of curves requested in B3 (i.e. use the monthly fitted curves for the first 10 years and use the annually fitted curves after 10 years). This avoids re-estimating resource use in the model to adjust for cycle length.

As of today, there is no clinical evidence confirming that there will be "late" relapses in patients who have received dinutuximab beta and who are considered as long-term stable (EFS) patients (confirmed by expert opinion). Thus, relapsed and refractory patients are still considered in the base case model as cured from their disease after 10 years of being in EFS.

Still to comply to ERG's request, the model incorporates an option to run the analysis based on "no cure at 10 years". Please see "ScenarioB5" worksheet of the model for results.

Table 22: Scenario analysis outcomes B5

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
Comparator - Isotretinoin 1st Line	£190'521	13.9729	—	—	—
Dinutuximab Beta EUSA 1st Line	**£311'608**	**19.3918**	**£121'087**	**5.4189**	**£22'345**
Comparator - Isotretinoin Relapsed/Refractory	£107'073	2.4325	—	—	—
Dinutuximab Beta EUSA Relapsed Refractory	**£313'121**	**5.4170**	**£206'048**	**2.9845**	**£69'040**

Health related quality of life

B6. **Priority question**. The ERG in the suspended single technology appraisal of dinutuximab (ID799) used the mapping algorithm reported in Rowen *et al*. 2009 to map the SF-36 quality of life data in Nathan *et al.* 2007 into EQ-5D utility data. Please carry out a scenario analysis using the EQ-5D values estimated by the ERG in ID799 .

The company applied a 12.5% reduction to the general population health utility estimate, based on evidence from Portwine et al. (5), to reflect potential morbidity in this health state after 5 years. Portwine et al. was chosen because it included patients with neuroblastoma and had the largest number of patients (n=99) of the studies the company had found. As an alternative, the ERG calculated a decrement in utility of 31.5% relative to the general population, using the same approach as the company, based on a study by Nathan et al. (6)

Please see "ScenarioB6" worksheet of the model for results.

Table 23: Scenario analysis outcome B6

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
Comparator - Isotretinoin 1st Line	£127'986	9.1504	—	—	—
Dinutuximab Beta EUSA 1st Line	**£263'334**	**12.4459**	**£135'348**	**3.2955**	**£41'070**
Comparator - Isotretinoin Relapsed/Refractory	£100'134	2.2620	—	—	—
Dinutuximab Beta EUSA Relapsed Refractory	**£260'025**	**5.6703**	**£159'892**	**3.4083**	**£46'913**

Please note that the Company doesn't believe that this analysis reflects reasonable estimates for health utility values of neuroblastoma patients.

Additionally, the committee has already set a precedent during the evaluation of Unituxin for high-risk neuroblastoma.

"*The committee heard from the clinical experts that although patients who survive neuroblastoma will have a lower quality of life than the general population, a reduction of 31.5% seemed excessive. The clinical experts also pointed out that the Nathan et al. study included patients with low-risk neuroblastoma, which can result in more long-term disabilities such as paralysis, and that this study does not necessarily represent patients who survive high-risk neuroblastoma. The patient expert commented that quality of life can be well maintained in patients who survive neuroblastoma. The committee heard from the clinical and patient experts that the utility decrement of 13% applied by the company in its base case seemed the most reasonable estimate and could possibly be smaller for patients who survive neuroblastoma in the stable health state. The committee concluded that there was considerable uncertainty about accurately determining the size of the decrement in health-related quality of life, but having heard from the experts,* ***it agreed that the 13% decrement in health-related quality of life applied by the company was a reasonable assumption***."

B7. **Priority question**. After 5 years, any patients in the failure health state are assumed to have a 41.7% decrement to the age adjusted UK EQ-5D population norms. Please provide a scenario where the constant utility value of 0.56 (based on Barr *et al.* 1999[7]) is assumed for the failure health state.

The base case considers that increasing age has an impact on utilities and is indexed to UK EQ-5D population norms.

As requested, we applied in the model a constant utility value of 0.56 after 5 years.

Please see “ScenarioB7” worksheet of the model for results.

Table 24: Scenario analysis outcome B7

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
Comparator - Isotretinoin 1st Line	£190'521	14.0520	—	—	—
Dinutuximab Beta EUSA 1st Line	**£311'569**	**19.4483**	**£121'048**	**5.3963**	**£22'432**
Comparator - Isotretinoin Relapsed/Refractory	£124'621	3.1430	—	—	—
Dinutuximab Beta EUSA Relapsed Refractory	**£263'115**	**8.1192**	**£138'493**	**4.9762**	**£27'831**

B8. Please provide the clinical rationale for attributing a lower utility value (compared to the general population) to patients in the stable disease state after 5 years, when these patients are assumed to be cured.

Stable state and failure state were assigned with utility values of 0.81 and 0.56 respectively for the first part of the model (5 or 10 years) (7). After 5 or 10 years depending on the model, patients in the stable state continue to experience a health utility decrement of 12.5% compared to that of the general population (5)to account for potential morbidities among neuroblastoma survivors. Patients in the failure state are assumed to continue to experience a health utility of 0.56 decreasing with age based on UK EQ-5D population norms.

B9. Please provide the clinical rationale for attributing the same utility value to patients in the stable disease state in the first-line and in the r/r population. Please provide a similar justification for patients in the failure state.

No published data have been found to support any difference, thus we have sought expert opinions. They did not see why there will be a difference in the stable/failure disease state in first-line and in the R/R population.

<u>Adverse events</u>

B10. **Priority question**. Please clarify how the proportions of patients experiencing dinutuximab beta-related adverse events (reported in Table 56 and used in the model) were estimated.

Due to different methods of AE collection across studies, ADR frequencies were calculated either on the totality of the safety database (N=514) when possible/relevant or on the subpopulation of studies APN311-101, -201, -202, -303 (N=148) (Dinutuximab beta EUSA EPAR).

B11. **Priority question**. Please use the appropriate clinical source to model adverse events in the model. For example, if Yu *et al.* 2010 is used to model the clinical effectiveness of isotretinoin, please use the adverse events reported in the paper. If

the historical control R1 data are used, then please use the adverse events reported in the R1 study or provide a rationale for not doing so. This applies to all treatment arms across both models. When this is not feasible, please provide the rationale for not following this approach.

In the historical control R1, no adverse event tables were available. Thus, the company has used the data of Yu et al for the control arm (1).

B12. **Priority question**. Please clarify the criteria used for inclusion of adverse events in the model, and please clarify which proportions/adverse event rates used in the economic model are treatment-related adverse events and which events are treatment-emergent events. Please justify why one or the other was selected.

Only treatment-emergent adverse events were used in the economic model (source: SmPC). This is a conservative assumption considering relatively high frequency of adverse events are included in the economic model for Dinutuximab beta EUSA arm.

B13. Please run a scenario analysis using only the rates of adverse events on the subset of patients in the analysis who received dinutuximab beta as a continuous infusion.

Please find below the treatment-emergent adverse events for APN311-202 (long-term infusion of Dinutuximab beta EUSA) that are considered as input in this scenario analysis.

Table 25: Scenario input for B13

Risk of Adverse events			
	Pain (including abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia)		
	Dinutuximab Beta EUSA Arm	63.60%	CSR study APN311-202
	Comparator Arm	6.00%	Yu AL. Et al. 2010
	Hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release syndrome, serious anaphylactic reactions)		
	Dinutuximab Beta EUSA Arm	50.00%	CSR study APN311-202
	Comparator Arm	2.00%	Yu AL. Et al. 2010
	Severe Capillary Leak Syndrome		
	Dinutuximab Beta EUSA Arm	6.80%	CSR study APN311-202
	Comparator Arm	7.00%	Yu AL. Et al. 2010
	Eye problems		
	Dinutuximab Beta EUSA Arm	22.70%	CSR study APN311-202
	Comparator Arm	1.00%	Yu AL. Et al. 2010
	Peripheral neuropathy		
	Dinutuximab Beta EUSA Arm	2.30%	CSR study APN311-202
	Comparator Arm	6.00%	Yu AL. Et al. 2010
	Pyrexia, Infection		
	Dinutuximab Beta EUSA Arm	95.50%	CSR study APN311-202
	Comparator Arm	22.00%	Yu AL. Et al. 2010
	Vomiting, Diarrhoea		
	Dinutuximab Beta EUSA Arm	56.80%	CSR study APN311-202
	Comparator Arm	3.00%	Yu AL. Et al. 2010

This scenario and results can be found in the worksheet entitled “ScenarioB13”.

Table 26: Scenario analysis outcome B13

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
Comparator - Isotretinoin 1st Line	£190'521	13.9729	—	—	—
Dinutuximab Beta EUSA 1st Line	**£311'425**	**19.3918**	**£120'904**	**5.4189**	**£22'312**
Comparator - Isotretinoin Relapsed/Refractory	£124'621	3.0627	—	—	—
Dinutuximab Beta EUSA Relapsed Refractory	**£262'971**	**8.1136**	**£138'350**	**5.0510**	**£27'391**

Resource use and costs

B14. **Priority question**. Clinical expert opinion sought by the ERG suggested that stable patients are seen every 3 months for the first year, then between 3-6 months between the first and the fifth year with yearly visits after 5 years. Please provide a scenario where costs associated in the stable health state reflect a follow-up of every 3 months for the first 5 years and yearly thereafter.

As requested, please see "ScenarioB14" worksheet of the model for results and reported in the Table 27.

Table 27: Scenario analysis outcome B14

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
Comparator - Isotretinoin 1st Line	£179'633	13.9729	—	—	—
Dinutuximab Beta EUSA 1st Line	**£295'251**	**19.3918**	**£115'618**	**5.4189**	**£21'336**
Comparator - Isotretinoin Relapsed/Refractory	£123'566	3.0627	—	—	—
Dinutuximab Beta EUSA Relapsed Refractory	**£256'746**	**8.1136**	**£133'180**	**5.0510**	**£26'367**

B15. **Priority question**. In the relapsed model, the weight adjustment is based on the age of the population of the high-risk model. Please correct this.

We thank the ERG and the NICE technical team for pointing out this error. The revised model has been corrected regarding the weight adjustment of the high-risk model.

B16. **Priority question**. As described on page 137 of the CS, patients assigned to TOPO/CTX received intravenous topotecan 0.75mg/m^2/d and cyclophosphamide 250mg/m^2/d for 5 days. Cycles were 21 days, starting subcutaneous filgrastim 5

µg/kg/d on day 6. However, in the economic model costs are based on the unit cost of the drug. Please correct the high risk and relapsed models to include body surface area and weight in the cost calculations for the failure health state, taking in to account that the two models have different starting ages (3 years for high risk and 6 years for relapsed) and that weight and surface area change over time.

As requested, the model has been revised to include your comment.

B17. **Priority question**. Please include the costs IL-2 has in the high-risk model (and associated administration and hospitalisation costs) to accurately reflect the proportion of patients who received IL-2 in the clinical studies used as the source for clinical effectiveness in the economic model. For example, if the entire population from study 302 is used, please use the total number (or percentage) of patients in 302 who received IL-2 to cost the treatment in the economic model.

In study APN311-302, the objective of the clinical study was to investigate the patient outcome of having IL-2 or not with dinutuximab beta. So far, the results, as detailed in the CS document (2.6.1), have shown that concomitant administration of IL-2 does not improve EFS nor OS. Thus, the patient population will not receive IL-2 in clinical practice.

To confirm this last statement, the company sought the opinion of experts who confirmed that IL-2 in clinical practice is not routinely used in high-risk neuroblastoma patients.

B18. **Priority question**. Please provide the mean number of hospital days from APN311-302 and APN311-202. If possible, please perform a scenario implementing the mean hospital days into the hospitalisation costs for each arm of the high-risk and relapse model.

The mean number of hospital days from APN311-302 could not be reported because no dates for admission and discharge were documented in the case report form.

For the study APN311-202, the mean duration of hospitalization for antibody treatment prior to discharge to outpatient treatment was [redacted] in cycles 1, 2 and 4, and [redacted] in cycles 3 and 5 (Appendix L, 1.7 APN311-202 CSR, table 14.1.7.5).

B19. Please specify which costs used in the model are from the National tariff or the Payment by Results tariff and why NHS reference costs were not deemed appropriate in these cases.

Only NHS reference costs 2015-2016 are included in the model.

B20. Please provide the mean treatment duration with dinutuximab beta in APN311-302 and APN311-202.

In the study APN311-302, the mean treatment duration with dinutuximab beta (+/- IL2) was [redacted] in cycles 1 and 2, and [redacted] in cycles 3, 4 and 5.

In the study APN311-202 (continuous infusion), the mean treatment duration with dinutuximab beta was [redacted] in cycle 1, 10.4 days in cycle 2, and [redacted] in cycles 3, 4 and 5. The treatment duration was calculated using the start and end day dinutuximab beta treatment.

B21. Please provide the mean treatment duration with isotretinoin in the Yu *et al.* 2010 study and in the historical control studies R1 and Garaventa.

The article Yu et al. (1) describes that isotretinoin was administered for 14 consecutive days within each of six consecutive 28-day cycles. However, information about the mean treatment duration with isotretinoin was not reported and was not found in any other publically available document.
For the historical control studies R1, the start date isotretinoin was documented, however no other information on this treatment could be found in the available data. Information about treatment with isotretinoin is not part of the Garaventa data we have access to.

B22. Table 65 of the CS reports 15 hospital days in the first cycle. However, dinutuximab beta and IL-2 require 10 days of hospitalisation. Please clarify what the 15-days assumption is based on.

IL-2 requires 5 days of hospitalisation one week prior to dinutuximab beta treatment, which itself requires 10 days of hospitalisation. The sum of these two hospitalisation periods gives 15 hospital days.

B23. Please include a scenario analysis using the mean weight from the clinical studies used as the source for clinical effectiveness in the economic model. For example, if the entire population from study 302 is used, please use the mean weight of patients in 302 to estimate treatment costs in the economic model. Please do this for all treatments in both economic models.

Most treatment costs included in the model are derived from BSA. Whenever the treatment cost needs to be derived from weight, this calculation is included in the base case economic model.

B24. Please review how weight and body surface area have been implemented in the estimation of treatment costs in both models, ensuring calculations for each model refer to the correct population (high-risk relates to 3-year olds and relapsed relates to 6-year olds) and correct the models if necessary.

These parameters have been reviewed and corrected.

B25. Please provide a breakdown of the calculations used to derive the average monthly units of resources consumed based on Rebholz *et al.* 2011 (8) presented in Table 68 of the company submission.

These assumptions are based on the modelling approach presented in the suspended single technology appraisal of dinutuximab. Briefly, the company has performed sensitivity analyses around parameter estimates from the Rebholz et al study (8), since the specifics regarding the percentage of the population consisted of high-risk patients were not provided. The breakdown of the calculations is presented in the worksheet entitled “InputGeneral”.

B26. In Table 64 and 65 of the CS, for Cycle 2, a second administration inpatient cost is reported instead of a first administration inpatient cost as outlined in the text explanation. Please clarify what was done in the economic model and if necessary, correct the model to reflect the right assumption.

As stated in the CS text, administration costs per cycle assume that a patient starting the treatment will be considered as in-patient at the resuscitation setting during the first-cycle and only during the first part of the second-cycle. In Tables 64 and 65, the first administration

during the second cycle is performed as inpatient and the second as outpatient. These costs are used in the model.

B27. The ERG identified a discrepancy in the outpatient unit cost assumed in the model in Cell I85 of the "InputGeneral" tab and the unit cost reported in Table 68 of the CS. Please clarify which is the correct value.

The value in the economic model was the correct value, however an error occurred in the Table 68 reported. The row "Attended hospital outpatient department in the last 3 months", column "unit cost (£)", should report £163.57.

Literature search & assumptions

B28. Please clarify which assumptions (if any) made in the economic model for this analysis are informed by the modelling approach taken by the company or by the recommendations of the appraisal committee in the suspended single technology appraisal of dinutuximab (ID799)

The following assumptions informed by the appraisal of dinutuximab:

- Discount at 1.5%
- Failure state resource use for both populations (treatment regimens)
- Stable state resource use for both populations (Rebholz sensitivity analysis)
- The hospital code rate for paediatric neoplasms with no comorbidities (PM43C)

B29. Please clarify the source used to obtain the standard error estimates (reported in Table 71, page 138), particularly for 5-year OS and EFS outcomes for dinutuximab beta and isotretinoin for the first-line population (SD 0.2%) and the r/r population (0.16%; 0.15%; 0.18% and 0.08%)

The standard error estimates for OS and EFS were based on beta distribution for both population. For the other standard error estimates were based on normal, beta or gamma distributions depending which one was the most appropriate.

Section C: Textual clarifications and additional points

C1. **Priority question**. The ERG encountered errors when running both the deterministic and probabilistic sensitivity analysis in the model. Please ensure that these are running correctly in any model submitted in response to clarification, or the original model if no new models are provided during the clarification stage.

We apologized that the previous version was somehow corrupted, it seems that the file extension "[noACIC]" was the source of the problem. The revised model is now fully functional.

C2. Please report the updated sensitivity analyses results for the updated models together with the updated base case results.

As a summary, please find below the main assumptions considered for the base case economic model:

- A 1.5% discount on costs and benefits
- A 5.6 mortality ratio for stable health
- Relapsed and refractory patients are assumed to have the same clinical outcomes

- Kaplan–Meier observed values from APN311-302 (high-risk population) and APN311-202 (relapsed and refractory population) for event-free and overall survival
- Kaplan–Meier observed OS values from Historical control R1 study (for the comparison with the high-risk population) and combined results of relapsed only patients from Historical control R1 study and Garaventa study (for the comparison with the relapsed and refractory population) for event-free and overall survival
- A cure threshold of 10 years for both populations
- Best visual and minimized fit applied for the high-risk population survival function estimates
- Best visual fit applied for the relapsed and refractory population survival function estimates
- Mean BSA and weight are coming from APN311-302 and APN311-202 for high-risk and relapsed/refractory population respectively
- A decrement utility value of 12.5% (5) and 41.7% (7) for high-risk and relapsed/refractory neuroblastoma patients respectively compared to general population
- To overcome the lack of EFS data for the comparator arms, the absolute separation (in %) between OS and EFS observed in the active arm is the same for the comparator arm over time

The resulting ICERs for the Dinutuximab beta EUSA regimen compared with isotretinoin, based on the evidence available, are £22’338 per QALY gained for the high-risk population and £27’419 per QALY gained for the relapsed and refractory population (Table 28).

Please find below the main outcomes from the base case economic model.

Table 28: Base-case results

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
Comparator - Isotretinoin 1st Line	£190'521	13,9729	—	—	—
Dinutuximab Beta EUSA 1st Line	**£311'569**	**19,3918**	**£121'048**	**5,4189**	**£22'338**
Comparator - Isotretinoin Relapsed/Refractory	£124'621	3,0627	—	—	—
Dinutuximab Beta EUSA Relapsed Refractory	**£263'115**	**8,1136**	**£138'493**	**5,0510**	**£27'419**

Table 29: Summary of predicted resource use by category of cost

Item	1st Line					Relapsed/refractory				
	Cost (£), Dinutuximab	Cost (£), Isotretinoin	Increment	Absolute Increment	% Absolute Increment	Cost (£), Dinutuximab	Cost (£), Isotretinoin	Increment	Absolute Increment	% Absolute Increment
Drug Cost	£145'472	£5'505	£139'967	£139'967	115,6%	£130'109	£183	£129'925	£129'925	93,8%
Administration & Hospitalization Costs	£12'760	£0	£12'760	£12'760	10,5%	£72'092	£0	£72'092	£72'092	52,1%
Concomitant medication cost	£912	£0	£912	£912	0,8%	£912	£0	£912	£912	0,7%
Monitoring cost	£547	£0	£547	£547	0,5%	£489	£0	£489	£489	0,4%
Adverse event cost	£1'319	£337	£981	£981	0,8%	£1'319	£337	£981	£981	0,7%
Failure cost	£128'916	£169'889	-£40'973	£40'973	33,8%	£49'232	£122'457	-£73'225	£73'225	52,9%
Ongoing healthcare cost	£21'643	£14'790	£6'853	£6'853	5,7%	£8'963	£1'644	£7'319	£7'319	5,3%
Total	£311'569	£190'521	£121'048	Total absolute increment	100%	£263'115	£124'621	£138'493	Total absolute increment	100%

Please find below the sensitivity analyses from the base case economic model for the High-risk population:

Figure 1: Tornado diagram for DSA results (ICER) for Dinutuximab beta Apeiron for the first-line population (revised model)

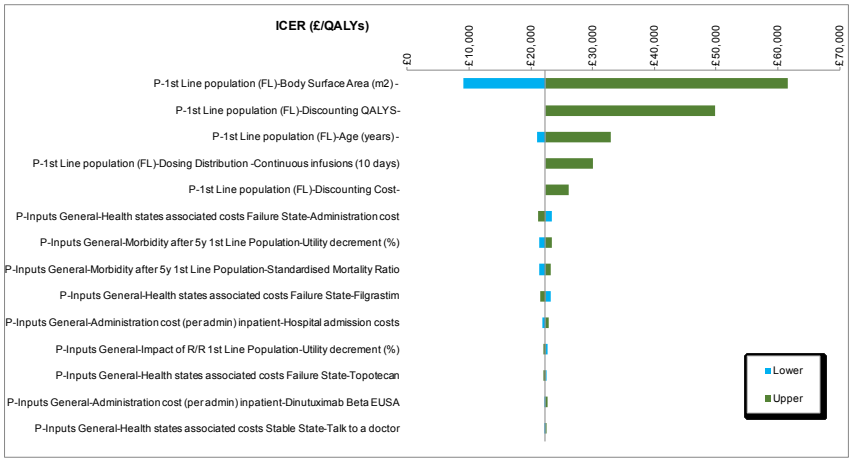


Figure 2: Cost-effectiveness plane for Dinutuximab beta Apeiron for the first-line population with a £30,000/QALY threshold (revised model)

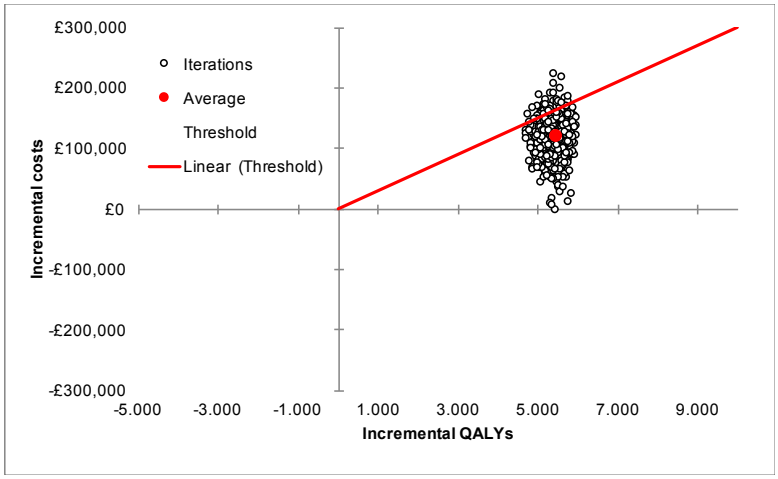


Figure 3: CEAC for Dinutuximab beta Apeiron for the first-line population (revised model)

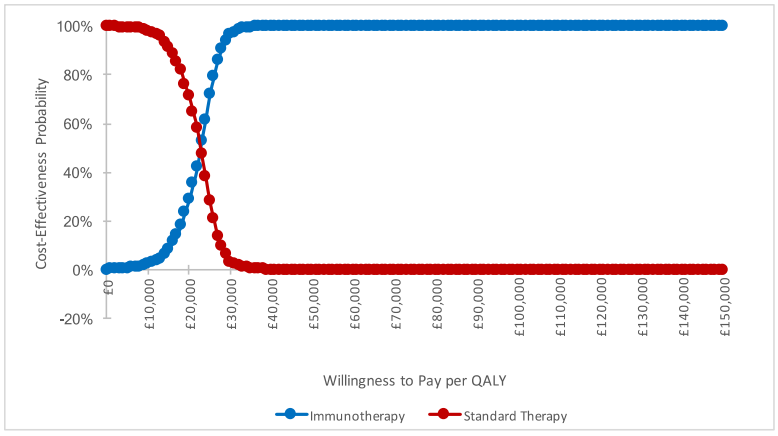


Table 30: PSA results for Dinutuximab beta Apeiron for the first-line population (revised model)

	Immunotherapy				Standard Therapy			
	Mean	Median	Lower 95% Confidence Interval	Upper 95% Confidence Interval	Mean	Median	Lower 95% Confidence Interval	Upper 95% Confidence Interval
Cost (£)	£311'576	£294'530	£306'433	£316'719	£191'005	£167'786	£184'419	£197'590
QALY	19,49	19,51	19,44	19,53	14,04	14,06	14,01	14,07
Mean ICER	£22'171							

Please find below the sensitivity analyses from the base case economic model for the relapsed/refractory population:

Figure 4: Tornado diagram for DSA results (ICER) for Dinutuximab beta Apeiron for the relapsed/refractory population (revised model)

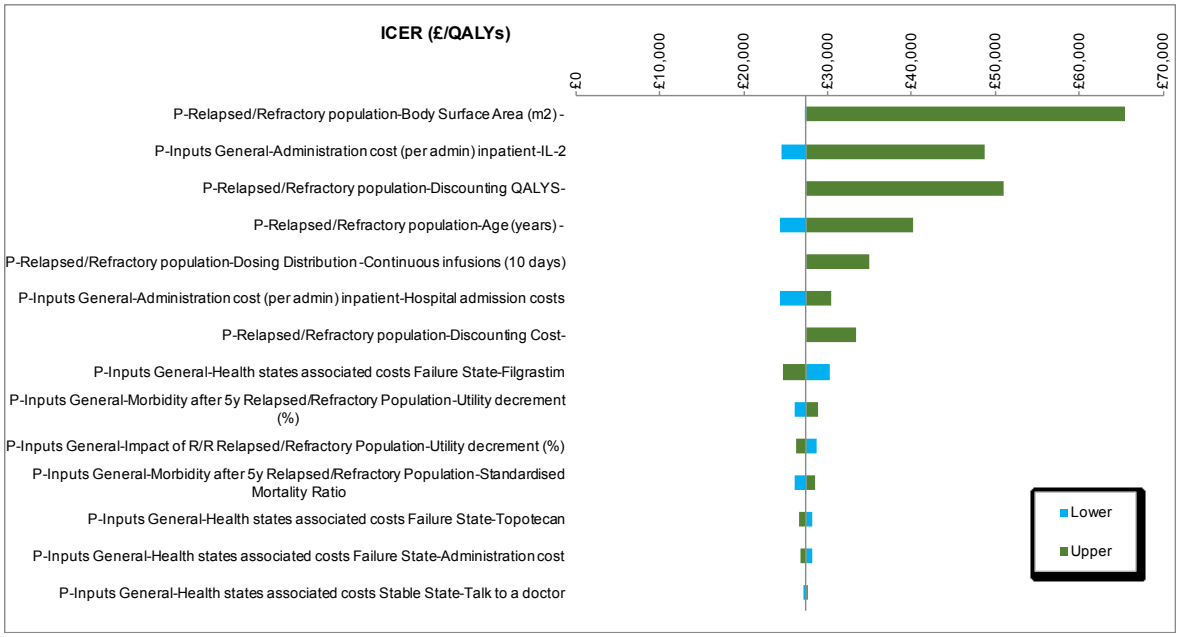


Figure 5: Cost-effectiveness plane for Dinutuximab beta Apeiron for the relapsed/refractory population with a £30,000/QALY threshold (revised model)

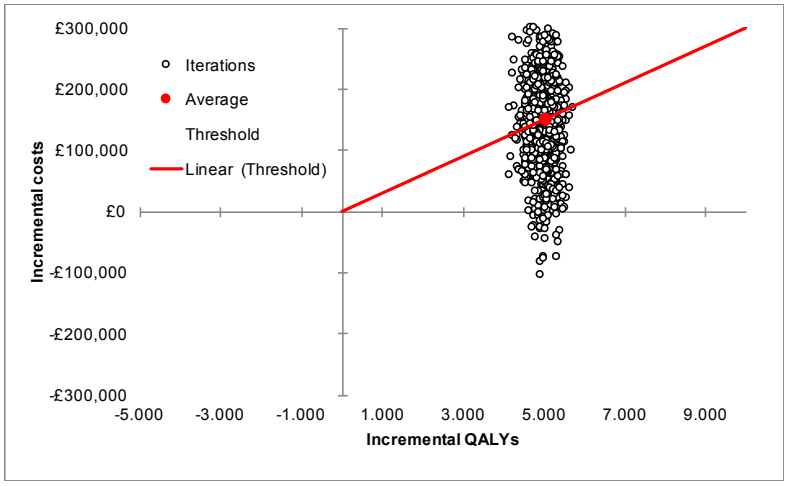


Figure 6: CEAC for Dinutuximab beta Apeiron for the relapsed/refractory population (revised model)

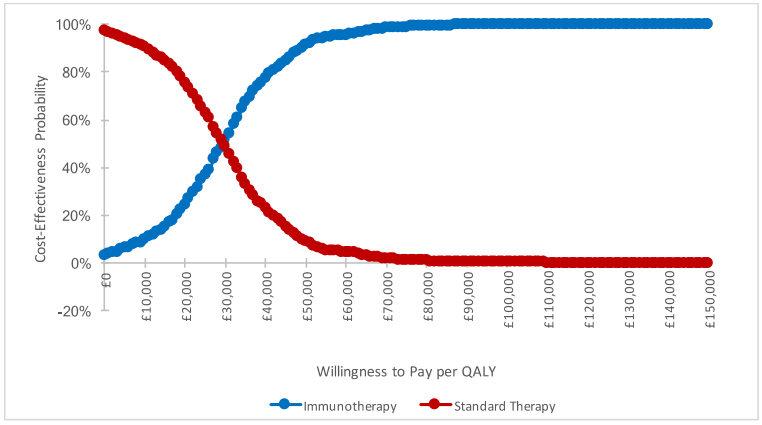


Table 31: PSA results for Dinutuximab beta Apeiron for the relapsed/refractory population (revised model)

	Immunotherapy				Standard Therapy			
	Mean	Median	Lower 95% Confidence Interval	Upper 95% Confidence Interval	Mean	Median	Lower 95% Confidence Interval	Upper 95% Confidence Interval
Cost (£)	£276'425	£264'864	£271'954	£280'896	£126'753	£110'863	£121'904	£131'602
QALY	8,10	8,13	8,09	8,12	3,07	3,07	3,06	3,08
Mean ICER	£29'839							

C3. Please clarify which service provider was used to carry out the literature search of EMBASE.

The access rights to EMBASE database were obtained through Elsevier.

C4. Please clarify whether the data presented in Table 14 of the CS should be marked as AiC: the data are also presented in Table 15 of the CS and are not marked as AiC.

We do not believe that we made a mistake in the marking. The two tables contain different information, being the demographic profile of patients from the APN311-303 study who were enrolled in CU-LTI program presented in Table 14 and the baseline disease status of patients from the same study presented in Table 15. Table 14 is properly marked as AiC (academic in confidence), since this data is not already reported in the CHMP AR nor the SmPC published by EMA, therefore, these data are reported only in a clinical study report, and were included in the CS to provide additional detail for the NICE evaluation. Part of this data may be a part of a manuscript in the future. Table 15 is not highlighted, and therefore has already been published in a publically available document (EMA EPAR).

C5. In Table 37 of the CS, please confirm that the unit for data reported in the row labelled, "Time between diagnosis and first relapse" is years. Also, please validate and confirm the data reported for 95% CI, Median, and Min, Max.

Yes, we confirm that the unit for data reported in the row labelled "Time between diagnosis and first relapse" is years, and added this information in the revised table below.

We thank the ERG and the NICE technical team for pointing out the issue with the rows 95%CI, Median and Min, Max. An error seems to have occurred at the EMA submission by the previous MoH (Table 18: Patient Characteristics of the current EPAR public assessment report available from EMA). Please find below the corrections in the Table 37 CS document.

Table 32: Patient characteristics – APN311-303 vs Historical Control Garaventa

Patient Characteristics		Historical Control Garaventa (N = 29)	APN311-303 (N = 30)
Period of diagnosis		1999-2004	2000-2010
Gender, n (%)	Male Female	20 (69.0) 9 (31.0)	15 (50.0) 15 (50.0)
Age (years) at initial diagnosis[1]	N Mean (SD) Median Min, Max	29 4.3 (2.4) 4.0 1, 13	30 4.8 (4.1) 3.5 1, 17
Age category at initial diagnosis[1], n (%)	≤ 5 years > 5 years	21 (72.4) 8 (27.6)	22 (73.3) 8 (26.7)
INSS Stage, n (%)	1 2A 3 4 Missing	0 (0.0) 0 (0.0) 1 (3.4) 28 (96.6) 0 (0.0)	1 (3.3) 1 (3.3) 2 (6.7) 25 (83.3) 1 (3.3)
MYCN status, n (%)	Amplified Not amplified Missing	8 (27.6) 21 (72.4) 0 (0.0)	4 (13.3) 17 (56.7) 9 (30.0)
Time between diagnosis and first relapse, years	N Mean (SD) Median Min, max	29 1.87 (1.00) 1.70 0.3, 5.8	30 1.96 (0.85) 1.60 1.0, 4.3
INSS = International Neuroblastoma Staging System, MYCN = v-myc myelocytomatosis viral related oncogene, SD = standard deviation [1] Age was calculated as year of initial diagnosis – year of birth			

C6. Please provide the footnotes to Table 41 of the CS.

This table of the CS was taken from Table 37 of the current EPAR public assessment report available from EMA. By looking closely to these footnotes, not described by the previous MoH, we could define “a” as Dinutuximab beta EUSA long-term infusion and “b” as Dinutuximab beta EUSA short-term infusion. As this information is already in the text of the table, we have removed them in the revised table.

Please find below the revised Table 41 CS document.

Table 33: Summary of dinutuximab beta, IL-2 and 13-cis-RA administration in APN311 studies

Study		Dinutuximab beta EUSA - i.v.	IL-2 – s.c.	13-cis-RA – p.o.	Cycles
APN311-303 (Compassionate Use)	Patient 1-4	Days 1-11 (10 days) Continuous (24h) 5-10 mg/m^2/day	Days 1-5 (5 days) 6 x 10^6 IU/m^2/day	Days 15-28 (14 days) 80 mg/m^2/day b.i.d.	3-6 cycles, 1 cycle = 28-35 days
	Patient 5-54	Days 8-18 (10 days) Continuous (24h) 10 mg/m^2/day	Days 1-5 & 8-12 (2 x 5 days) 6 x 10^6 IU/m^2/day	Days 19-32 (14 days) 80 mg/m^2/day b.i.d	5/6 cycles, 1 cycle = 35 days
APN311-202		Days 8-18 (10 days) Continuous (24h) 10 mg/m^2/day	Days 1-5 & 8-12 (2 x 5 days) 6 x 10^6 IU/m^2/day	Days 19-32 (14 days) 80 mg/m^2/day b.i.d.	5 cycles, 1 cycle = 35 days
APN311-302	- IL2	Days 8-12 (5 days) Short-term (8h) 20 mg/m^2/day	NA	14 days 80 mg/m^2/day b.i.d. Weeks: 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21, 22	5 cycles ch14.18 & IL-2, 6 cycles RA, start with RA 1 cycle = 4 weeks (28 days)
	+ IL2		Days 1-5 & 8-12 (2 x 5 days) 6 x 10^6 IU/m^2/day 2 h after stop of ch14.18 infusion		

References

1. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010;363(14):1324-34.
2. Siebert N, Jensen C, Troschke-Meurer S, Zumpe M, Juttner M, Ehlert K, et al. Neuroblastoma patients with high-affinity FCGR2A, -3A and stimulatory KIR 2DS2 treated by long-term infusion of anti-GD2 antibody ch14.18/CHO show higher ADCC levels and improved event-free survival. Oncoimmunology. 2016;5(11):e1235108.
3. Zhou MJ, Doral MY, DuBois SG, Villablanca JG, Yanik GA, Matthay KK. Different outcomes for relapsed versus refractory neuroblastoma after therapy with 131I-metaiodobenzylguanidine (131I-MIBG). European Journal of Cancer. 2015;51(16):2465-72.
4. Moreno L, Rubie H, Varo A, Le Deley MC, Amoroso L, Chevance A, et al. Outcome of children with relapsed or refractory neuroblastoma: A meta-analysis of ITCC/SIOPEN European phase II clinical trials. Pediatric Blood and Cancer. 2017;64(1):25-31.
5. Portwine C, Rae C, Davis J, Teira P, Schechter T, Lewis V, et al. Health-Related Quality of Life in Survivors of High-Risk Neuroblastoma After Stem Cell Transplant: A National Population-Based Perspective. Pediatr Blood Cancer. 2016;63(9):1615-21.
6. Nathan PC, Ness KK, Greenberg ML, Hudson M, Wolden S, Davidoff A, et al. Health-related quality of life in adult survivors of childhood Wilms tumor or neuroblastoma: A report from the childhood cancer survivor study. Pediatr Blood Cancer. 2007;49(5):704-15.
7. Barr RD, Simpson T, Whitton A, Rush B, Furlong W, Feeny DH. Health-related quality of life in survivors of tumours of the central nervous system in childhood--a preference-based approach to measurement in a cross-sectional study. Eur J Cancer. 1999;35(2):248-55.
8. Rebholz CE, Reulen RC, Toogood AA, Frobisher C, Lancashire ER, Winter DL, et al. Health care use of long-term survivors of childhood cancer: the British Childhood Cancer Survivor Study. J Clin Oncol. 2011;29(31):4181-8.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Dinutuximab beta EUSA [ID910]

Clarification Letter – Additional questions

[6 September 2017]

Version 2

Date of preparation: 6 September 2017

File name	Version	Contains confidential information	Date
ID910 dinutuximab beta clarification letter–Additional questions 06092017 [noACIC]	**2**	**No [noACIC]**	**6 September 2017**

Question 1) Please confirm that the data provided in the response dated 16th August to address A2 have been adjusted for all requested factors. On reviewing the data closely, data in Tables 9 onwards are similar to the unadjusted data presented in Tables 1-8 of the same response.

Yes, we confirm that the data provided in the response dated 16th August to address A2 have been adjusted for all requested factors (i.e. prior treatment, age at diagnosis, MYCN status, and INSS stage). The data appears similar to the unadjusted data, but are not the same. For example, in treatment group Dinutuximab beta EUSA and isotretinoin of APN311-302, data at 1737 months in Table 3 (unadjusted, [redacted] survivor function estimate) is not the same as the one in Table 11 (adjusted, [redacted] survivor function estimate).

Question 2) For A4, please provide an HR for OS for APN311-302 versus historical control R1 (450 people) that has been adjusted cumulatively for all four factors listed below (akin to the reanalysis requested for A2):
a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS);
b. Age at diagnosis;
c. MYCN status;
d. INSS stage.
- If possible, for historical control R1, please provide the unadjusted and adjusted KM data as supplied in, for example, Table 10 of the response dated 16th August.

The tables for the adjusted OS in the Cox model for APN311-302 versus historical control R1 have been provided in A4 for each individual prognostic factor (i.e. prior treatment, age at diagnosis, MYCN status, INSS stage). Please find below the results for all four factors together, bearing in mind that the results must be taken cautiously because the **model is unstable due to overfitting**.

Table 1: Cox proportional hazard model: Overall survival adjusted for prior treatment, age at diagnosis, MYCN status and INSS stage for treatment group APN311-302 versus historical control R1

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group	1	[redacted]	[redacted]
Age (categories)	3	[redacted]	[redacted]
MYCN status	1	[redacted]	[redacted]
INSS stage at initial diagnosis (2 combined)	3	[redacted]	[redacted]
MAT	1	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group	MAT vs MAT and immunotherapy	[redacted]	[redacted]
Age (categories)	< 1 yrs vs > 5 yrs	[redacted]	[redacted]
Age (categories)	< 1 yrs vs > 1.5 - <= 5 yrs	[redacted]	[redacted]
Age (categories)	< 1 yrs vs >= 1 - <= 1.5 yrs	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Age (categories)	> 5 yrs vs > 1.5 - <= 5 yrs	[redacted]	[redacted]
Age (categories)	> 5 yrs vs >= 1 - <= 1.5 yrs	[redacted]	[redacted]
Age (categories)	> 1.5 - <= 5 yrs vs >= 1 - <= 1.5 yrs	[redacted]	[redacted]
MYCN status	amplified vs not amplified	[redacted]	[redacted]
INSS stage at initial diagnosis (2 combined)	2 comb. vs 4S	[redacted]	[redacted]
INSS stage at initial diagnosis (2 combined)	3 vs 4S	[redacted]	[redacted]
INSS stage at initial diagnosis (2 combined)	4 vs 4S	[redacted]	[redacted]
MAT	Bumel vs Cem	[redacted]	[redacted]

The unadjusted KM data for historical control R1 can be found in the "ObservedSurvivalFunctions" worksheet of the model (column E displays unadjusted KM data for R1 historical control per month, column AD displays unadjusted KM data for R1 historical control per year). F
or historical control R1, the size of subgroups (defined by the single categories of all the factors) is too small to provide adjusted KM curves.

Question 3) For A5, please provide adjusted HRs for OS for two separate analyses of (i) APN311-202 versus R1 (52 people) and (ii) APN311-202 versus Garaventa. Please adjust HRs cumulatively for:
a. prior treatment (BuMel + autologous stem cell transplant [ASCT] versus CEM + ASCT), as reported has been carried out in Table 23 of the company submission (CS);
b. Age at diagnosis;
c. MYCN status;
d. INSS stage.

i)

The table of OS adjusted for all prognostic factors (i.e. prior treatment, age at diagnosis, MYCN status, INSS stage) for APN311-202 versus historical control R1 is presented below, however the results must be taken cautiously because the **model is unstable due to overfitting.**

Table 2: Cox proportional hazard model: Overall survival adjusted for all prognostic factors

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group 3	1	[redacted]	[redacted]
Age (categories)	3	[redacted]	[redacted]
MYCN status	1	[redacted]	[redacted]

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
INSS stage at initial diagnosis (combined)	1	[redacted]	[redacted]
MAT	1	[redacted]	[redacted]

Hazard ratios in Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group 3	APN311-202 vs Historic Control R1	[redacted]	[redacted]
Age (categories)	< 1 yrs vs >= 1 - < 2 yrs	[redacted]	[redacted]
Age (categories)	< 1 yrs vs >= 2 - < 5 yrs	[redacted]	[redacted]
Age (categories)	< 1 yrs vs >= 5 yrs	[redacted]	[redacted]
Age (categories)	>= 1 - < 2 yrs vs >= 2 - < 5 yrs	[redacted]	[redacted]
Age (categories)	>= 1 - < 2 yrs vs >= 5 yrs	[redacted]	[redacted]
Age (categories)	>= 2 - < 5 yrs vs >= 5 yrs	[redacted]	[redacted]
MYCN status	amplified vs not amplified	[redacted]	[redacted]
INSS stage at initial diagnosis (combined)	1,2A,3 vs 4	[redacted]	[redacted]
MAT	Bumel vs Cem	[redacted]	[redacted]

ii)

The results adjusted for all prognostic factors for study 202 versus Garaventa historical control are presented in a manner similar to the previous question, however the results must be taken cautiously because the **model is unstable due to overfitting**. In the Garaventa historical control, there were no records of “prior treatment”, thus it was excluded in this analysis.

Table 3: Cox proportional hazard model: Overall survival adjusted for all prognostic factors (i.e, age at diagnosis, MYCN status, INSS stage) for study 202 versus Garaventa.

Type 3 tests in final Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Treatment group	1	[redacted]	[redacted]
Age (categories)	1	[redacted]	[redacted]
MYCN status	1	[redacted]	[redacted]
INSS stage at initial diagnosis	2	[redacted]	[redacted]

Hazard ratios in final Cox model			
Variable	**Comparison**	**Estimate**	**95%-CI**
Treatment group	APN311-202 vs Garaventa Historical control	[redacted]	[redacted]
Age (categories)	<= 5 yrs vs > 5 yrs	[redacted]	[redacted]
MYCN status	amplified vs not amplified	[redacted]	[redacted]
INSS stage at initial diagnosis	1 vs 4	[redacted]	[redacted]
INSS stage at initial diagnosis	3 vs 4	[redacted]	[redacted]

Question 4) If the adjusted KM curves received in response to clarification question A2 are the cumulatively adjusted KM curves for all prognostic factors, please replace the unadjusted KM curves used in the economic model with the adjusted ones. Please repeat the fitting exercise with the adjusted KM curves and replace the fitted curves as necessary in the economic model, for both the high-risk and the R/R model. If this is not possible, please use the adjusted HRs requested in 2) and 3) and use them in the economic model to estimate the OS and EFS curves in the comparator arms in the economic model for both the high risk and the R/R populations.

The unadjusted KM curves are used as the base case in the economic model since the differences between the unadjusted and adjusted KM curves are minimal (as explained and raised by the ERG in question 1), and the HR ratios adjusted for each prognostic factor were not reliable (as explained in questions 2 and 3).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Dinutuximab beta EUSA [ID910]

Clarification Letter – Additional questions 2

[7 September 2017]

Version 2

Date of preparation: 7 September 2017

File name	Version	Contains confidential information	Date
ID910 dinutuximab beta clarification letter–Additional questions 2 07092017 [noACIC]	2	No [noACIC]	7 September 2017

Question 1) Please confirm that the HR_[redacted] is the cumulatively adjusted (i.e. HR adjusted for age, MYCN, INSS and MAT) comparing MAT vs MAT and immunotherapy?

The HR of [redacted] provided in the response to question 2 dated 6th September (Table 1) resulted from a model including the factors treatment group, age, MYCN status, INSS stage, and MAT. However, the results must be taken cautiously because the **model is unstable due to overfitting.**

Question 2) Please confirm that the adjustments carried in the analysis producing the [redacted] are adjusting for the baseline characteristics for prognostic factors in R1, in comparison with the baseline prognostic factors in 302 (for example, the MAT adjustment is taking into account that half of the population in R1 received Bumel, while 90% of the population in 302 received Bumel)?

This HR is the plain point estimate of the hazard ratio for treatment group resulting from a Cox model that was calculated on the basis of the 302 patients (R1 vs. R2) and that included the factors treatment group, age, MYCN status, INSS stage, and MAT.

Question 3) Please confirm that the adjustments made to the [redacted] are not within-study adjustments (or subgroup analysis) only taking into account the baseline characteristics related to the prognostic factors in the 302 population?

This HR resulted from an analysis of 302 patients only. No results from any other studies/populations were considered in this analysis.

NHS England submission on the NICE Technology Appraisal of dinutuximab beta in the treatment of neuroblastoma

1. NHS England notes that dinutuximab beta in this indication has conditional approval by the EMA and thus carries a black inverted triangle on its SPC. This conditional approval is as a consequence of the immaturity of the clinical data in respect of efficacy and toxicity.
2. NHS England observes that the EMA has recorded that a dinutuximab beta registry (SAFARY) will provide further long term information as to efficacy and safety, the latter in particular relating to the effect of dinutuximab beta on the peripheral and central nervous systems, including visual impairment.
3. NHS England regards the indication of dinutuximab beta as part of 1st line therapy for high risk patients to be much more clinically important than the indication of dinutuximab beta for treating relapsed/refractory disease as most of the relapsed/refractory group will have already received dinutuximab beta as a consequence of being high risk at 1st presentation. The timing of the relapse and the previous treatment already received will largely determine whether successful salvage therapy is thought to be possible and thus whether there is the likelihood of long term survival gain with use or re-use of dinutuximab beta in this setting.
4. Dinutuximab beta is in the unusual setting of neither having an evidence base containing a direct comparison of a treatment programme with dinutuximab beta versus a treatment programme without nor a direct comparison with dinutuximab alpha. The most robust evidence of survival gain for the two formulations of dinutuximab lies with that of dinutuximab alpha which did have a direct comparison of treating high risk neuroblastoma patients with and without dinutuximab. The EMA recognised this exceptional setting stating that 'for ethical reasons it has not been possible to obtain complete information on this product. The EMA will review any new information which may become available every year'. Dinutuximab alpha had its European marketing authorisation withdrawn on 22 March 2017 on account of an inability of its manufacturer to supply dinutuximab alpha to Europe.
5. The clinical experts in this appraisal state that the long term cure rate for the high risk neuroblastoma patients is 30-35%. NHS England observes that this range of figures is significantly lower than the 3 year overall survival figures in the dinutuximab beta randomised study which examined the contribution of interleukin-2. The dinutuximab alpha study showed that late relapses occurred well beyond 3 years and thus NHS England regards the current survival data on dinutuximab beta as being immature.
6. NHS England is concerned that the results of the phase III trial of dinutuximab beta with or without interleukin-2 was not analysed on an intent to treat basis as 36 patients were excluded from the analysis. The bias introduced by this failure to analyse on an ITT basis is not known.

7. NHS England notes too that there were no plans to collect event free and overall survival in the 2 dinutuximab beta phase II studies in relapsed/refractory patients and that the EMA stated that there was no explanation for the better event free and overall survival data in the refractory vs the relapsed patients in one of these studies. NHS England therefore regards the evidence for long term survival in the relapsed/refractory setting as being very uncertain.
8. NHS England is surprised that none of the dinutuximab studies made any attempt to collect quality of life data even though NHS England recognises the difficulty of so doing as a consequence of the age of the patients in these studies. This lack of QoL data is especially surprising given the toxicity of the drug particularly on the central and peripheral nervous systems including on vision.
9. Wastage of dinutiximab beta is important to include in the economic model given the need for either 10 days worth of drug as a continuous infusion or 5 daily infusions as 8 hour infusions.
10. Given the data from the dinutuximab alpha studies and the near identical nature of the 2 dinutuximab drugs, NHS England regards the long term survival benefit of dinutuximab as being uncertain but likely to be real although of relatively modest size. NHS England does not consider that the company has incorporated into its pricing of dinutuximab beta the significant weaknesses of both its evidence base and indirect comparison as well as the immaturity of its clinical data.

Prof Peter Clark

NHS England National Chemotherapy Lead and Clinical Lead for the Cancer Drugs Fund

November 2017

NICE National Institute for Health and Care Excellence

Clinical expert statement

APN311 for treating high-risk neuroblastoma [ID910]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Martin Elliott**
2. Name of organisation	**National Cancer Research Institute (NCRI)– Children's Cancer and Leukaemia Clinical Studies Group.** **Children's Cancer and Leukaemia Group (CCLG)**

3. Job title or position	**Consultant Paediatric Oncologist, Leeds Children's Hospital, Leeds Teaching Hospitals NHS Trust**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve event free and overall survival of patients with high-risk neuroblastoma..
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in event free or overall survival. Tolerable toxicity.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a clear unmet need for more effective treatments in patients with high risk and relapsed neuroblastoma. Approximately 30-35% of patients with high-risk neuroblastoma are cured with current multi-modality treatment strategies. Patients with relapse neuroblastoma have a very poor long -term prognosis, especially if they have relapsed, following initial high-risk neuroblastoma treatment. However, the prognosis for new diagnosis high-risk neuroblastoma patients has improved from 10% in early 1990's to the current 30-35%. There is no single intervention that can account for this improvement but a series of interventions including dose intensive induction chemotherapy, use of myeloablative

chemotherapy and autologous stem cell transplant (ASCT), differentiation therapy with *cis*-retinoic acid and improvements in supportive care. Individually none of these interventions have independently resulted in a statistically significant improvement in EFS or OS, but cumulatively the survival outcomes have improved significantly over recent decades as shown in graphs below produced by the National Registry of Childhood Tumours (Stiller *et al*).

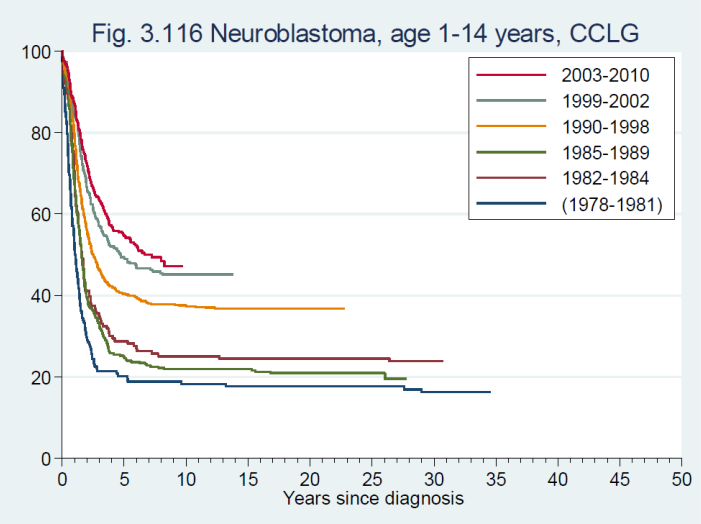
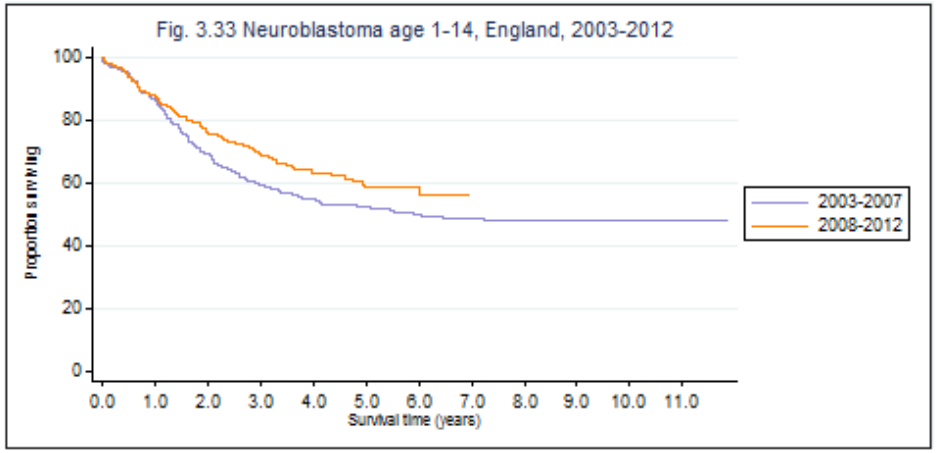


Figure 3.33 Population-based survival of children aged 1-14 years with neuroblastoma in England diagnosed 2003-2012.



Many children continue to die from neuroblastoma and new treatment modalities are needed. It is very unlikely that further modifications to conventional cytotoxic chemotherapy protocols will lead to improved outcomes and hence immunotherapy as a new treatment strategy is novel and trials to date have shown evidence that this treatment can improve survival.

What is the expected place of the technology in current practice?

10. How is the condition currently treated in the NHS?	New diagnosis patients have multi-modality treatment including: 1. Induction chemotherapy 2. Surgical resection of primary tumour 3. Myeloablative chemotherapy and autologous stem cell transplant (ASCT). 4. Radiotherapy to primary tumour

	5. Differentiation treatment (*cis*-retinoic acid). 6. Immunotherapy (given concurrently with differentiation therapy). Since 2009 patients with high-risk neuroblastoma have been treated with dinutuximab beta in the context of SIOPEN clinical trials. The two main trials are: 1. **SIOPEN HR-NBL-1 (2002-2017)** has recruited > 500 UK patients. This trial has recruited patients with a new diagnosis of neuroblastoma and has included 5 randomised research questions over a 15 year period. Virtually all high risk neuroblastoma patients in the UK have been recruited to this trial and since 2009 have received dinutuximab beta as part of the trial. The randomised immunotherapy questions have related to investigation of dinutuximab beta alone or in conjunction with a cytokine interleukin-2 (IL-2). This clinical trial closed to recruitment of new patients in May 2017 and therefore current patients on trial will receive dinutuximab beta subject to meeting the protocol specific response criteria and treatment time-frames. The majority of patients diagnosed after May 2017 will need immunotherapy in late 2017 / early 2018. 2. **SIOPEN LTI (long-term infusion antibody trial) -** This trial has been open to patients with relapse / refractory and slowly responding high-risk neuroblastoma. New diagnosis patients with high-risk neuroblastoma initially registered on the HR-NBL-1 trial but not achieving the protocol specific time frames were able to access immunotherapy via this LTI trial. This trial has established a more tolerable infusion regime of diutuximab beta, which in 2013 was adopted into the HR-NBL-1 trial and has also investigated the addition of IL-2 to dinutuximab beta. This trial closed to recruitment in UK in 2017. These clinical trials have established immunotherapy as routine practice in patients with high-risk neuroblastoma since 2009, and is now considered standard care in this patient population even though access has been via clinical trials.
• Are any clinical guidelines used in the	When the trial was closed in May 2017 the Children's Cancer and Leukaemia Group (CCLG) – neuroblastoma group produced guidance for the management of high-risk neuroblastoma patients, which

treatment of the condition, and if so, which?	adopts the treatment modalities in the SIOPEN HR-NBL-1 trial protocol, including the use of dinutuximab-beta.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined for patients with a new diagnosis of high-risk neuroblastoma as per the CCLG guidance. I am not aware of any clinicians in UK (or Europe) who advise an alternative treatment strategy for these patients.
• What impact would the technology have on the current pathway of care?	The technology would continue current clinical practice (adopted in 2009), but with funded immunotherapy, rather than supply through a clinical trial. The randomised aspect of the current trial (IL-2) would not be used in new diagnosis high-risk neuroblastoma patients as there is no evidence to support use of IL-2 to date in this patient group.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The administration of dinutuximab beta, would be the same as current practice but in a non-trial context. All centres treating patients with neuroblastoma are very familiar with the technology and would not require any significant training / new equipment or facilities.
• How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Designated paediatric oncology principal treatment centres only.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None – all relevant centres already use the technology and are familiar with the technology and would not require any new investment, training etc.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This is difficult to answer as current care has effectively been use of the technology since 2009 and I would expect on-going use of the technology to maintain current EFS and OS for patients with high-risk neuroblastoma. SIOPEN HR-NBL-1 data presented at SIOP 2017 conference (Washington) - compared patients treated with (2009-2013) and without (2002-2009) dinutuximab beta and showed a significant 5 yr EFS and OS advantage in favour of those treated with dinutuximab beta (EFS 57 vs 42 %) and OS 64 vs 50%). It has to be acknowledged that this data is non-randomised and includes patients treated from different time periods, but all within a single clinical trial.
• Do you expect the technology to increase length of life more than current care?	As current care includes dinutuximab beta via clinical trial access, I expect the technology to continue to increase length of life compared to time period before the use of dinutuximab beta.
• Do you expect the technology to increase health-related quality of	

life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It is possible that amount of tumour burden pre-immunotherapy may relate to response to immunotherapy - this is likely to be investigated further once the data from the SIOPEN HR-NBL-1 trial matures and is analysed. Patients have specific genetic dependent differences in their immune system (Fc-gamma-receptor (FCGR) genes and killer cell immunoglobulin-like receptor (KIR) and KIR ligand (KIRL) repertoires) and these natural variations may cause variations in response to an antibody mediated immunotherapy. Early data from patients in the SIOPEN LTI trial, investigating this has been published online (Oncoimmunology. 2016; 5(11): e1235108).
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	As above.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The technology has significant toxicity and comprehensive safety data has been collected in SIOPEN trials and incorporated into the SPC. It has been shown in SIOPEN trials that the toxicity can be significantly reduced by: 1. Slow continuous infusion of the dinutuximab beta (10 days). This continuous schedule does not compromise the dinutuximab beta levels on pK monitoring and dose not reduce the effectiveness of the treatment based on relevant immune assays. 2. Toxicity is significantly higher if dinutuximab beta is administered with IL-2. Patients treated with dinutuximab beta and IL-2 had a significantly higher number of cycles of treatment interrupted or stopped early.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The technology introduces a new treatment modality into a multi-modality treatment regime. A randomised trial of a similar (but different) technology – dinutuximab, has shown significant improvement in 2 year EFS and OS in those receiving dinutuximab (in conjunction with cytokines IL-2 and GM-CSF), compared to those treated with *cis*-retinoic acid alone (Yu *et al*, NEJM 2010) . Data presented at SIOP 2017 conference (Washington) compared results (EFS and OS) of patients treated with dinutuximab beta on the SIOPEN HR-NBL-1 trial with those treated with dinutuximab in the NEJM paper. The outcomes are shown to be comparable, suggesting, that efficacy of dinutuximab and dinutuximab beta may be similar. This trial comparison cannot substitute a direct randomised trial of dinutuximab beta vs control, but it would no longer be acceptable to professionals, parents and families to perform the ideal randomised trial of

	diutuximab beta vs no immunotherapy treatment, because of these data and adoption of immunotherapy as standard treatment in of high risk neuroblastoma in Europe and the USA.
• Does the use of the technology address any particular unmet need of the patient population?	As above.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As above.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	As above.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important	Survival data – EFS and OS.

outcomes, and were they measured in the trials?	Toxicity
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Most patients have been treated within clinical trials and safety data has been recorded and incorporated in to the IB and SPC of the product. I am not aware of any adverse effects in patients treated out with clinical trials with dinutuximab beta.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No. The complete data set for the HR-NBL-1 patients and LTI patients will need to mature and be completely analysed before many questions relating to dinutuximab beta (and IL-2) are answered.
21. How do data on real-world experience compare with the trial data?	As almost all patients treated with dinutuximab beta date have been registered on a clinical trial and hence contributed to the trial data,the trial data is very comparable with the “real-world”
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23a. The company indicated that dinutuximab beta is always given as a first line treatment and they do not support re-treatment with dinutuximab beta. Do you consider dinutuximab beta as a treatment option in UK clinical practice for those experiencing	Since 2009 dinutuximab beta has been given to patients with high-risk neuroblastoma who have a response to one or more lines of chemotherapy sufficient to proceed to myeloablatove chemotherapy and ASCT. Any patients suffering a relapse following this treatment have not been eligible for further dinutuximab beta within any clinical trial – these patients have relapsed despite previous dinutuximab beta treatment and there is no clear rationale for treatment with further dinutuximab beta. There is a small group of patients who relapse following initial treatment for low or intermediate risk neuroblastoma (ie no previous treatment with dinutuximab beta) and these patients are likely to benefit from dinutiximb beta in a relapse setting.

relapse of high-risk neuroblastoma?	
23b. Would you consider dinutuximab beta as standard of care, and therefore would not treat patients with isotretinoin without dinutuximab beta?	I consider dinutuximab beta as standard care. If in a situation of not being able to prescribe dinutuximb beta or a patient was unable to tolerate dinutuximab beta then I would still prescribe differentiation therapy ie *cis*-retinoic acid. There is no evidence to support *cis*-retinoic acid as a single intervention but the combination of myeloablative chemotherapy and ASCT followed by *cis*-retinoic acid treatment showed significantly better outcomes compared to continued standard chemotherapy and no *cis*-retinoic acid. *Cis*-retinoic is generally well tolerated and has a low toxicity profile, compared to the other treatments that these patients receive.
23c. Are relapsed/refractory and high-risk neuroblastoma clinically distinct or is it appropriate to combine them?	They are different. Refractory patients have disease that is either non-responsive or more frequently slowly responsive to first line induction chemotherapy. This is more frequent in patients with either `MYCN non-amplified neuroblastoma and / or older (> 5 years) patients. This group of patients often require multiple lines of chemotherapy or other treatment strategies to achieve an adequate clinical response to proceed to myeloablative chemotherapy and ASCT.

	Relapse patients can be separated into two groups: 1. Relapse having had previous dinutuximab beta (ie previous high-risk neuroblastoma) 2. Relapse and no previous dinutuximab beta treatment. This group of patients is small and likely to have had previous low or intermediate risk neuroblastoma.
23d. Is there a treatment pathway in the UK for people with relapsed or refractory neuroblastoma and people who experiencing relapse or who are refractory to treatment?	Yes. CCLG document. The pathway for relapse / refractory patients is not as well defined as for new diagnosis high-risk neuroblastoma patients, as options depend on previous treatments, site of relapse etc. Clinicians use the CCLG document - "Options for the treatment of patients with relapsed / progressive high risk neuroblastoma" as a guide and also have the option of referring their patient for discussion at a national neuroblastoma advisory panel.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Clear unmet need – many children still die from neuroblastoma
- Dinutuximab beta is an Innovative treatment modality to complement other modalities used in this condition
- Evidence – there is randomised trial data of a similar technology (dinutuximab) showing improved outcomes compared to controls and data to suggest that this technology results in comparable outcomes.
- A tolerable schedule of administration has been developed, without compromise to pK and immune assay data, allowing this treatment to be delivered as out-patient / day case treatment in many patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

APN311 for treating high-risk neuroblastoma [ID910]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Juliet Gray**
2. Name of organisation	**National Cancer Research Institute (NCRI)– Children's Cancer and Leukaemia Clinical Studies Group.** **Children's Cancer and Leukaemia Group (CCLG)**

3. Job title or position	**Associate Professor and Consultant in Paediatric Oncology, University of Southampton / University of Southampton NHS Foundation Trust**
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve event free and overall survival of children with high risk neuroblastoma.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in event free / overall survival
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, significant unmet need. There are approximately 100 children per year in UK with neuroblastoma, over 50% of whom will have metastatic disease or adverse cytogenetic (myc-n amplification). The outcome for these children is poor – approximately 30% long term survival with intensive treatment, including myeloablative chemotherapy and autologous stem cell transplant, radiotherapy and surgery. Toxicity from these treatments is significant with 3-5% treatment related mortality, so there is therefore little room to further intensify existing treatments. Although survival and outcome for many childhood cancers have improved significant, outcome for children with high risk neuroblastoma has lagged behind, and it accounts for a disproportionately high number of childhood cancer deaths (8% of paediatric malignancies and 15%

	childhood cancer deaths). This means that neuroblastoma is one of the commonest causes of death in children aged 1-14yrs.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Treatment across Europe consists of: i) Induction chemotherapy (chemotherapy every 10 days for 3 months) ii) Surgical resection of the primary tumour iii) Myeloablative chemotherapy (high dose Busulfan /melphalan) and autologous stem cell transplant. iv) Radiotherapy to primary tumour site v) Differentiation therapy (cis-retinoic acid) for 6 months with concurrent anti-GD2 immunotherapy Since 2010 almost all patients within the UK with high risk neuroblastoma have received anti-GD2 (Dinutuximab beta / APN311) in the context of one of two European Research Network (SIOPEN) neuroblastoma trials: 1. **SIOPEN HR-NBL-1 (2002-2017)**: This trial has recruited patients with a new diagnosis of neuroblastoma and has included a series of randomised research questions over the 15 year period. Virtually all high risk neuroblastoma patients in the UK have been recruited to this trial and have all patients (with adequate disease response) have received dinutuximab beta as part of the trial since 2010. The randomised immunotherapy questions have related to investigation of dinutuximab beta alone or in conjunction with a cytokine interleukin-2 (IL-2). 2. **SIOPEN LTI (long-term infusion antibody trial):** This trial has been open to patients with relapse / refractory and slowly responding high-risk neuroblastoma. New diagnosis patients with high-risk neuroblastoma initially registered on the HR-NBL-1 trial but not achieving the protocol specific time frames were able to access immunotherapy via this LTI trial. This trial has established a more tolerable infusion regime of diutuximab beta, which in 2013 was adopted into the HR-NBL-1 trial and has also investigated the addition of IL-2 to dinutuximab beta. This trial closed to recruitment in UK in 2017.

	Since all patients in the UK since 2010 have received Dinutuximab beta, this has become a standard of care, even though access has been largely via clinical trials. Some form of anti-GD2 antibody therapy (Dinutuximab or dinutixmab beta) is now considered a standard of care for children with high risk neuroblastoma, in the UK, across Europe and the US.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The Children's Cancer and Leukaemia Group (CCLG) produced guidelines in for the treatment of high risk neuroblastoma in May 2017, to guide treatment of these patients following the closure of SIOPEN HR NBL-1. These guidelines follow the standard arm of treatment recommended in SIOPEN HR NBL-1, including dinutuximab beta (APN311 (without IL-2). The European Neuroblastoma Network (SIOPEN) are have also produced guidelines for first line management of patients with High Risk neuroblasotma, with similar recommendations – these are currently in draft form but may be ready by the time of the Committee meeting in November 2017. The CCLG also has guidelines for relapsed / refractory neuroblastoma, which includes treatment with anti-GD2 immunotherapy as consolidation therapy for patients with disease that is responding to chemotherapy that have have not previously received anti-GD2 therapy.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined pathway, with little variation across UK, or indeed across Europe. All 20 UK paediatric oncology centres recruited patients to the SIOPEN HR NBL-1 trial and now follow the CCLG guidelines.
• What impact would the technology have on the current pathway of care?	The technology would continue the now established standard of care, in place since 2009/2010. It would be a retrograde step to lose the technology, and is likely to result in a worse outcome for this population..

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, would continue same practice as has been in place since 2009/10.
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist paediatric oncology treatment centres only
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil. All paediatric oncology centres in UK already experienced in delivering to patients.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I would anticipate deterioration in outcome for these patients if the technology was not adopted (as use of the last 7 years has resulted in improved outcome) Furthermore, it is likely that further improvements in outcome will be achieved in the future by novel combinational therapies (e.g APN311 + different immune adjuvants).

• Do you expect the technology to increase length of life more than current care?	In 2009 the Children's Oncology Group in the US reported a 20% improvement (68 v 48%) in 2 year event free survival in children with high risk neuroblastoma receiving the anti-GD2 antibody dinutuximab with IL-2 and GM-CSF, in addition to standard neuroblastoma therapy – Yu et al NEJM 2010. Since then some form of anti-GD2 immunotherapy has been considered a 'standard of care' for children with high risk neruoblastoam in the US and Europe. APN311 (Dinutuximab beta) is closely related to dinutuximab. In view of the results of the Yu et al study, it was considered that anti-GD2 antibody therapy may offer significant benefit, and that it would not be acceptable to conduct a trial in Europe in which some children received such an antibody and others did not. Trials in Europe (SIOPEN HR NB-1 and Long Term Infusion studies) have therefore focused on investigating the role of cytokines (IL-2) and optimising the infusion schedule to minimise toxicity and improve pharmacokinetics. There are therefore no randomised trials demonstrating the APN311 improved life expectancy in the upfront treatment of children with high risk neuroblastoma (although this has been demonstrated for dinutuximab) but over this period of time (since 2009/10) there has been an improvement in outcome within the SIOPEN HR NBL-1 study and an improvement in population based survival outcome. I think continued use of the technology would maintain this improvement in survival / length of life already achieved. In the context of relapsed/refractory disease, treatment with APN311 with IL-2 has been reported to extend life expectancy compared to historical controls. *(H. Lode et al Phase II clinical trial with long-term infusion of anti-GD2 antibody ch14.18/CHO in combination with interleukin-2 (IL2) showed clinical efficacy and improved toxicity in patients with high risk neuroblastoma. ASCO 2016)*
• Do you expect the technology to increase health-related quality of life more than current care?	

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with specific immune receptor (FcR/KIR) polymorphism / phenotype may benefit more from this type of antibody therapy than others. However, the use of such biomarkers is as yet unvalidated and is not yet used within standard practice (Oncoimmunology 2016 5 (11)e1235108)
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Same as current standard care.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will ordinarily be delivered over 5 cycles but may be modified / aborted if: i) progression of disease during treatment ii) unacceptable toxicity that can not be managed by slowing infusion or reducing the dose of antibody. The majority of patients will tolerate the slow (10 day) infusion of APN311 given without IL-2, with minimal toxicity, and minimal opioid requirement.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The technology has resulted in a step change in the outcome of children with high risk neuroblastoma.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	As above
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The majority of patients will tolerate the slow (10 day) infusion of APN311 given without IL-2, with minimal toxicity, and minimal opioid requirement. The majority of toxicities are acute, and resolve quickly once infusion completed.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	EFS and OS
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No, toxicities have been well documented within clinical trials described above.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Outcome from SIOPEN studies not yet published but has been presented at ASCO and SIOP. Some data from both trials yet to be released.

21. How do data on real-world experience compare with the trial data?	Almost all UK patients have been recruited to the above trials, so trials are reflective of the whole population.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/a
Topic-specific questions	
23a. The company indicated that dinutuximab beta is always given as a first line treatment and they do not support re-treatment with dinutuximab beta. Do you	There is scientific rationale to treating patients with Dinutuximab beta at relapse even when they have received the antibody as part of their initial first line therapy – as the incidence of GD2 regulation is rare, and there are reported cases of second response. However the trials to date have all been conducted in antibody naive patients and it has not been standard practice to re-treat

consider dinutuximab beta as a treatment option in UK clinical practice for those experiencing relapse of high-risk neuroblastoma?	patients. At the moment I would consider patients who have received anti-GD2 previously, should only receive anti-GD2 again in the context of a clinical trial. There are a small number of patients with relapsed disease who have not previously received anti-GD2, and I would consider it a standard of care that these patients receive anti-GD2 to consolidate a response to chemotherapy.
23b. Would you consider dinutuximab beta as standard of care, and therefore would not treat patients with isotretinoin without dinutuximab beta?	I would consider Dinutuximab beta (or an equivalent anti-GD2 antibody) antibody a standard of care. However if it was not possible to give it to a patient (because of availability or eg. allergy) then I would treat the patient with isotretinoin alone.
23c. Are relapsed/refractory and high-risk neuroblastoma clinically distinct or is it appropriate to combine them?	I would consider these to be distinct. Refractory patients have disease that is either non-responsive or slowly responsive to first line induction chemotherapy. This group of patients often require multiple lines of chemotherapy or other treatment strategies to achieve an adequate clinical response to proceed to myeloablative chemotherapy and ASCT. If sufficient response is achieved in this patients (with multiple lines of induction chemotherapy +/- MIBG

	therapy) to proceed to myeloablative therapy, then I would consider the patients to benefit from consolidation with APN311, and would consider this a standard of care. Relapse patients can be separated into two groups: 1. Relapse having had previous dinutuximab beta (i.e. previous high-risk neuroblastoma). I would consider re-treatment of these patients with APN311 to be experimental, and would only do within the context of a trial. 2. Relapse having not had previous dinutuximab beta treatment. This group of patients is small and likely to have had previous low or intermediate risk neuroblastoma.
23d. Is there a treatment pathway in the UK for people with relapsed or refractory neuroblastoma and people who experiencing relapse or who are refractory to treatment?	Yes, there is a CCLG document.: "Options for the treatment of patients with relapsed / progressive high risk neuroblastoma" The pathway for relapse / refractory patients is not as well defined as for new diagnosis high-risk neuroblastoma patients, as options depend on previous treatments, site of relapse etc. Clinicians use the CCLG document and also have the option of referring their patient for discussion at a national neuroblastoma advisory panel.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Since the Yu et al (NEJM 2010) reported trial of Dinuximab (closely related to APN31) with IL-2 and GM-CSF, some form of anti-GD2 immunotherapy has been considered a standard of care, in the US and Europe, for children with high risk neuroblastoma.
- Given the marked benefit seen in the of the Yu et al trial results, it was deemed unacceptable (to families and clinicians) not to give APN311 to all children taking part in the European SIOPEN HR NBL-1 and LTI studies, and there is therefore no randomised data demonstrating the benefits of this antibody. However, the SIOPEN HR-NBL-1 study (R2 randomisation) has shown similar event free survival to that achieved in the US Yu study. Furthermore, within the SIOPEN HR-NBL-1 study (which ran from 2002 to 2017), an improvement in EFS and OS is seen following the introduction of the R2 randomisation, when APN311 (Dinutuximab beta) was given to all patients. UK population based survival data has also shown improvement in OS over this time period.
- The SIOPEN HR-NBL-1 R2 randomisation has shown similar EFS with or without IL-2 (and without GM-SCF) – suggesting these cytokines are not needed to achieve efficacy in this population.
- In patients with relapsed / refractory disease, 40-50% objective response rates are seen with APN311 (+IL-2) and significant increase in survival is observed compared to historical controls.
- Some form of anti-GD2 monoclonal antibody is now considered a key component and a standard of care across the world, of the treatment of high risk neuroblastoma. Almost all children with high risk neuroblastoma in the UK

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

APN311 for treating high-risk neuroblastoma [ID910]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Nicholas James Bird**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☒ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Solving Kids Cancer - Europe
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As a parent of a child with high-risk neuroblastoma you live every day in fear that your child is going to die. The treatment regimen of chemotherapy, surgery, mega-dose chemotherapy with stem cell rescue, radiotherapy, retinoid therapy and immunotherapy is the most intensive of any cancer – child or adult. When not in hospital for scheduled treatment, your child is most likely in their local shared care hospital for treatment side-effects such as neutropenic fevers, bacterial infections, sickness, etc. As a parent your life is no longer, and never again will be, the same.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There is a belief in some quarters that current treatments on the NHS are inferior to countries such as America and Germany. As a rule, this is not true for standard-of-care frontline treatment. At any given time, there may be more promising experimental therapies available in other countries, but this is the nature of research. If immunotherapy is no longer available in the UK, but continues to be in America and across continental Europe, then clearly frontline treatment options for newly diagnosed children with high-risk neuroblastoma will become inferior.
10. Is there an unmet need for patients with this condition?	Neuroblastoma is a condition affecting around 100 children in the UK each year. Of those, 90% are diagnosed before the age of 5 years of age. It is responsible for the death of 35-40 children each year. Put differently a child dies of neuroblastoma every 10 days on average. There is a clear and obvious unmet need. The long-term survival rate for high-risk neuroblastoma is between 30% and 50%.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Anti-GD2 immunotherapy has become a recognised standard-of-care internationally for the treatment of neuroblastoma. There are several (4+) anti-GD2 antibodies being used in clinical trials, and at various institutions, however, the accepted view across leading experts across the world is that this therapy benefits patients by extending periods of remission for some children, leading to an improved long-term survival rate with more children being cured. On the back of this families quite rightly and obviously think and believe that it is a vital component of neuroblastoma treatment, and that their child is not being afforded the best chance at life, and will be at greater risk of relapse and ultimately death if they do not receive it.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The treatment, particularly when given in combination with IL-2, can make children seriously unwell. Neuropathic pain that must be controlled with strong opioids and other pain medication being the most common. Other, potentially more serious side-effects such as capillary leak syndrome can also occur. Watching your child suffer is horrendous as a parent. However, the side-effects (generally) resolve themselves once each cycle of treatment has been completed.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There are subsets of patients with particularly poor prognosis; those with amplification of the MYCN oncogene which confers a particularly aggressive disease phenotype, and those children diagnosed when they are slightly older which is generally associated with a more indolent and slow growing, but ultimately fatal, disease phenotype. These groups of patients with the poorest survival have the greatest unmet need for new and effective treatments.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No.
Other issues	
15. Are there any other issues that you would like the committee to consider?	Families will seek to fund this treatment privately if it becomes unavailable on the NHS – which it will if NICE issues a negative guidance. With anti-GD2 being approved and readily available in both America and Europe somewhere between 20 and 30 families per year will seek to fundraise either through charities or crowdfunding sites to raise the £250,000-£500,000 that it is likely to cost to receive this therapy privately – either in the UK or abroad.

	I would also ask the committee to take into consideration the patient population, and the lack of treatments have been developed for, and are available to treat, children with neuroblastoma.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Clear unment need in a very vulnerable patient population of children most whom are under the age of 5.
- Paucity of treatments developed to target this disease.
- UK will fall behind international peers if anti-GD2 antibody therapy is not made available on the NHS.
- Families will seek to raise the money to travel abroad or pay privately for immunotherapy in the UK.
- The above two statements will make the lack of anti-GD2 antibody therapy in the UK a political issue.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

APN311 for treating high-risk neuroblastoma [ID910]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Tony Heddon**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: I have interviewed families with experience of the condition and families who are about to start the technology, are in the middle of the technology and who have recently completed the technology/treatment
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	It is all consuming and affects not only the patient and parents but the entire family and friendship network. It puts a high degree of strain on the family trying to balance the visits to hospital, clinic appointments, work, childcare and the needs of siblings. The level of commitment often means a parent giving up work which, in turn, can lead to financial uncertainty. Relationships can become fragmented with the constant strain. The level of stress leads to tiredness, but sleep can be difficult. Parents describe being in 'robotic state' and going through the motions almost as if it was happening to someone else.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	For low and medium risk patients, the standard regime of chemotherapy, surgery and radiotherapy is effective although can be aggressive and not without issue. For high risk patients, the options are more limited. The situation over technology trials can cause uncertainty for the parents. Firstly, as a trial, the implication is that the technology is not proven. Once a trial has been selected, there is a doubt or fear that the trial your child is undertaking may not be the best option and maybe another trial would be more beneficial. The level of toxicity and side effects form treatments can be greater than anticipated and lead to concerns regarding long term health issues. The perceived limitations of the NHS can make the option of treatment abroad appear a risk worth contemplating. The NHS care for the patient is beyond reproach, they are the patient's and parent's support structure
10. Is there an unmet need for patients with this condition?	Communication and explanation of activity and treatments can be hit and miss and in some cases conflicting. Often patients and parents are unable to take in what is being explained to them during consultations and resort to the internet for answers as they do not wish to seem either ignorant or to be wasting people's time. Greater time with less jargon would be of help. The support for parents of Children in HDU is not as strong as on paediatric units
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Compared to previous immunotherapy treatments - The longer infusion process reduces impact of toxicity and reduced pain relief without impacting efficacy - Fewer side effects in some patients - If technology progresses in a smooth manner, then there is potential for outpatient rather than hospitalisation which has lower impact on patient and parent. Financial benefit? - It has shown promise in improving outcomes for patients in regard to event free survival and overall survival rates

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	- There is a limited amount of statistical data - There remains a number of potential side effects - Concern that toxicity can lead to significant pain - It is a complex disease and technology, so patients can react in different ways. Uncertainty - It is expensive - Uncertainty as to whether the technology is better solo or in tandem with GNCSF or IL2 etc
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The technology is targeted oh high risk Neuroblastoma patients and those in relapse so may not be needed by those at lower risk. There is a feeling amongst the parents I spoke with that certain patients may be more receptive to the immunotherapy treatment than others. Specifically, those whose treatments have been largely event free (or as much as can be) in the lead up to the therapy. Such as, surgery being successful at removing the majority of the tumour, those who have had limited side effects, those who have had a manageable pain relief procedure. Although there appears no analysis on this situation most parents questioned whether their child 'ticked the boxes' sufficiently to undertake the therapy to maximise success
Equality	
14. Are there any potential equality issues that should be taken into account when	

considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	Currently within the UK we have no children undertaking the therapy outside of the clinical trial. If the internationally recognised treatment is not approved, then UK Children will be disadvantaged and may need to look at other European or Global opportunities to maximise their life expectancy.
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • The proposed technology is the most promising treatment for children with high risk neuroblastoma, without it, options are limited • Although data points are not complete, there are positive indications about improvement in event free survival and overall survival rates • The therapy has side effects and, although work has been undertaken to lessen these, this remains an area of concern • There appears a need for more debate into whether the therapy works most efficiently on a solo basis or in conjunction with other treatments such as GMCSF or IL2 • Whilst undergoing the therapy, parents and patients need greater clarity and understanding as to what is entails so they can support the process and prepared for any issues that may arise	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

APN311 for treating high-risk neuroblastoma

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 15/194/02

BMJ Technology Assessment Group

APN311 for treating high-risk neuroblastoma

Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Head of Health Technology Assessment, BMJ-TAG, London Samantha Barton, Senior Health Technology Assessment Analyst, BMJ-TAG, London Mariana Bacelar, Senior Health Economist, BMJ-TAG, London Natalie Masento, Associate Health Technology Assessment Analyst, BMJ-TAG, London Tracey Jhita, Health Economics Manager, BMJ-TAG, London Charlotta Karner, Health Technology Assessment Analysis Manager, BMJ-TAG, London Fatima Salih, Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JP.
Date completed:	12/10/2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/194/02.

Declared competing interests of the authors:
No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of *The BMJ* work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

Acknowledgements:
The ERG would like to thank Dr Guy Makin (Consultant Paediatric Oncologist, Royal Manchester Children's Hospital) and Dr Francis Mussai (Consultant Paediatric Oncologist, Birmingham Children's Hospital) for providing clinical advice throughout the project, and to Dr Kate Wheeler (Consultant Paediatric Oncologist, Oxford University Hospital) for providing comments on the clinical sections of the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Edwards SJ, Barton S, Bacelar M, Masento N, Jhita T, Karner C, Salih F. APN311 for treating high-risk neuroblastoma: A Single Technology Appraisal. BMJ-TAG, 2017.

Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Sam Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, and clinical results sections
Natalie Masento	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the background and decision problem sections
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and provided feedback on the clinical sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Fatima Salih	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

TABLE OF CONTENTS

Table of contents 4
List of tables 7
List of figures 11
Table of abbreviations 13
1 SUMMARY 15
1.1 Critique of the decision problem in the company's submission 15
1.2 Summary of clinical effectiveness evidence submitted by the company 18
1.2.1 Clinical effectiveness in high-risk neuroblastoma 18
1.2.2 Clinical effectiveness in relapsed neuroblastoma 21
1.2.3 Adverse effects 23
1.2.4 Subgroup analyses 24
1.3 Summary of cost effectiveness evidence submitted by the company 25
1.4 ERG commentary on the robustness of evidence submitted by the company 28
1.4.1 Strengths 28
1.4.2 Weaknesses and areas of uncertainty 28
1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG 41
1.5.1 Economic 42
2 BACKGROUND 45
2.1 Critique of company's description of underlying health problems 45
2.2 Critique of company's overview of current service provision 50
2.2.1 Management of neuroblastoma 50
2.2.2 Resource use for implementing treatment with dinutuximab beta 54
2.2.3 Estimated number of eligible patients 54
3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM 56
3.1 Population 57
3.2 Intervention 59
3.3 Comparators 61
3.3.1 High-risk neuroblastoma 61
3.3.2 Relapsed or refractory neuroblastoma 62
3.4 Outcomes 62
3.5 Other relevant factors 64
4 CLINICAL EFFECTIVENESS 66
4.1 Critique of the methods of review 66
4.1.1 Searches 66
4.1.2 Inclusion criteria 69
4.1.3 Critique of screening process and data extraction 71
4.1.4 Quality assessment 72
4.1.5 Evidence synthesis 75
4.2 Critique of trials of the technology of interest, their analysis and interpretation 76

4.2.1 Trial conduct 78
4.2.2 Baseline characteristics 87
4.2.3 Description and critique of statistical approach used 95
4.2.4 Summary statement 96
4.3 Clinical effectiveness results 100
4.3.1 Event-free survival 101
4.3.2 Overall survival 107
4.3.3 Subgroup analyses 111
4.3.4 Adverse effects 113
4.4 Critique of indirect comparisons 118
4.4.1 Included studies 120
4.4.2 Methods 126
4.4.3 Results 127
4.5 Summary and conclusions of clinical effectiveness sections 135
4.5.1 Clinical issues 138
5 COST EFFECTIVENESS 140
5.1 Introduction 140
5.2 Summary of the company's key results 140
5.3 ERG comment on company's review of cost-effectiveness evidence 141
5.4 Overview and critique of company's economic evaluation 142
5.4.1 NICE reference case checklist 142
5.4.2 Population 143
5.4.3 Interventions and comparators 145
5.4.4 Modelling approach and model structure 147
5.4.5 Treatment effectiveness 149
5.4.6 Adverse events 169
5.4.7 Mortality and disease progression in the long-term model 171
5.4.8 Health-related quality of life 173
5.4.9 Resources and costs 8
5.5 Results included in company's submission 12
5.5.1 Base case results 12
5.5.2 Sensitivity analysis 12
5.5.3 Model validation 16
6 ADDITIONAL WORK UNDERTAKEN BY THE ERG 17
6.1 Model corrections 17
6.2 ERG's recommended scenario analysis 19
7 END OF LIFE 21
8 OVERALL CONCLUSIONS 23
8.1 Implications for research 27
9 REFERENCES 28

10 APPENDICES 37
10.1 Modified International Neuroblastoma Response Group criteria to determine level of risk of relapse 37
10.2 PRISMA flow schematics 38
10.3 Quality assessment 39
10.4 Participant flow for APN311-302 (reproduced from company's response to initial ERG questions dated 11/07/2017) 41
10.5 Data on analysis of event-free survival for APN311-302 42
10.6 Data on analysis of overall survival for APN311-302 46
10.7 Additional details on adverse effects 49
10.8 Company's response to the ERG's request to provide clinical and cost effectiveness analysis for those with refractory neuroblastoma 51
10.9 Previous treatments in people experiencing relapse 53

LIST OF TABLES

Table 1. Neuroblastoma clinical signs and symptoms (adapted from CS, Table 3 [pg. 12]) 46
Table 2. International Neuroblastoma Staging System (adapted from CS, Table 4 [pg. 14]) 47
Table 3. International Neuroblastoma Risk Group Staging System (adapted from CS, Table 5 [pg. 14]) 47
Table 4. Proportion of people, together with 5-year event-free survival, in risk strata (adapted from Cohn et al. 2009[7]) 48
Table 5. International Neuroblastoma Response Criteria[13] 48
Table 6. Calculation of number of people in the UK likely to be eligible for treatment with dinutuximab beta (adpated from CS, Table 54 [pg. 113]) 54
Table 7. Summary of decision problem as outlined in the company's submission (adapted from CS, Table 1 [pg. 9]) 56
Table 8. Summary of the technology, dinutuximab beta (adapted from CS, Section 1.2 [pg. 11]) 60
Table 9. Relevant outcomes for APN311-202, APN311-302 and APN311-303 (adapted from the CS, Table 11 [pg. 37]) 64
Table 10. Eligibility criteria for review of clinical effectiveness of dinutuximab beta (adapted from CS, Tables 7 [pg. 23] and 8 [pg. 55]) 69
Table 11. Overview of APN311-101 and APN311-201 (adapted from CS, Table 9, pg. 27) 77
Table 12. Demographics and baseline characteristics of people in the full analysis set of APN311-302 (adapted from CS, Tables 12 [pg. 39] and 13 [pg. 40]) 88
Table 13. Demographics and baseline characteristics of people in APN311-202 (adapted from CS, Tables 18 [pg. 44] and 19 [pg. 44]) 91
Table 14. Relapse and progression status before receiving dinutuximab beta in APN311-202 and APN311-303 (adapted from CS, Table 20 [pg. 45] and clarification response dated 25 August 2017) 92
Table 15. Demographics and baseline characteristics of people enrolled in a compassionate use program (CU-LTI) providing the results for APN311-303 (adapted from CS, Tables 14 [pg. 40] and 16 [pg. 42]) 92
Table 16. Demographics and baseline characteristics of people enrolled in the compassionate use program (CU-LTI) that provides results for APN311-303 by baseline disease status (adapted from CS, Tables 15 [pg.41] and 17 [pg. 42]) 94
Table 17. Summary of event-free survival for APN311-302 (adapted from CS, Tables 23 [pg. 55] and 24 [pg. 56], and from response to clarification dated 10 August 2017, Tables 4 [pg. 9] and 8 [pg. 11], and dated 16 August 2017, Tables 2 [pg. 6] and 4 [pg. 9]) 103
Table 18. Reported event-free survival at different time points for dinutuximab alpha and isotretinoin 105

Table 19. KM estimates of event-free survival in relapsed and refractory neuroblastoma derived from APN311-202 and APN311-303 (reported from CS [Appendix E] and EPAR[40]) 106
Table 20. Summary of overall survival for APN311-302 (adapted from CS, Table 25 [pg. 54], and from response to clarification dated 10 August 2017, Tables 2 [pgs 8–9] and 6 [pg. 10], and dated 16 August 2017, Tables 1 [pg. 5] and 3 [pg. 8]) 108
Table 21. Reported overall survival at different time points for dinutuximab alpha and isotretinoin 110
Table 22. KM estimates of overall survival in relapsed and refractory neuroblastoma derived from APN311-202 and APN311-303 (reported from CS [Appendix E] and EPAR[40]) 111
Table 23. Summary of event-free survival and overall survival from APN311-302 by subgroup of those with or without evidence of disease at baseline (adapted from CS, Appendix E, tables on pages 1–2) 112
Table 24. Summary of completed number of treatment cycles for APN311-202 and APN311-303.. 114
Table 25. Summary of treatment-emergent adverse events in APN311-202 and APN311-303 (adapted from CS, Table 42 [pg. 87]) 116
Table 26. Summary of adverse effects of special interest experienced by ≥20% of people and thought to be related to dinutuximab beta (adapted from response to clarification dated 25 August 2017, Table 18 [pgs 24–25]) 116
Table 27. Summary of serious adverse events occurring in >1 person in any study (adapted from CS, Table 45 [pg 93 and 94]) 117
Table 28. Main baseline characteristics for APN311-302 versus historical Control R1 (adapted from CS, Table 35 [pgs 79–80]) 121
Table 29. Baseline characteristics for APN311-202 and APN311-303 and the two historical controls referred to as Garaventa and R1 (adapted from CS, Tables 34 [pgs 78–79] and 37 [pg. 82]) 125
Table 30. KM estimates for overall survival for the comparison of dinutuximab beta versus no dinutuximab beta (adapted from CS, Table 36 [pg. 81]) 129
Table 31. Effect estimates generated for isotretinoin alone versus dinutuximab beta plus isotretinoin with or without IL-2 adjusted for various prognostic factors (adapted from clarification responses dated 25 August 2017 and 6 September 2017) 130
Table 32. Mean and median overall survival for all groups (adapted from CS, Tables 38 [pg. 82], 39 [pg. 84] and 40 [pg. 85] and from CSR, Tables 3.1.1 [pg. 8145] and 3.1.3 [pg. 8151]) 132
Table 33. Summary of analyses of overall survival for dinutuximab beta in combination with isotretinoin and IL-2 versus historical control in the treatment of relapsed neuroblastoma (adapted from CS, Tables 37 [pg. 82], 38 [pg. 82] and 39 [pg. 83], CSR for APN311-202 and APN311-303, and clarification response dated 6 September 2017) 132
Table 34. Company's revised base case results – high-risk population 141
Table 35. NICE reference checklist 142

Table 36. Effect estimates for OS generated for isotretinoin alone versus dinutuximab beta plus isotretinoin with or without IL-2 adjusted for various prognostic factors (adapted from clarification responses dated 25th August 2017 and 6th September 2017) 157
Table 37. Hazard ratios estimated by the ERG in the dinutuximab alpha STA 164
Table 38. Summary of fundamental problems in CS and ERG's ammendmants 165
Table 39. Adverse events included in the high-risk model (based on Table 56 in the CS) 169
Table 40. Proportion of adverse events 170
Table 41. HRQoL studies identified by the company (CS, pg 123-128, Table 57) 1
Table 42. Utility values used by the company in the economic analysis 3
Table 43. Summary of utility assumptions for the high-risk population used in the STA for dinutuximab and dintuximab beta 5
Table 44. Studies reporting resource use and costs identified in company's systematic literature search (CS, Appendix I, Table 1) 1
Table 45. Drug acquisition costs in the high-risk model (adapted from Table 62 in the CS) 1
Table 46. Administration and hospitalisation costs – high-risk model (adapted from Table 64 in the CS) 2
Table 47. Concomitant medication costs (Table 66 from the CS, costs corrected to reflect used values in economic model) 3
Table 48. Monitoring costs per cycle (Table 67 in the CS) 5
Table 49. Stable state resource use and costs (Table 68 in the CS) 6
Table 50. Failure state costs and resource use (Table 69 in the CS) 7
Table 51. Resource use and costs for managing adverse events (Table 70 in the CS) 8
Table 52. Body surface area deterministic sensitivity analysis 9
Table 53. Company's revised base case results – high-risk population 12
Table 54. Parameters included in PSA influencing QALY estimation 14
Table 55. PSA results for the high-risk model (Table 30, company clarification response part 2) 14
Table 56. Company's corrected base case results – high-risk population 18
Table 57. Company's corrected base case ICER with HRs incorporated 19
Table 58. End of life considerations 21
Table 59. Modified INRG criteria (adapted from CS, Table 6 [pg. 15]) 37
Table 60. Quality assessment for APN311-302 (adapated from CS, Table 22, pg. 53) 39
Table 61. Survival analysis on event-free survival for dinutuximab beta plus isotretinoin [redacted] reproduced from company's response to clarification dated 16 August 2017, Table 23 [pgs 33–34] 42
Table 62. Survival analysis on event-free survival for dinutuximab beta plus isotretinoin plus IL-2, [redacted] reproduced from company's response to clarification dated 16 August 2017, Table 26 [pgs 38–39] 44

Table 63. Survival analysis on overall survival for dinutuximab beta plus isotretinoin, [redacted]reproduced from company's response to clarification dated 16 August 2017, Table 11 [pgs 19–20] 46
Table 64. Survival analysis on overall survival for dinutuximab beta plus isotretinoin plus IL-2, [redacted](reproduced from company's response to clarification dated 16 August 2017, Table 14 [pgs 23–24] 47
Table 65. Summary of treatment-emergent adverse events possibly related to dinutuxumab beta experienced by ≥20% people (adapted from company's response to clarification dated 25 August 2017, Table 18, [pgs 24–25]) 49
Table 66. Adverse effects from APN311-302 (adapted from CS, Table 46 [pgs 94–95]) 50
Table 67. Treatment at first-line and prior to diagnosis of relapse or refractory neuroblastoma in APN311-202, APN311-303, and Garaventa (adapted from CSR for relevant study and company clarification response dated 25 August 2017) 53

LIST OF FIGURES

Figure 1. Treatment pathway for high-risk neuroblastoma 52
Figure 2. The R1 and R2 randomisation stages in the HR-NBL-1 trial[28] 79
Figure 3. Unadjusted KM curve for event-free survival for the full analysis set of APN311-302 (adapted from CS, Figure 4 [pg. 57]) 104
Figure 4. Adjusted KM curve for event-free survival for APN311-302 (estimated by ERG) 104
Figure 5. Adjusted KM curves for event-free survival for APN311-202 and APN311-303 (reproduced from company's clarification response dated 16 August 2017, Figures 28 [pg. 31] and 31 [pg. 44]) 107
Figure 6. Unadjusted KM curve for overall survival for the full analysis set of APN311-302 (adapted from CS, Figure 5 [pg. 57]) 109
Figure 7. Adjusted KM curve for overall survival for APN311-302 (estimated by ERG) 109
Figure 8. Adjusted KM curves for overall survival for APN311-202 and APN311-303 (reproduced from company's clarification response dated 16 August 2017, Figures 16 [pg. 26] and 19 [pg. 29]) 111
Figure 9. Change in OS and EFS KM curves over time 128
Figure 10. KM curves for overall survival curves of isotretinoin alone (labelled as treatment group) versus dinutuximab beta-containing treatment (labelled as MAT and immunotherapy) (adapted from CS, Figure 7 [pg. 81]) 130
Figure 11. Observed event-free and overall survival data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis for dinutuximab alpha (Figures 19 and 20 in ERG report for dinutuximab alpha submission, pg. 87)[46] 131
Figure 12. KM curves for overall survival for APN311-202 versus R1 (relapsed) (adapted from CSR, Graph 3.1.3 [pg. 8254]) 133
Figure 13. KM curves for overall survival for APN311-303 versus R1 (relapsed) (adapted from CSR, Graph 3.1.1 [pg. 8250]) 134
Figure 14. [redacted] 134
Figure 15. [redacted] 135
Figure 16. [redacted] 135
Figure 17. Kaplan-Meier curves for OS and PFS in APN311-302 153
Figure 18. Failure state KM data 153
Figure 19. Change in OS and EFS KM curves over time 154
Figure 20. KM data for OS and EFS for APN311-302 155
Figure 21. KM data for OS for R1 and estimated KM data for EFS for R1 155
Figure 22. Change in OS and EFS fitted Gompertz curves over time 156
Figure 23. Unadjusted OS KM curves 160

Figure 24. Unadjusted OS curve for dinutuximab beta and estimated isotretinoin OS curve with adjusted HR 161
Figure 25. Observed OS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis (Figure 20 in ERG report for dinutuximab alpha [GID-TAG507], page 87) 161
Figure 26. Unadjusted EFS curve for dinutuximab beta and estimated unadjusted EFS curve for isotretinoin 163
Figure 27. Observed EFS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis (Figure 19 in ERG report for dinutuximab alpha submission, page 86) 163
Figure 28. Unadjusted EFS curve for dinutuximab beta and estimated isotretinoin EFS curve with adjusted HR 165
Figure 29. Gomperz OS and EFS curves for dinutuximab beta 167
Figure 30. Gomperz OS and EFS curves for isotretinoin 168
Figure 31. Long-term OS in the economic analysis 172
Figure 32. Long-term EFS in the economic analysis 173
Figure 33. Utility trace with numbers at risk 7
Figure 34. Tornado diagram for deterministic sensitivity analysis results for the high risk model (Figure 1, company clarification response part 2) 13
Figure 35. Cost-effectiveness plane for dinutuximab beta for the high-risk model with a £30,000/QALY threshold - revised model (Figure 2, company clarification response part 2) 15
Figure 36. Cost effectiveness acceptibility curve for dinutuximab beta for the high-risk model - revised model (Figure 3, company clarification response part 2) 15
Figure 37. Schematic for the search of the literature on high-risk neuroblastoma (reproduced from CS, pg. 24, Figure 2) 38
Figure 38. Schematic for the search of the literature on relapsed or refractory neuroblastoma (reproduced from CS, pg. 26, Figure 3) 38
Figure 39. Participant flow in APN311-302 41
Figure 40. Adjusted KM curves for event-free survival by treatment group in APN311-302 (reproduced from company's clarification response dated 16 August 2017, Figures 22 [pg. 32] and 25 [pg. 37]) 42
Figure 41. Adjusted KM curves for overall survival by treatment group in APN311-302 (reproduced from company's clarification response dated 16 August 2017, Figures 9 [pg. 17] and 13 [pg. 22]) 46

TABLE OF ABBREVIATIONS

Abbreviation	In full
13-cis RA	13-cis retinoic acid (also referred to as isotretinoin)
AE	Adverse event
AIC	Akaike Information Criterion
ASCT	Autologous stem cell transplant
AUC	Area under the curve
BIC	Bayesian Information Criterion
BSA	Body surface area
BuMel	Busulfan and melphalan hydrochloride
CCLG	Children's Cancer and Leukaemia Group
CE	Cost effectiveness
CEAC	Cost-effectiveness acceptability curve
CEM	Carboplatin, etoposide and melphalan
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CLS	Capillary leak syndrome
COJEC	Cisplatin, vincristine, carboplatin, etoposide, cyclophosphamide
CR	Complete response
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CU-LTI	Compassionate use–long-term continuous infusion
DSU	Decision Support Unit
EFS	Event-free survival
EMA	European Medicines Agency
eMC	Electronic medicines compendium
EPAR	European public assessment report
ERG	Evidence Review Group
FDA	US Food and Drug Administration
FS	Failure state
GM-CSF	Granulocyte macrophage colony-stimulating factor
HR	Hazard ratio
HR-NBL-1	High-risk neuroblastoma study 1 (SIOPEN)
HRQoL	Health-related quality of life
HTA	Health technology assessment
HUI	Health utility index
ICER	Incremental cost-effectiveness ratio
IL-2	Interleukin-2
INRC	International Neuroblastoma Response Criteria

INRGSS	International Neuroblastoma Risk Group Staging System
INSS	International Neuroblastoma Staging System
ITT	Intention to treat
KM	Kaplan–Meier
MAIC	Matching-adjusted indirect comparison
MAT	Myeloablative chemotherapy
mIBG	Meta-iodobenzylguanidine
MR	Mixed response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MYCN	N-myc proto-oncogene protein
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analyses
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazard
PI	Proteasome inhibitor
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
S.D.	Stable disease
SE	Standard error
SIOPEN	International Society of Paediatric Oncology Europe Neuroblastoma
SmPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
VGPR	Very good partial response

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of APN311 (dinutuximab beta EUSA; EUSA Pharma) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of APN311 (hereafter referred to as dinutuximab beta) as a maintenance therapy in the front-line multimodal, multiagent treatment of high-risk neuroblastoma. Evidence is also submitted on the effectiveness of dinutuximab beta in the treatment of relapsed or refractory neuroblastoma in predominantly those not previously treated with an anti-GD2 (disialoganglioside) monoclonal antibody, such as dinutuximab beta.

In May 2017, dinutuximab beta was granted a European marketing authorisation under exceptional circumstances for the treatment of high-risk neuroblastoma in people aged 12 months and above, who achieved at least a partial response to induction chemotherapy, and who went on to receive subsequent consolidation treatment with myeloablative therapy and autologous stem cell transplant (ASCT). The marketing authorisation additionally covered treatment of people with history of relapsed or refractory neuroblastoma. Dinutuximab beta can be given as a treatment irrespective of presence or absence of residual disease. The marketing authorisation specifies that dinutuximab beta be given in combination with interleukin-2 (IL-2) in those with high-risk neuroblastoma and not achieving a complete response to induction therapy and those with relapsed or refractory disease. A marketing authorisation under exceptional circumstances is awarded when an applicant can demonstrate that they are unable to provide comprehensive data on the efficacy and safety of the agent for which they are seeking authorisation. The applicant (APEIRON Biologics AG) backed the European Medicines Agency's proposal for a marketing authorisation under exceptional circumstances.

The clinical evidence presented in the company's submission (CS) is derived from one randomised controlled trial (RCT) in high-risk neuroblastoma, APN311-302, and two observational studies in relapsed or refractory disease, APN311-202 (prospective design) and APN11-303 (retrospective design). None of the identified studies provides direct evidence on the clinical effectiveness of dinutuximab beta versus the comparators of interest to the decision problem. Estimates of comparative clinical effectiveness are generated from naïve indirect comparisons of the identified studies with historical cohorts.

The final scope issued by NICE specified the population of interest to be those with high-risk neuroblastoma who have had myeloablative therapy and ASCT, with no specification on level of response to induction therapy. APN311-302 enrolled those who achieved a partial response to induction therapy and, therefore, represents a population that is narrower than that defined in the NICE scope but is in line with the marketing authorisation for dinutuximab beta for the treatment of high-risk

neuroblastoma. The Evidence Review Group (ERG) considers the population enrolled in APN311-302 to be representative of people with the high-risk neuroblastoma in England and the wider UK. The ERG notes that neuroblastoma predominantly affects children, and most people diagnosed with the disease are younger than five years, with a median age at diagnosis of 18 months.

Those with relapsed or refractory neuroblastoma are specified in the NICE scope as subgroups of interest. Clinical experts advised the ERG that relapsed and refractory disease are relevant to the decision problem, and, moreover, recommended that the two disease states are distinct populations that should be evaluated separately. The ERG's experts also fed back that, in UK clinical practice, those with relapsed neuroblastoma that was categorised as high risk of relapse at diagnosis are likely to have received dinutuximab beta as part of front-line multiagent therapy through participation in the High-Risk Neuroblastoma-1 (HR-NBL-1) study. As part of the clarification process, the company indicated that they do not support re-treatment with dinutuximab beta. Taking comments from clinical experts and the company together, the ERG considers that dinutuximab beta would not be considered as a treatment option in UK clinical practice for those experiencing relapse of high-risk neuroblastoma, which forms the largest proportion of those who relapse. At the time of writing the ERG's report, data on subsequent re-treatment with dinutuximab beta in people experiencing relapse previously treated with dinutuximab beta are not available. During clarification, the company confirmed that there are no ongoing or planned studies to assess re-treatment with dinutuximab beta in those with relapsed neuroblastoma.

Eligibility criteria for refractory neuroblastoma differed slightly between APN311-202 and APN311-303, and it is possible that some people with refractory disease in the studies could have previously received dinutuximab beta. Importantly, the ERG's experts highlighted that it is likely that a proportion of those enrolled in APN311-202 and APN311-303 and classified as refractory to treatment are people who originally participated in APN311-302 who, rather than being truly refractory, did not achieve an adequate response to induction therapy in APN311-302, where inadequate response could include partial response. Finally, the company did not provide estimates of comparative clinical effectiveness for dinutuximab beta in refractory neuroblastoma, highlighting that the evidence available precluded an indirect comparison. In summary, the ERG has reservations about the comparability of those with relapsed and refractory neuroblastoma in APN311-202 and APN311-303 with people of the same disease status in England, particularly in terms of prior dinutuximab beta treatment and with the company not supporting re-treatment with dinutuximab beta. For completeness, in subsequent sections, the ERG presents a critique of the identified studies and clinical effectiveness results for relapsed and refractory neuroblastoma.

Dinutuximab beta is administered through intravenous infusion to give a total dose of 100 mg of the agent. There are two recommended infusion schedules:

- continuous infusion over the first 10 days of each course at a daily dose of 10 mg/m^2;
- a daily infusion of 20 mg/m^2 infused over 8 hours for the first 5 days of each course.

The ERG notes that APN311-302 utilised the short infusion schedule for dinutuximab beta (over 5 days), whereas, in APN311-202 and APN311-303, dinutuximab beta was given as a continuous infusion. In the CS, the company states that, compared with the short infusion schedule, continuous infusion of dinutuximab beta is associated with a reduction in risk of hypersensitivity events, and is the recommended route because of its improved safety profile. The ERG's clinical experts agreed with the company, indicating that continuous infusion of dinutuximab beta would be the preferred schedule in UK clinical practice, for all stages of neuroblastoma. No study comparing the clinical effectiveness of the two infusion rates is available.

The final scope issued by NICE identified the comparators of interest in high-risk neuroblastoma to be isotretinoin and a second monoclonal antibody, dinutuximab (for clarity, hereafter referred to as dinutuximab alpha). The company outlined that they did not consider dinutuximab alpha a comparator of interest because the European marketing authorisation for the immunotherapy is no longer in place, being withdrawn at the request of the holder. The ERG agrees with the company that the withdrawal of the marketing authorisation renders dinutuximab alpha no longer directly relevant to the decision problem. However, within the CS, the company reports that the two immunotherapies are separate entities, but refers to results on clinical effectiveness of dinutuximab alpha to underscore effect estimates for dinutuximab beta in a narrative comparison. To date, there has been no clinical study directly comparing the two monoclonal antibodies. In brief, the first iteration of dinutuximab, that is dinutuximab alpha, was produced in the SP2/0 cell line. By contrast, dinutuximab beta is produced in the Chinese Hamster Ovary (CHO) cell line. Although the two dinutuximab antibodies have identical amino acid sequences, because they are produced in different cell lines (SP2/0 and CHO), there are marked differences in glycosylation patterns between the two interventions and they are considered distinct from each other, with potential differences in clinical effectiveness and adverse effect profile. However, given that the alpha and beta forms of dinutuximab bind to the same target, the ERG considers that, as with other agents belonging to the same drug class, they could elicit similar effects, and, although comparable clinical effectiveness of the two immunotherapies cannot be assumed, results for dinutuximab alpha are an evidence base to help inform the long-term effects of immunotherapy.

The primary objective of APN311-302 was to assess whether adding IL-2 to dinutuximab beta, in addition to differentiation therapy with isotretinoin, would improve 3-year EFS in those with high-risk neuroblastoma who achieved at least a partial response to prior first-line, multiagent, multimodality therapy. No comparators of interest for relapsed or refractory neuroblastoma were listed in the NICE scope. Although the company submitted evidence in support of dinutuximab beta-containing regimens

in relapsed or refractory neuroblastoma, they did not discuss appropriate comparators for these groups. The ERG's clinical experts advised that there is no accepted treatment pathway for relapsed or refractory neuroblastoma and people experiencing relapse or who are refractory to treatment would likely be enrolled into a clinical trial. APN311-202 and APN311-303 are both single-arm observational studies and therefore have no comparator group. In summary, none of the studies from which data on clinical effectiveness of dinutuximab beta has a comparator group that is relevant to this STA, and there is no direct evidence of dinutuximab beta in comparison with a relevant intervention.

Overall survival (OS) and adverse effects were reported for the three studies, but event-free survival (EFS) was substituted for progression-free survival (PFS) across studies. Health-related quality of life (HRQoL) was not reported for any included study. In APN311-302, EFS was assessed as the primary outcome and was defined as the time to an event from randomisation until the first occurrence of relapse, disease progression, secondary neoplasm or death from any cause. EFS was captured as a secondary outcome in APN311-303, but was not prespecified in APN311-202. In addition, development of a second neoplasm was not counted as an EFS event in APN311-202. The ERG's clinical experts fed back that development of a second neoplasm is a rare event, and its omission from EFS in APN311-202 is likely to have minimal impact on estimates of effect. As most events occurring in the studies were relapse, progression or death from any cause, EFS is similar to PFS. The company also presented data on tumour response in relapsed or refractory neuroblastoma, which the ERG decided against reporting. Best response achieved at any point after initiation of dinutuximab beta was captured, rather than tumour response at end of treatment: best response might not be the most clinically relevant outcome as it encompasses responses of short duration.

1.2 Summary of clinical effectiveness evidence submitted by the company

1.2.1 Clinical effectiveness in high-risk neuroblastoma

APN311-302 is a component of the phase III HR-NBL-1 study established by the Société Internationale D'Oncologie Pédiatrique Europe. HR-NBL-1 is an investigator-initiated, international, open-label, randomized trial established to test various hypotheses in treating high-risk neuroblastoma and the study involved several randomisation steps. The stage of HR-NBL-1 from which APN311-302 is formed was initially designed to assess whether adding dinutuximab beta to isotretinoin after consolidation treatment improved EFS at 3 years compared with isotretinoin alone. Publication of the results of a trial establishing the clinical effectiveness of dinutuximab alpha-based regimen over isotretinoin alone in improvement of EFS at 3 years led to anti-GD2 monoclonal antibody immunotherapy (such as dinutuximab alpha) becoming a component of standard care after consolidation therapy in high-risk neuroblastoma. Consequently, the protocol of HR-NBL-1 was amended such that everyone randomised in the immunotherapy phase would receive dinutuximab beta. The primary hypothesis became to assess

whether adding IL-2 to dinutuximab beta in addition to differentiation therapy with isotretinoin would improve 3-year EFS in those who achieved at least a partial response to prior first-line, multiagent, multimodality therapy.

Recruitment sites for APN311-302 were located in Israel, Australia, and 10 countries across Europe, including Great Britain and Ireland. Of the 406 people randomised to IL-2 or no IL-2, 370 made up the final analysis set, of which [redacted] people ([redacted]%) were recruited from Great Britain and Ireland. Baseline characteristics of the population of APN311-302 are comparable with those of people in the UK likely to be eligible for treatment with dinutuximab beta.

To inform a naïve indirect comparison versus isotretinoin, the company created a historical cohort (450 people) derived from people enrolled in an earlier phase of the HR-NBL-1 study than those enrolled in APN311-302. People forming the historical control R1 were randomised in the R1 phase of HR-NBL-1, which was designed to compare the effectiveness of BuMel (busulfan and melphalan hydrochloride) versus CEM (carboplatin, etoposide and melphalan) as consolidation myeloablative therapy in high-risk neuroblastoma. After induction therapy and myeloablative therapy followed by ASCT, people received only isotretinoin during the maintenance phase. The ERG agrees with the company's proposal that those treated during the R1 phase of HR-NBL-1 form a valid historical control group for those in APN311-302 who received treatment with dinutuximab beta with or without IL-2.

The company uses the full data set from APN311-302 to inform the indirect comparison, that is, combining data from those who received IL-2 with data from those who did not. The KM curves for OS and EFS in APN311-302 suggest that addition of IL-2 to dinutuximab beta and isotretinoin confers [redacted]. The ERG considers it reasonable to combine data from the two groups to give a larger sample size as the basis for an appropriately adjusted indirect comparison. One caveat that should be borne in mind is that subgroup analyses indicate that IL-2 affords greater clinical benefit for those with residual disease at baseline than those without evidence of disease, and it is unclear from details available in the CS whether the populations of APN311-302 and the historical control R1 are comparable in terms of this baseline characteristic. The ERG considers that without adjustment an imbalance between groups in proportion of people without residual disease could introduce bias into the result.

Baseline characteristics for the full population of APN311-302 and the historical control R1 indicate that the groups are similar in terms of key observed prognostic factors. However, one key difference between APN311-302 and the historical control R1 is the proportion of people receiving BuMel as their consolidation myeloablative therapy: the R1 phase of HR-NBL-1 established that BuMel was the more effective consolidation therapy and the regimen became the standard of care. In APN311-302, 383

people from the 406 (94.3%) initially randomised received BuMel. By contrast, because the R1 randomisation phase of HR-NBL-1 was designed to compare the effectiveness of BuMel versus CEM, half of the people in the R1 phase received CEM as their consolidation therapy (302/598; 50.5%). The exact proportion of the 450 people in the historical control R1 who received CEM as consolidation therapy is unclear from the CS, but it is likely to be substantially lower than that in APN311-302: the ERG considers that the maximum number of people who could have received CEM in the historical control is 71.1% (302/450).

A comparative estimate of clinical effectiveness of dinutuximab beta-containing regimen versus isotretinoin in high-risk neuroblastoma is available for only OS. EFS was not captured for the historical control R1. Difference in OS between the two groups was statistically significant when evaluated using the log rank test ($p<0.0001$; unadjusted HR not available) and favoured treatment including dinutuximab beta. As part of the clarification process, the ERG requested that the company provide adjusted hazard ratios (HRs) with accompany 95% confidence intervals (CIs). Dinutuximab beta-based treatment, with or without IL-2, was associated with [redacted] in OS compared with isotretinoin alone ([redacted]; Table A and Figure A): the reported HR is adjusted for age, INSS stage at initial diagnosis, MYCN status, and prior myeloablative therapy. Mean OS was substantially longer in those receiving isotretinoin alone (2,447.1 days) compared with those receiving dinutuximab beta plus isotretinoin with or without IL-2 (1,359.4 days). Similarly, there was variation between groups in median OS, with a median OS of 1,869 days for those receiving isotretinoin and median OS yet to be reached in the group receiving the dinutuximab beta-containing regimen. The company proposes that the large difference in mean OS between the groups is likely due to those in the isotretinoin group being followed for longer. The ERG considers that data from the combined analysis for APN311-302 is immature and has concerns about the disparity in length of follow-up between the two studies.

Table A. Effect estimates generated for isotretinoin alone versus dinutuximab beta plus isotretinoin with or without IL-2 adjusted for various prognostic factors

Factors adjusted for	HR[a]	95% CI
Age and INSS stage at initial diagnosis, MYCN status, and prior myeloablative therapy	[redacted]	[redacted]
Age	[redacted]	[redacted]
INSS stage at initial diagnosis	[redacted]	[redacted]
MYCN status	[redacted]	[redacted]
Prior myeloablative therapy	[redacted]	[redacted]

[a] [redacted].

Abbreviations: CI, confidence interval; HR, hazard ratio; IL-2, interleukin 2; [redacted].

Figure A. KM curves for overall survival of isotretinoin alone (labelled as treatment group) versus dinutuximab beta-containing treatment (labelled as MAT and immunotherapy) (naïve comparison)

1.2.2 Clinical effectiveness in relapsed neuroblastoma

APN311-202 is a prospective, multinational, observational study that is ongoing and presented results are derived from an interim analysis of data. To be eligible for enrolment in APN311-202, people had to have primary refractory neuroblastoma or be experiencing relapse. APN311-303 was designed to retrospectively evaluate data collected under a compassionate use programme (CU-LTI) carried out in a single site in Germany. People who could not obtain adequate treatment for their neuroblastoma through routine medical treatment or were not eligible for clinical trials were included in the CU-LTI. The CU-LTI introduced the treatment approach of a prolonged continuous infusion of dinutuximab beta (rather than a rapid infusion over 8 hours). The primary objective of both APN311-202 and APN311-303 was to identify a tolerable treatment schedule of dinutuximab beta that reduced the pain and toxicity profile yet maintained the immunomodulatory effect the immunotherapy.

To generate estimates of comparative clinical effectiveness, the company utilises two historical cohorts derived from people with relapsed or progressed neuroblastoma. One historical cohort was generated from people enrolled in the R1 phase of the HR-NBL-1 study who experienced relapse during follow-up, referred to here as historical control R1 (relapsed). People were included who had [redacted]. The historical control R1 (relapsed) comprised 52 people. The second historical control was based on data from a retrospective study of children with relapse or progression of neuroblastoma and captured in the Italian Neuroblastoma Registry from 1979 to 2006. Hereafter, the second historical control is referred to as Garaventa. People forming the Garaventa cohort had received tumour resection,

chemotherapy, radiotherapy, and myeloablation followed by ASCT, but no immunotherapy, and are therefore representative of treatments used before dinutuximab beta-containing regimens in APN311-202 and APN311-303. Due to changes in neuroblastoma management, for the purposes of comparison with APN311-202 and APN311-303, Garaventa comprised only those with a date of initial diagnosis of 1999 or later, which led to a historical cohort of 29 people.

In the CS, the company focuses on the naïve indirect comparison of APN311-303 versus Garaventa to support the treatment effect of dinutuximab beta-containing regimens in the subgroup of people with relapsed neuroblastoma. In support of the presented results, the company also report an analysis of pooled data from APN311-202 and APN311-303 versus each historical control. Given the retrospective nature of APN311-303, during clarification, the ERG requested the company carry out an adjusted indirect comparison of APN311-202 alone versus each historical control. Considering the results in totality, the ERG considers it important to summarise effect estimates from all available analyses to [redacted]. In addition, the ERG notes substantial differences between mean and median OS within each cohort, in particular for R1 (relapsed), which, in the ERG's view, suggests that the data are skewed and likely to be influenced by outliers.

[redacted] (Table B). Considering the quality of the studies informing the analysis, together with the naive indirect nature of the comparison, the ERG considers the results of the presented analyses to be unreliable and advises that the results are interpreted with extreme caution.

Table B. Summary of overall survival for dinutuximab beta in combination with isotretinoin and IL-2 versus historical control in the treatment of relapsed neuroblastoma

Comparison	KM estimate		HR	95% CI
Unadjusted analyses taken from CSR				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]
Unadjusted analyses as reported in CS				
APN311-303 versus R1 (relapsed)	Not available			
APN311-303 versus Garaventa[a]	APN311-303	Control		
KM estimate at 1 year	0.90	0.56	–	–
KM estimate at 2 years	0.69	0.46	–	–
KM estimate at 3 years	0.55	0.28	–	–
APN311-202 + APN311-303 versus R1 (relapsed)[b]	APN311 studies	Control		
KM estimate at 1 year	0.83	0.56	–	–
KM estimate at 2 years	0.60	0.46	–	–

KM estimate at 3 years	0.50	0.28	–	–
APN311-202 + APN311-303 versus Garaventa[c]	APN311 studies	Control		
KM estimate at 1 year	0.83	0.45	–	–
KM estimate at 2 years	0.60	0.31	–	–
KM estimate at 3 years	0.50	0.24	–	–
Adjusted analyses provided during clarification				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]

[a] Log rank p value of 0.0009.

[b] Log rank p value of 0.0302.

[c] Log rank p value of 0.0031.

[d] Adjusted for [redacted].

[e] Adjusted for [redacted].

Abbreviations: CI, confidence interval; CS, company submission; CSR, clinical study report; HR, hazard ratio; KM, Kaplan–Meier; [redacted].

1.2.3 Adverse effects

Data on the adverse effect profile of dinutuximab beta are primarily derived from a safety database comprising 514 people who have undergone treatment with the immunotherapy, with a focus on 98 people who received dinutuximab beta as a continuous infusion over 10 days. Administration of dinutuximab beta is known to be associated with pain, hypersensitivity reactions, and capillary leak syndrome. Each person in APN311-202 and APN311-303 experienced a treatment-emergent adverse effect (TEAE). The company reported that, although the number of TEAEs decreased substantially with each treatment cycle, the proportion of people experiencing a TEAE remained high throughout the study (data not presented).

Adverse effects noted in the Summary of Product Characteristics (SmPC) as special warnings and precautions for use include pain, hypersensitivity reactions and capillary leak syndrome. Of the adverse effects of special note, pain and hypotension were each experienced by a similar proportion of people in APN311-202 (28/44 [63.6%]) compared with APN311-303 (35/54 [64.8%]). By contrast, a considerably larger proportion of people experienced capillary leak syndrome in APN311-303 (83.3%) compared with APN311-202 (34.1%). The marked difference between APN311-202 and APN311-303 in proportion of people experiencing capillary leak syndrome is attributed to the lack of standardisation in data reporting and emphasis on this particular adverse drug reaction between the studies. Other frequently reported treatment-emergent adverse effects possibly related to dinutuximab beta were general disorders and administration site conditions (43/44 [97.7%] in APN311-202 vs 54/54 [100.0%] in APN311-303), and gastrointestinal disorders (33/44 [75.0%] in APN311-202 vs 49/54 [90.7%] in APN311-303).

In APN311-302, dose reductions or premature discontinuations of dinutuximab beta or IL-2 (if applicable) were [redacted] in patients receiving concomitant treatment with IL-2.

Mean [redacted] of dinutuximab beta was [redacted], as was the total amount of dinutuximab beta [redacted] of the study ([redacted]). In addition, [redacted] of dinutuximab beta occurred [redacted] treatment ([redacted]). Changes in dinutuximab beta treatment in both groups were predominantly because of toxicity. Of those receiving IL-2, [redacted] had a [redacted]. Exposure to [redacted] the two groups ([redacted]).

1.2.4 Subgroup analyses

The company evaluated the potential benefit of adding IL-2 to dinutuximab beta in combination with isotretinoin in the subgroup of those achieving a complete response to prior multimodal, multiagent induction therapy followed by myeloablative chemotherapy and ASCT, and, as a separate subgroup, those who did not: that is, subgroups of those with and without evidence of disease prior to treatment with dinutuximab beta-containing regimen.

Compared with the 3-year EFS for the full trial population, the proportion of people achieving 3-year EFS was smaller in people with evidence of disease at baseline and larger in those without evidence of disease at baseline (Table C). The Committee for Medicinal Products for Human Use (CHMP) concluded that the data indicate there is no, or only limited added, benefit of the addition of IL-2 to treatment with dinutuximab beta and isotretinoin as a first-line treatment in those achieving a complete response to induction therapy (i.e., without residual disease). The CHMP went on to comment that, based on the results from APN311-302, the same conclusion could not be drawn for people with evidence of disease after induction therapy and recommended the inclusion of IL-2 in the dinutuximab beta-containing regimen for those not achieving complete response to induction therapy (specified in the marketing authorisation).

Inferences on the benefit of adding IL-2 to dinutuximab beta and isotretinoin in those with relapsed or refractory neuroblastoma cannot be made as all people in APN311-202 and APN311-303 received IL-2. The CHMP cautioned against extrapolating findings from APN311-302 study to the relapsed or refractory setting.

Table C. Summary of event-free survival and overall survival from APN311-302 by subgroup of those with or without evidence of disease at baseline

	Evidence of disease at baseline		Without evidence of disease at baseline	
	Dinutuximab beta plus isotretinoin (N=73)	**Dinutuximab beta plus isotretinoin plus IL-2 (N=76)[c]**	**Dinutuximab beta plus isotretinoin (N=104)[d]**	**Dinutuximab beta plus isotretinoin plus IL-2 (N=107)**
EFS				
KM estimate				
1 year (%)	66.6%	72.3%	76.5%	72.6%
2 years (%)	58.1%	61.6%	66.7%	69.5%
3 years (%)	45.9%	53.8%	61.7%	66.2%
Log-rank test[a]	p = 0.4944[b]		p = 0.5648[b]	
Events	36 (49.3)	31 (41.3)	41 (39.8)	36 (33.6)
Censored, n (%)	37 (50.7)	44 (58.7)	62 (60.2)	71 (66.4)
OS				
KM estimate				
1 year (%)	82.9%	86.0%	89.2%	88.5%
2 years (%)	73.1%	71.2%	78.2%	77.8%
3 years (%)	54.2%	63.3%	71.0%	72.2%
Log-rank test[a]	p = 0.5710[b]		p = 0.9571[b]	
Events	29 (39.7)	26 (35.1)	30 (29.1)	29 (27.1)
Censored, n (%)	44 (60.3)	48 (64.9)	73 (70.9)	78 (72.9)

[a] Log-rank adjusted for previous treatment (busulfan and melphalan vs carboplatin, etoposide and melphalan).

[b] The p-value refers to the analysis based on 3 years' follow-up.

[c] One person with missing date of death and without progression was excluded from the analysis of EFS and OS.

[d] One person with missing date of death and without progression was excluded from the analysis of EFS and two people with missing date of death were excluded from the analysis of OS.

Abbreviations: CS, company submission; EFS, event-free survival; IL-2, interleukin 2; KM, Kaplan–Meier; OS, overall survival; pg, page.

1.3 Summary of cost effectiveness evidence submitted by the company

The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of dinutuximab beta given in combination with isotretinoin, in comparison with isotretinoin. The model includes three health states: the event-free state (EFS), the failure state (FS) and death. The proportion of patients occupying the different health states from cycle 0 until the point of the cure threshold (hereafter referred to as the short-term model) are estimated in a cohort-based partitioned survival model. The economic outcomes for the first five cycles (i.e. the first five months) of the model are estimated in a decision-tree-based model. The economic model after the cure threshold point (hereafter referred to as long-term model) is a separate structure, and is also based on a cohort-based partitioned survival model.

The starting age of the cohort is three years. Children are initially allocated to the EFS state at the beginning of the economic analysis and are assumed to initiate treatment with dinutuximab beta plus isotretinoin or isotretinoin alone for a maximum of five months (in treatment cycles of 10 days per month for dinutuximab beta and 14 days for isotretinoin). The treatment and comparator arms in the model, include IL-2 as a treatment, even though this is not reported in the CS. This issue is further explored in Section 5.4.3 and Section 5.4.9. Patients occupying the EFS state are at risk of disease progression or death. Patients in the FS state are also at risk of death and cannot enter remission in the model. The model includes two possible scenarios for a cure threshold. While one assumes that patients on the EFS state for five years are cured, the other assumes that only after 10 years of EFS, a patient can be assumed cured. When patients reach the cure threshold, the patients in the EFS and the FS state can only move to the death state, as patients cannot progress in the model anymore. At this point in the model, patients in the EFS and in FS states die at different rates, to simulate that some patients are considered cured while others are relapsed patients. This is further explored in Section 5.4.7 of the report. The partitioned survival (or area under the curve [AUC]) approach means that the proportion of patients modelled in each health state is based on parametric survival curves for each clinical outcome. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 5.4.5.

A life time horizon of 90 years is adopted in the model and time is discretised into monthly cycles for the short-term model and yearly cycles for the long-term model. A half-cycle correction was not applied in the model. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at a non-reference-case discount rate of 1.5%.

Treatment effectiveness within the updated short-term model was implemented through a partitioned survival method, which used the OS and EFS data from APN311-302 to determine mortality and disease progression for each cycle of the economic model, respectively. The use of survival analysis in the model depends on the cure threshold assumed for the analysis. In the updated analysis, the company considered their base case analysis to be based on the 10-year threshold. The company used the KM curves from APN311-302 for the time period where KM data were available (approximately seven years in APN311-302), and then used a parametric curve to extrapolate the clinical data for the rest of the short-term model's time horizon (three years). The final OS and EFS curves used in the model are therefore based on the respective KM curves available, followed by a parametric tail fitted with Gompertz models for both clinical outcomes.

To estimate OS in the isotretinoin arm of the model, the company used the unadjusted KM data from the historical control R1. Therefore, the company's approach to estimating treatment effectiveness in the model was based on a naïve comparison of KM (and fitted) data from unadjusted APN311-302 data with unadjusted R1 data. However, R1 does not report EFS data, therefore the company assumed that

the absolute separation between OS and EFS observed in the dinutuximab beta arm of the model at year 5 will be the same difference between OS and EFS in the comparator arm. Nonetheless, based on an investigation of the economic model, the ERG considers that the approach taken by the company was to estimate EFS KM data for isotretinoin for each cycle by using the following formula: [$OS_{isotretinoin} - (OS_{dinutuximab} - EFS_{isotretinoin})$]. The ERG assumes that these KM data were then used to fit an EFS curve in the comparator arm. A similar approach was taken for the intervention arm; the company seems to have used the OS KM curve from R1 (and estimated KM for EFS) for the time period where KM data were available. However, because there are 10-years' worth of OS KM data in R1, the company model never incorporated the fitted Gompertz curves (which were nonetheless provided in the Excel-based model).

When patients reach the cure threshold in the model, the proportion of patients in the EFS and the FS state can only move to the death state, as patients cannot progress or enter remission in the model anymore. From this point onwards in the analysis, patients in the EFS and in FS states die at different rates, to translate the fact that some patients are considered cured while others are relapsed patients.

Cured patients do not follow the same mortality rates as those observed in the UK general population. Instead, the company assumes that cured patients (i.e. patients in the EFS state at the cure threshold) will experience a higher standardised annual mortality increased by a factor of 5.6 (95% CI 4.4 to 6.9), compared with the UK general population, based on a report from the Childhood Cancer Survival Study (Laverdiere *et al.* 2009). Therefore, the company applied a 5.6 factor to the age and gender matched mortality in the UK general population. For patients in the FS state at the cure threshold, the company assumed their mortality to be 90% higher than the mortality assumed for EFS patients (whose mortality is assumed 5.6 times that of the general population matched for age and gender).

The health state utility values (HSUVs) used in the model were estimated by applying utility decrements to age-specific UK EQ-5D general population norms. Given that UK EQ-5D norms data are only available for ages between 18-75+, the company used a logistic regression to estimate interpolated utility values for age 0 onwards. To estimate the utility value associated with the EFS and the failure states for each model cycle (and therefore age) in the economic model, the company applied a decrement to the UK EQ-5D general population values to reflect the fact that patients in the model have neuroblastoma. The percentage decrement associated with the EFS state for the high-risk model was calculated using data from a study by Portwine *et al*. 2016, identified in the systematic literature review of HRQoL. The study estimated utility values for high-risk neuroblastoma survivors (0.84) and the general population (0.96) based on the Health Utility Index (HUI)3. Using these values, the company estimated a percentage decrement of 12.5% associated with having the disease compared with the general population. Therefore, for each cycle in the economic model, the age-specific UK EQ-5D general population norms were adjusted using the 12.5% decrement. For the failure health state in the

high-risk model, the percentage decrement was based on data obtained from a study by Barr *et al*.1999. The estimated the utility value associated with recurrent disease based on the HUI2 was 0.56. The company used this value and compared it with the general population HUI3 utility value (0.96), obtained previously from the Portwine *et al.* 2016 study, to calculate a percentage decrement of 41.7% associated with recurring disease. The company has assumed that utility values for each health state do not differ by treatment arm. In addition, the company did not identify any studies from the literature review which estimated the impact of AEs on patients' quality of life therefore, did not include utility values or decrements associated with AEs in the analysis.

The costs considered in the economic model consist of pharmacological costs (treatment acquisition, administration and concomitant treatment costs), disease management costs and AEs costs.

The company's base case results present an ICER of £22,338 per QALY gained for dinutuximab beta and isotretinoin, compared with isotretinoin alone.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

1.4.1.1 Clinical

The CS contained a systematic review that addressed the decision problem outlined in the final scope issued by NICE. The ERG appreciates that APN311-302 is the best available study evaluating dinutuximab beta in maintenance therapy for high-risk neuroblastoma. Moreover, the study included a [redacted] proportion of people from the UK ([redacted]), and the enrolled population is representative of those likely to be eligible for treatment with dinutuximab beta in England and the wider UK.

1.4.1.2 Economic

The partitioned survival approach employed by the company is appropriate. The company included a range of scenario analyses which attempted to explore some of the methodological and structural uncertainty in the analysis.

1.4.2 Weaknesses and areas of uncertainty

1.4.2.1 Clinical

The ERG has concerns around several aspects of the evidence provided in support of the clinical effectiveness of dinutuximab beta, including the methodology of the systematic review process, the lack of direct evidence, the design and conduct of APN311-302, the lack of long-term follow-up for

APN311-302, and the observational nature of APN311-202 and APN311-303. Each point is reviewed in more detail below.

The ERG has some reservations about the validity of the search methods followed to identify relevant evidence. The company's search strategies did not include index terms specific to the individual electronic database. Instead, each search is limited to the use of free-text terms for population, intervention, comparator, outcomes and study design, with the same terms implemented in all searches. Not incorporating index terms could result in potentially relevant studies being missed by the search. In addition, free text terms were limited and did not include multiple terms to account for variation in punctuation and spelling. Screening of full-text publications was carried out by a single reviewer, with quality control of a sample of records undertaken by a second reviewer. If necessary, differences in opinion were discussed with a third reviewer. The percentage of records reviewed as part of the quality control in each screening step is unclear. As a single reviewer is likely to have reviewed most records, it is possible that some studies have been included or excluded in error. The ERG considers it likely that all key data on dinutuximab beta have been identified but has some concerns that studies evaluating comparators might have been overlooked, during both search and screening processes. The ERG considers methods implemented to search and appraise the literature for clinical effectiveness undermine the robustness of the company's systematic review process.

APN311-302 is open-label in design. It is unclear whether there was an independent review of disease status at baseline or during follow-up after treatment. Potential sources of bias associated with the open label design include reporting bias, and performance bias. Although adequately randomised, it is unclear whether attempts were made to conceal allocation, which, if not implemented sufficiently, could lead to selection bias. In addition, no time point for assessment of disease status during or after treatment was pre-specified. So, for EFS, it is unclear whether the exact point of disease progression is captured.

Data presented for APN311-302 do not adhere to the ITT principle. The ERG considers that the company has carried out the equivalent of a complete case analysis. The company could have performed an IT analysis either by simplistically assuming a best or worst case scenario for people with missing data or by implementing formal statistical techniques. Initially, 406 people were randomised but analyses are based on the final analysis set, which comprised 370 people for whom for whom an eCRF was available, who received allocated treatment and for whom treatment data were available. An eCRF was not available for 21 people. It is unclear why an eCRF was not available for all randomised patients, or why some people did not receive any treatment.

In APN311-302, dinutuximab beta was infused following the short-term schedule of administration over 5 days, whereas preference in UK clinical practice would be to infuse the immunotherapy

continuously over 10 days. Evidence assessing whether rate of infusion affects clinical outcomes is not available.

Importantly, the ERG has reservations about the KM data provided by the company. Although EFS and OS KM curves for APN311-302 seem to be valid, on investigating the supplied data, the ERG considers that the differences between the curves lack validity (Figure B; section 1.4.2.2). The ERG noted an inconsistency in the proportion of patients moving out of the OS and EFS KM curves in the APN311-302 study, which is discussed in more detail in Section 1.4.2.2.

The ERG considers the data from APN311-302 to be immature and the length of follow-up to be insufficient to determine fully the clinical effectiveness of dinutuximab beta, particularly whether any clinical benefit is maintained in the longer term. Additionally, there is a [redacted] between treatment groups in APN311-302 in [redacted]: based on data supplied by the company during clarification, the most recently captured event occurred at [redacted] follow-up in the group given IL-2 compared with [redacted] for the group not receiving IL-2.

As no direct evidence on dinutuximab beta-based treatment versus comparators of interest is available, all estimates of comparative clinical effectiveness are based on naïve indirect comparisons. Furthermore, comparative effect estimates are available for only OS. EFS was not captured during the R1 phase of APN311-302 or in Garaventa, and so evaluation of EFS is not feasible. In a suspended STA (GID-TAG507) evaluating dinutuximab alpha, it was noted that immunotherapy might delay rather than prevent events (EFS in Figure C, Section 1.4.2.2). Taking the previous ERG's opinion together with the relatively short length of follow-up available for APN311-302, the ERG considers that the lack of availability of EFS estimates results in an incomplete representation of the short- and long-term clinical effectiveness of dinutuximab beta-containing regimens versus isotretinoin.

In support of the ERG's reservations about the maturity of the data presented for dinutuximab beta, the ERG proposes that results on clinical effectiveness of dinutuximab alpha could aid in understanding the clinical effectiveness, particularly in the long term, of dinutuximab beta. Considering OS, as raised by the ERG assessing dinutuximab alpha, there seems to be an abrupt change in the OS curve for the immunotherapy after approximately year 7, as depicted in Figure D (Section 1.4.2.2). Importantly, longer-term follow-up available for dinutuximab alpha (12 years) indicate a marked increase in mortality in the dinutuximab alpha group between 6.5 and 9 years (Figure D) and that the observed data for the immunotherapy-containing regimen and isotretinoin seem to converge between 6.5 and 11 years. OS at 10 years is only marginally higher for those receiving dinutuximab alpha compared with those allocated to isotretinoin alone (approximately 59% with immunotherapy vs 52% with no immunotherapy), but this observation is based on sparse data and it is unclear whether the difference is

clinically meaningful (as reported by the ERG assessing dinutuximab alpha). The ERG acknowledges that data from ANBL0032 cannot be used to draw strong conclusions on the comparative effectiveness of dinutuximab beta.

In the CS, the company stated that an indirect treatment comparison involving dinutuximab beta was not possible due to the lack of comparable clinical trials. The ERG proposes that a matching-adjusted indirect comparison (MAIC) or simulated treatment comparison (STC), depending on the assumptions made on the underlying nature of the data being compared, is viable and would be informative on comparative clinical effectiveness of dinutuximab beta-based treatment with isotretinoin alone. Moreover, an appropriately adjusted indirect comparison of dinutuximab beta versus dinutuximab alpha would consolidate understanding of the clinical benefit of adding dinutuximab beta, with or without IL-2, to differentiation therapy. The ERG also considers it important to bear in mind the potential for diminishing of the clinical benefit of dinutuximab beta-based therapy over no immunotherapy in the long-term.

In terms of the studies forming the evidence base for relapsed neuroblastoma, APN311-202 and APN311-303 are single-arm observational studies and are, by nature, inherently at a high risk of bias. In addition, both studies have a small sample size in each subgroup of relapsed and refractory neuroblastoma, which leads to considerable uncertainty in any estimates of effect. Single-arm studies, such as APN311-202 and APN311-303, are not considered appropriate design to capture time to event outcomes, for example, EFS and OS.

No formal statistical hypotheses, statistical analysis methods or power calculations were specified *a priori* for either APN311-202 or APN311-303. In APN311-202, no clinical outcome was pre-specified as an outcome of interest to the study.

In APN311-303, a substantial amount of data, particularly for prognostic factors, were not captured and, despite a review of the data, could not be retrieved. The retrospective nature of APN311-303 and absence of data could lead to selection bias, and a lack of standardisation in data recording and outcome assessment.

The population of those experiencing relapse in APN311-202 and APN311-303 might not be representative of those with relapsed neuroblastoma in the UK. Most people experiencing relapse of neuroblastoma are likely to have had an initial diagnosis of high-risk neuroblastoma. In the UK, people with newly diagnosed high-risk neuroblastoma are likely to have received dinutuximab beta as part of their multimodal multiagent front-line treatment through participation in the HR-NBL-1 study. However, based on the company's response to clarification, [redacted] in APN311-202 or APN311-303

had previously received dinutuximab beta, and evidence on re-treatment with the immunotherapy is not available.

1.4.2.2 Economic

The ERG has serious concerns with the robustness of the economic analysis undertaken by the company. The updated version of the company's model provided to the ERG, incorporated paramount changes in calculations and assumptions, which were not reported or justified by the company (or requested by the ERG during the clarification stage). Thus, most of the ERG's critique is based on the inspection of the economic model and not on written evidence submitted by the company. The consequences of this are twofold: the ERG cannot guarantee that some aspects of the economic analysis and/or economic model were not missed; and there were several instances where the ERG had to make assumptions with regards to what was the company's approach. The ERG identified implementation and formulae errors in the updated economic model (described throughout the ERG report). The ERG is concerned that this reflects a poor level of internal quality assessment of the model by the company.

Overall, the company's modelling approach and model structure is unnecessarily burdensome and removes transparency from the formulae and calculations within the model. It is the ERG's view that the use of a decision-tree structure to estimate short-term outcomes was unnecessary, especially when the cohort data populating the decision-tree is taken from the cohort-based partitioned survival model. The decision-tree model is extremely difficult to navigate and has several circular references in its data implementation. All this makes the ERG's review unnecessarily complex. This also leads to a higher probability of errors in formulae, and a lower probability of all errors being identified during the ERG's review process. In total, the company's model was structured in three different model engines, the decision-tree model, the short-term partitioned survival model and the long-term partitioned survival model. The company could have simplified the model structure, and have a single cohort-based partitioned survival model, which would have been more efficient and transparent, and potentially avoided formulae, and calculation errors.

The company built two separate models, one for the high-risk population and the other for the relapsed or refractory population. Overall, the ERG considers that the evidence base for the relapsed model is not robust enough to inform the decision-making process.. Furthermore, the company clearly states that it does not support the use of dinutuximab beta for relapsed or refractory patients. Therefore, while Section 4 of the report presents the clinical results for the relapsed population, the economic section does not explore the relapsed model any further. The justification for the ERG's decision is based on the following:

1) The evidence for the relapsed population is extremely poor and unfit for purpose. Study APN311-202 and APN311-303 are very small studies and APN311-303 is a retrospective study (please see Section 4 for more details on the studies' quality assessment);

2) The analysis provided by the company after the clarification stage, reporting the fully adjusted HRs, produced a HR below 1 for the relapsed population (when using the APN311-202 study), suggesting that dinutuximab is less effective that isotretinoin for this population. Therefore, the results, and thus the model results lack clinical meaningfulness;

3) Clinical expert opinion sought by the ERG reported that in the UK, dinutuximab beta is always given as a first line treatment to patients and added that they would not retreat patients with dinutuximab beta unless there was evidence substantiating the effectiveness of dinutuximab as a retreatment option (given that the company decided to not carry on with studies in the relapsed or refractory population, such studies are not foreseeable);

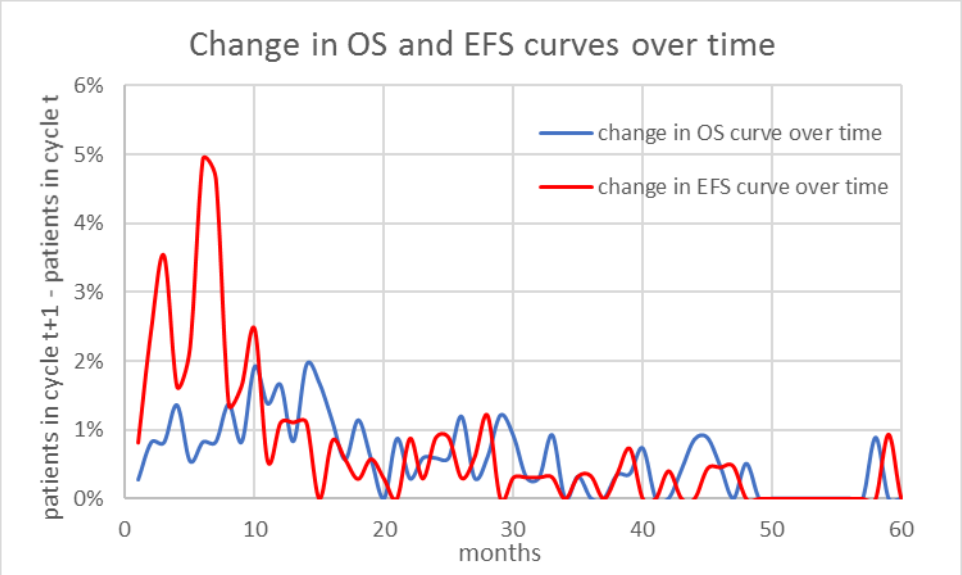
4) The company, in their reply to the ERG's clarification questions states that, "*given the lack of data for the use of dinutuximab beta EUSA in patients that may have already failed (relapsed) or those that are refractory to dinutuximab beta EUSA, EUSA Pharma does not support re-treatment with the drug*". The company adds that there are no on-going studies that evaluate the effectiveness of dinutuximab beta in relapsed or refractory patients;

The ERG has severe concerns with the estimation of treatment effectiveness in the economic analysis. These, stem mainly from three overarching issues. The first one is related to the lack of face validity of the OS and EFS KM data from APN311-302. The second relates to the lack of maturity of OS data and the non-existence of EFS data in historical control R1. Finally, the third issue relates to the naïve (unadjusted) analysis of the relative treatment effectiveness of dinutuximab beta, when compared with isotretinoin. The ERG summarises the key issues surrounding these aspects of the economic evaluation below:

1) The ERG investigated the KM data provided by the company in the model and noted an inexplicable inconsistency in the proportion of patients moving out of the OS and EFS KM curves in the APN311-302 trial. The ERG produced Figure B to show the proportion of patients in cycle t minus the proportion of patients in cycle t+1 in the OS and EFS KM curves in APN311-302. As the proportion of patients in the EFS and OS curves decreases over time (because patients progress or die), the difference in the proportion of patients each cycle is always positive (Figure B). The red curve in Figure B shows the proportion of patients who leave the EFS curve over time (representing the additional number of patients who progress, relapse or die in that cycle) and the blue curve shows the proportion of patients who leave the

OS curve over time (representing the additional number of patients who die that cycle). What would be expected is that the change in the EFS curve is always higher (or the same) as the change in the OS curve. This is because the OS curve only takes into account death events, while the EFS curve takes into account disease progression or relapse, second neoplasm and death events (according to the CS). Therefore, the ERG does not see any possible logical explanation for why the proportion of deaths in in the OS curve are higher than the proportion of deaths, added to the proportion of disease, relapse and neoplasm events (captured in the EFS curve). In Figure B, this is illustrated where the blue curve is above the red curve. This might be related with the company potentially misreporting the outcomes included in the KM curves (for example, if the EFS curve censored death events), or with the time intervals not being consistent across the OS and EFS curves. Either case is worrying, and removes the validity of the KM curves in APN311-302 provided by the company. Finally, the ERG is also concerned that the company did not provide numbers at risk to accompany the unadjusted KM data for APN311-302 and R1, despite the ERG's requests for these data at the clarification stage. In conclusion, the ERG considers that the uncertainty and the lack of face validity of the KM data from APN311-302 renders the use of these data inappropriate in the analysis. Using the fitted Gompertz curves to the KM data helps adding some face validity to the OS and EFS curves for dinutuximab beta, however, the fitted and extrapolated curves are still based on the underlying KM data from APN311-302, and are therefore, flawed.

Figure B. Change in OS and EFS KM curves over time



2) Equally concerning, is the fact that the company's model relies on the naïve (unadjusted) analysis of dinutuximab beta's relative effectiveness, compared with isotretinoin. As reported in the NICE Decision Support Unit's Technical Support Document 18, in the case of a

disconnected network of evidence, a naïve indirect comparison will include sampling error plus systematic error due to the imbalance in both prognostic factors and effect modifiers. In this case, children forming the historical control R1 were randomised in the R1 phase of HR-NBL-1 (see Section 4 for more details), which was designed to compare the effectiveness of BuMel versus CEM as consolidation myeloablative therapy in high-risk neuroblastoma. The consolidation treatment regimen included in the historical control R1 is, therefore, unlikely to be reflective of treatment received by UK neuroblastoma patients as half of the people in the R1 phase received CEM as their consolidation therapy. The clinical experts advising the ERG explained that in the UK, BuMel has become standard of care, and CEM is very rarely used given that BuMel has been shown to be a more effective consolidation therapy than CEM. This means R1 is likely to be a poor reflection of the maintenance treatment regimen for neuroblastoma patients in the UK, and that the clinical outcomes for R1 patients are negatively biased due to half of the patients receiving CEM instead of BuMel as consolidation therapy, before receiving isotretinoin. The implications of the latter are that the baseline health of the population receiving isotretinoin is likely to be poorer than that of the population receiving dinutuximab beta plus isotretinoin. In order to have a valid estimate of relative effectiveness of dinutuximab beta plus isotretinoin compared with isotretinoin, it needs to be adjusted for the type of consolidation therapy.

As part of the clarification process, the ERG requested that the company carry out an MAIC of the full trial population in APN311-302 versus the group receiving isotretinoin alone in the RCT published by Yu *et al*. (with the updated follow-up data from the dinutuximab alpha STA submission [GID-TAG507]), which would have constituted a better comparison than using R1 (and would have provided a source EFS data for the comparator arm). The company decided against carrying out an MAIC, and instead provided adjusted HRs for the indirect comparisons of OS in the APN311-302 study versus historical control R1, adjusting for prior treatment (BuMel vs CEM), MYCN status, and age and INSS stage at diagnosis. The ERG is concerned with the process underlying the estimation of the adjusted OS HR. Even though the ERG suggested that the company adjust the OS HR to take into account all the clinically relevant prognostic factors (prior treatment, MYCN status, and age and INSS stage at diagnosis), the ERG assumed that the company would undertake a stepwise approach in order to select the relevant prognostic factors. The company does not seem to have undertaken such approach, and thus it is unclear if the final OS HR included all the relevant covariates.

Considering the lack of robustness and appropriateness of the naïve comparison undertaken by the company in their updated analysis, allied to the fact that the company did not carry out an MAIC, the ERG could only use the adjusted OS HR as a means of improving the robustness of the company's naïve analysis, in the time given. Therefore, the ERG restructured the high-risk economic model to

incorporate the use of the OS HR ([redacted]) to estimate an OS curve for isotretinoin. From a methodological point of view, the ERG is uncertain if the use of HRs to estimate the isotretinoin arms of the model is a robust approach. An investigation of the PH assumption should have been undertaken by the company to substantiate the methodology of the analysis. Given the possibility that immunotherapy works in a different way from conventional chemotherapy, by potentially altering the disease pathway, it might be inappropriate to assume a constant HR between dinutuximab beta and isotretinoin. It is uncertain if the plateau that might be observed for immunotherapy agents is likely to be present for dinutuximab beta, and how this affects the comparison to isotretinoin.

As the ERG did not have any other available source of comparator data for EFS, it turned to the previous STA for dinutuximab alpha vs isotretinoin (GID-TAG507). Figure C and Figure D show the difference in OS and EFS KM curves when the latest data cut-off point became available for dinutuximab alpha and isotretinoin. The results show that the observed data for immunotherapy and standard therapy appear to converge between 4.5 and 11 years in the longer follow-up analysis. This could suggest that, had a longer follow-up period been allowed in APN311-302, the EFS and OS curves for dinutuximab beta would eventually drop to be closer to the EFS curve for isotretinoin. However, the unadjusted analysis of dinutuximab beta (Figure E and Figure F) shows a substantial separation of EFS and OS curves at around year 7. With regards to EFS, the ERG considers this separation to be unsubstantiated as it is not evidence-based (as R1 did not provide EFS data) and is very likely to represent an overestimation of the effect of dinutuximab beta in terms of preventing disease progression. Based on visual inspection of Figure C, long term EFS is only slightly better by 7% among immunotherapy patients (approximately 52% vs 45%) at 10 years. Despite the apparent difference between the two curves, this was not found to be statistically significant (p-value for log rank test: 0.153 as stated in the dinutuximab alpha ERG report).

Figure C. Observed EFS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis (Figure 19 in ERG report for dinutuximab alpha STA [GID-TAG507], page 86)

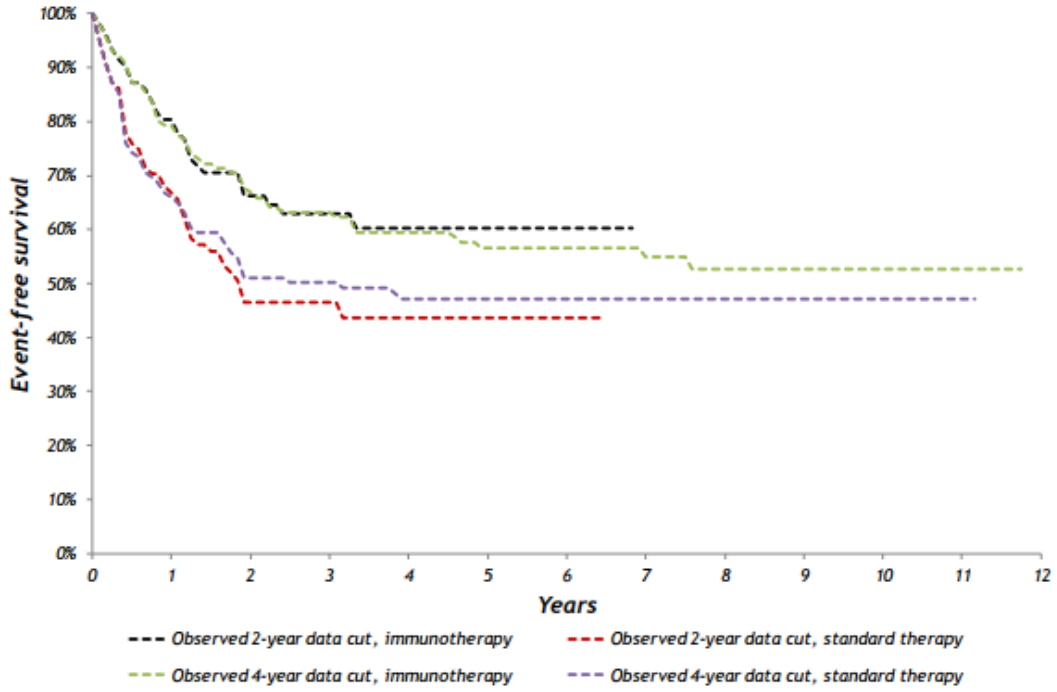


Figure D. Observed OS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis (Figure 20 in ERG report for dinutuximab alpha STA [GID-TAG507], page 87)

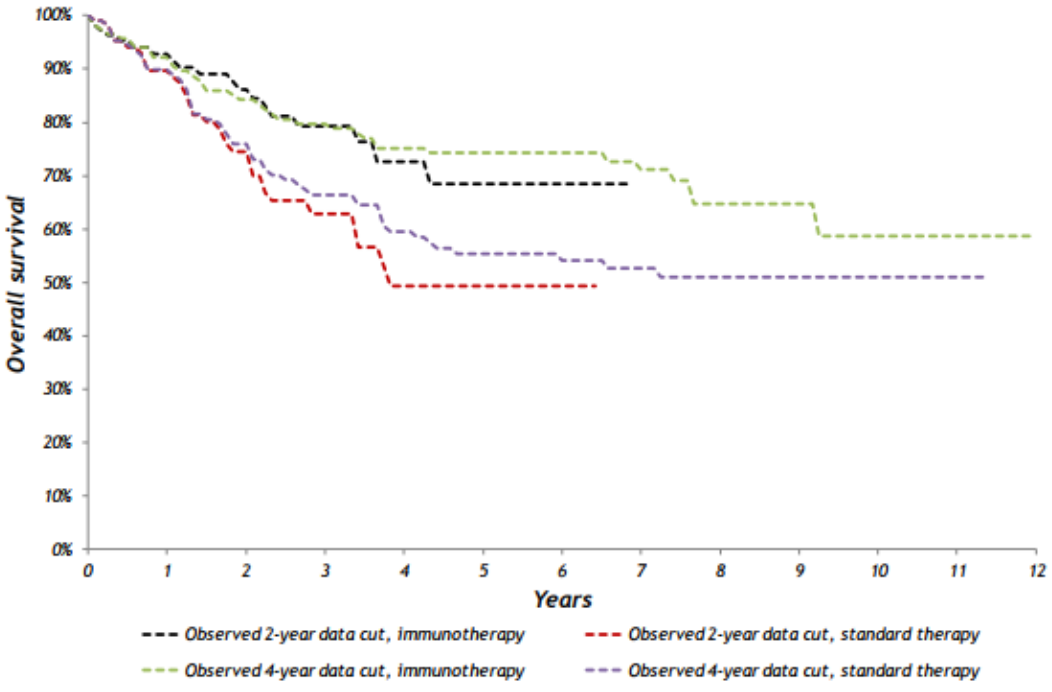


Figure E. Unadjusted EFS curve for dinutuximab beta and estimated unadjusted EFS curve for isotretinoin.

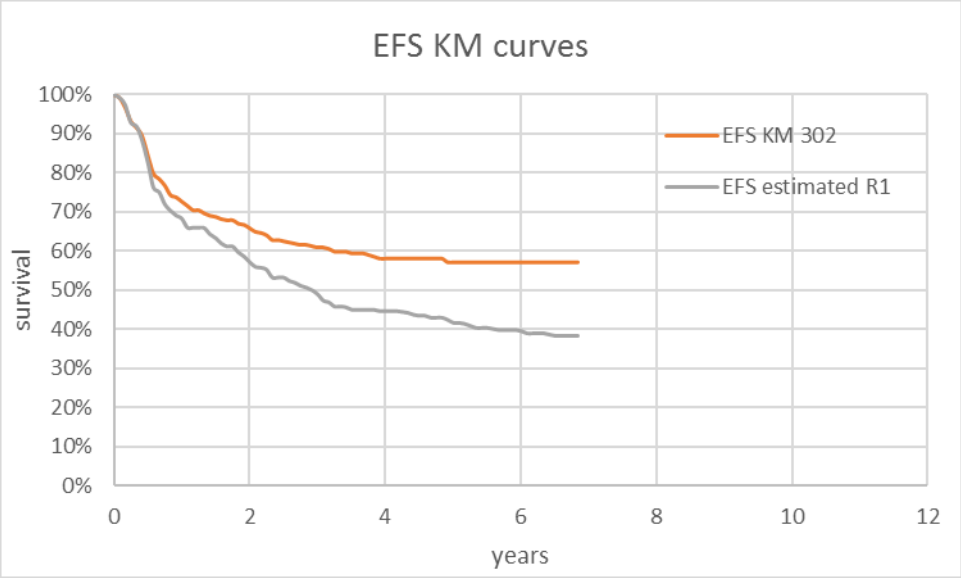
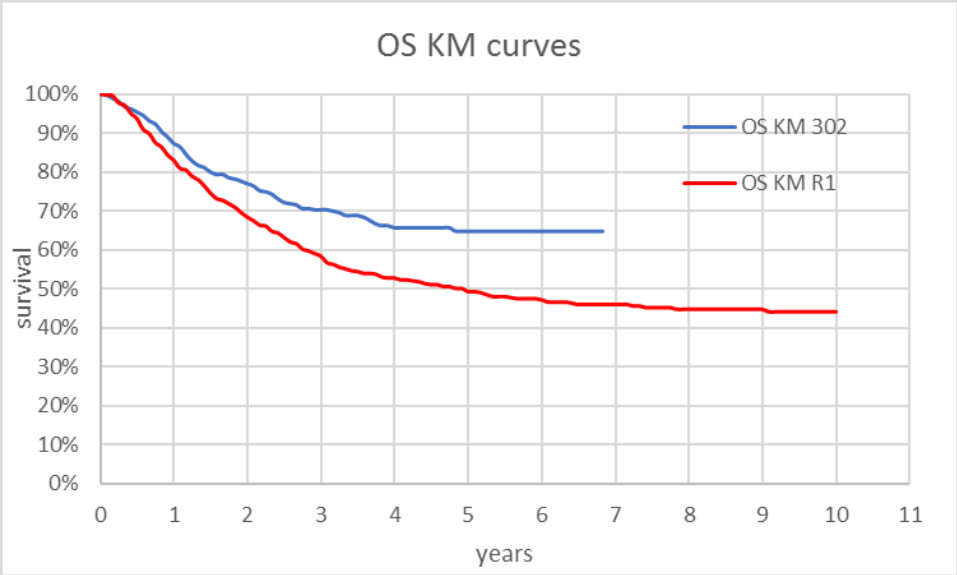


Figure F. Unadjusted OS KM curves

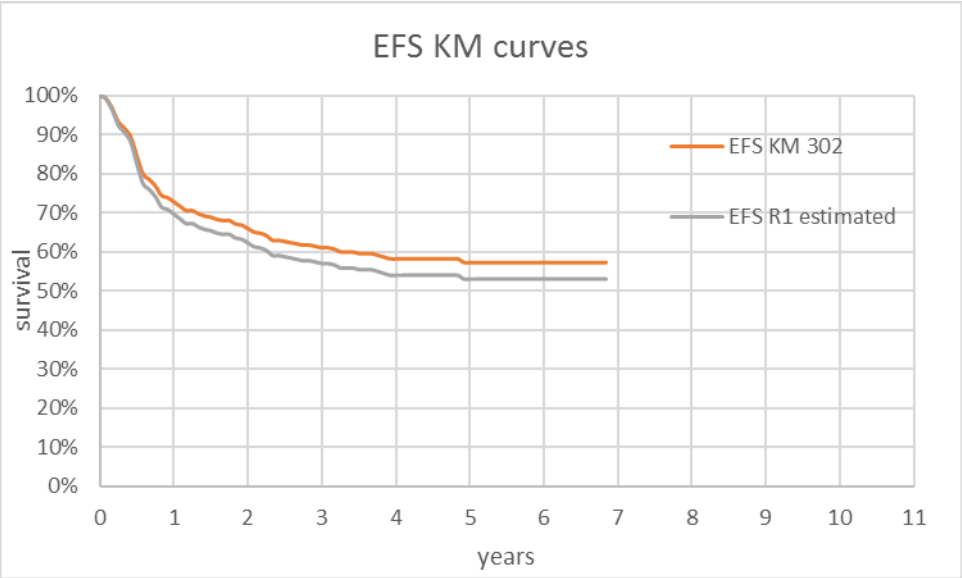


The ERG took the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission and applied it to the adjusted OS HR estimated for dinutuximab beta. The ERG estimated EFS HR for dinutuximab beta compared with isotretinoin is 1.656/1.319*[redacted]=[redacted].

The ERG acknowledges that the underlying assumption in the ERG's approach is that there is a constant relative risk between EFS and OS for dinutuximab alpha, and furthermore, that the latter relationship is also only observed for dinutuximab beta vs isotretinoin. This is a caveat to the ERG's approach as not only are these assumptions strong, but also the ERG has no evidence to corroborate these. However, the ERG notes that these were the best available data to overcome undertaking a naïve analysis of treatment effectiveness in the model.

After applying the HR of [redacted] to estimate the EFS curve for isotretinoin, the ERG arrived at the curves shown in Figure G. At year 7, the EFS curves seem to be separated by approximately 4% (57% vs 53%). This separation, albeit smaller than the 7% shown in Figure C, is likely to be a better approximation of the relative effectiveness of dinutuximab beta compared with isotretinoin than the 20%, shown in Figure E (resulting from non-evidence based assumptions made by the company, as R1 did not provide EFS data). Finally, the separation of the curves is also linked to the use of a HR to estimate the EFS curve for isotretinoin. As previously mentioned, the ERG cannot be certain if this is a correct methodological approach in this case.

Figure G. Unadjusted EFS curve for dinutuximab beta and estimated isotretinoin EFS curve with adjusted HR



The ERG also notes that about 50% of patients in Figure C were event-free at year 11, regardless of having received dinutuximab alpha or not. With regards to the other 50% of patients, who have progressed, it could be hypothesised that dinutuximab alpha delays, rather than prevents a further event. While it would appear that patients receiving isotretinoin experience the majority of their events over the first two years, a considerable number of events experienced by patients receiving dinutuximab alpha occur between year 2 and year 7. The ERG sought clinical expert opinion with regards to the role

of dinutuximab beta in preventing or delaying events. The clinical experts advising the ERG confirmed that dinutuximab beta was expected to delay events, rather than prevent them.

The ERG's proposed alternatives to overcome the several methodological shortcomings of the company's analysis are, to some degree, flawed, when considered in isolation (for example an assumption of proportional hazards in order to use HRs). However, when combined and incorporated in the final analysis, the synergies resulting from the individual changes made by the ERG, contribute to an increase in the level of uncertainty in the analysis. The ERG summarises the main methodological changes undertaken in Table D.

Table D. Summary of fundamental problems in CS and ERG's ammendmants

	Problem in CS	**ERG's amendment**	**Level of mitigation**	**Proposed approach**
	OS and EFS KM curves for dinutuximab beta, taken from APN311-302, are unreliable and unfit for purpose	Use Gompertz curves to predict OS and EFS for dinutuximab beta in the model	Problem not mitigated. While using the Gompertz curves helps increasing the face validity of the curves, the underlying data are flawed rendering the shape of curves equally unreliable (which is illustrated by the EFS curve crossing the OS curve).	The company needs to assess the reason for the problem of the inconsistency in the relationship between the OS and EFS KM curves in APN311-302
	Naïve comparison of OS data	Use of adjusted HR for OS	Problem partially mitigated. Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis. However, the HR estimation method is flawed and it is unlikely that the use of HRs is an appropriate method of analysis.	An indirect comparison of dinutuximab beta versus isotretinoin and versus dinutuximab alpha should be undertaken. The major methods outlined in the DSU TSD18 applicable in this case are an MAIC and/or an STC. The ERG considers that, depending on what assumptions are made on the nature of the data being compared (e.g. whether proportional hazards hold), an MAIC or an STC will be the most appropriate method to use (please see Section 4 for more details)
	Naïve comparison of EFS data + lack of EFS data for isotretinoin in historical control R1	Taking the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission and applying it to the adjusted OS HR estimated for dinutuximab beta.	Problem partially mitigated. Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis, through the adjusted OS HR. However, the EFS HR carries the same flaws as the OS HR. Furthermore, it relies on the naïve comparison of the relative treatment effectiveness of dinutuximab alpha vs isotretinoin and isotretinoin beta vs isotretinoin.	
Robustness of the final analysis	Economic analysis unfit for purpose. Resulting ICERs are meaningless	Economic analysis unfit for purpose	Problem partially mitigated	As above

When applying the OS and EFS HRs to the dinutuximab beta curves, the ERG obtained the curves shown in Figure I. The fact that the relative positioning of the dinutuximab beta curves (Figure H) was maintained, allied to the fact that the OS HR and the EFS HR used in the ERG's analysis come from different data sources (thus different populations), leads to the fact that the final relationship between the isotretinoin OS and EFS curves has different and cumulative layers of embedded uncertainty. This is illustrated by the EFS curve crossing the OS curve at approximately 70 months. The ERG had to subsequently cap the EFS curve by the OS curve in the isotretinoin arm of the model.

In conclusion, the ERG does not consider that the changes made to the company's model are robust enough to provide results suitable for robust decision making. The economic analysis needs reconsideration before a meaningful ICER can be produced.

Figure H. Gompertz OS and EFS curves for dinutuximab beta

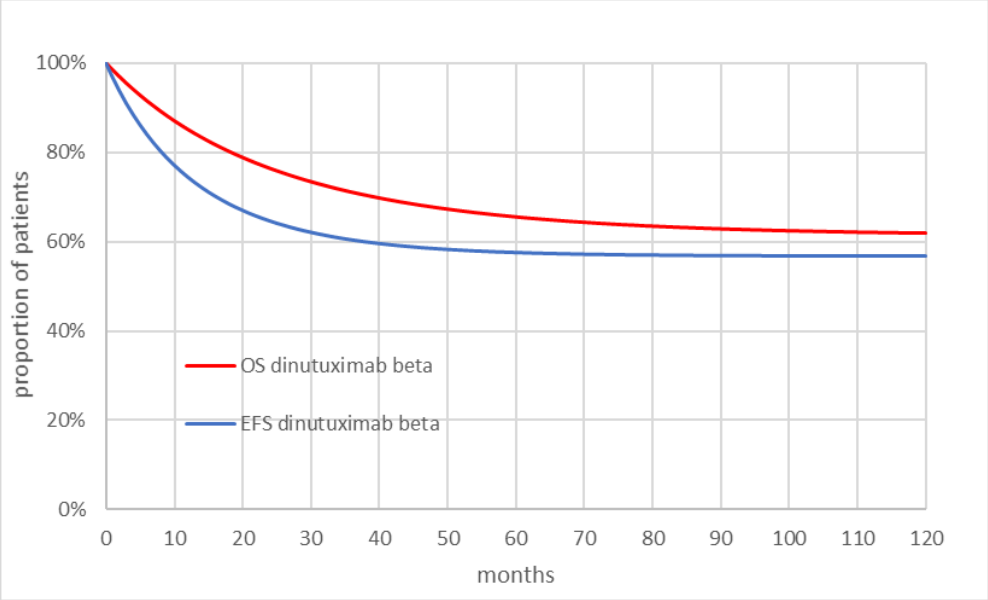
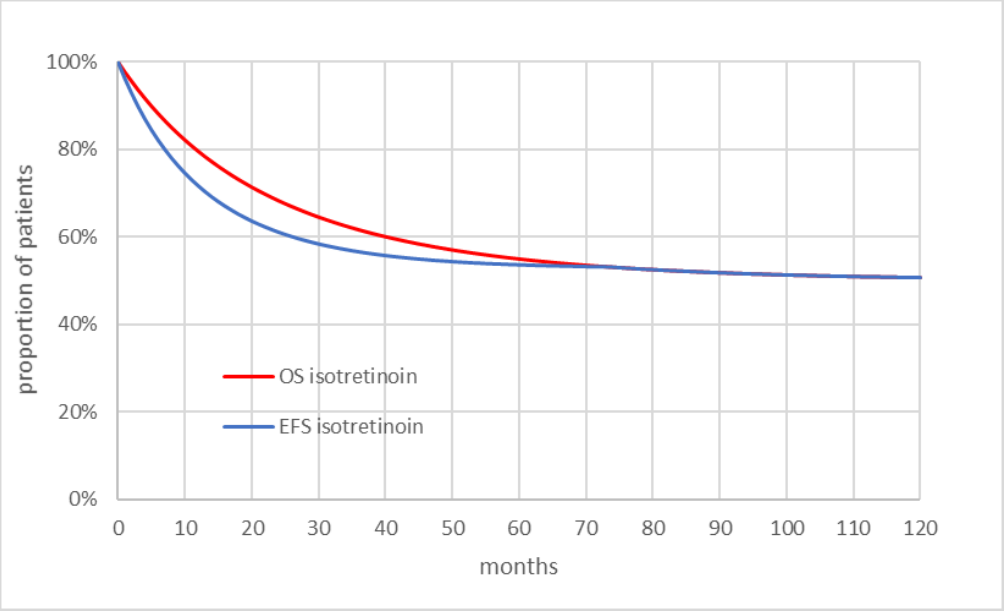


Figure I. Gompertz OS and EFS curves for isotretinoin



The ERG identified issues relating to the estimation of costs and utility values in the economic analysis. These, however, only become relevant once the aforementioned fundamental issues are addressed.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.5.1 Economic

The ERG describes the errors found in the company's analysis throughout Section 5 of the report. The company's base case ICER rose from £22,338 to £31,366 per QALY gained, when the ERG corrections were applied.

As the ERG disagrees with carrying out a naïve analysis of treatment effectiveness, two additional corrections were implemented in terms of relative treatment effectiveness in the model:

1. Restructuring the high-risk economic model to incorporate the use of the OS HR ([redacted]) to estimate OS for isotretinoin.

2. Using the relative difference between the OS HR and the EFS HR (for dinutuximab alpha compared with isotretinoin) in the dinutuximab alpha submission and applying it to the adjusted OS HR estimated for dinutuximab beta of [redacted]. To note is that the EFS HR for dinutuximab alpha vs isotretinoin was found to be not statistically significant in the dinutuximab alpha STA. The ERG's estimated EFS HR for dinutuximab beta compared with isotretinoin is 1.656/1.319*[redacted]=[redacted];

Furthermore, the ERG replaced the dinutuximab beta KM curves for OS and EFS by the fitted and extrapolated Gompertz curves in the short-term model, in order to estimate OS after the 7-year KM OS curve, and also to try and minimise the structural issues found in the KM data from APN311-302. In doing so, the ERG had to subsequently cap the EFS curve by the OS curve in the isotretinoin arm of the model as the curves cross in the model at approximately 70 months.

Using the Gompertz survival curves and the OS and EFS HRs to estimate relative treatment effectiveness in the model leads to an ICER of £111,858 per QALY gained (with all the ERG's corrections incorporated in the analysis).

The ERG considers that while some of the amendments made to the model provide step changes in the right direction, when combined in the final analysis these produce inconsistent outcomes and introduce a paramount level of uncertainty in the analysis. Therefore, the ERG does not consider that the changes made to the company's model are robust enough to produce an ICER fit for purpose and emphasises that the final ICER of £111,858 is provided for illustrative purposes only.

Given the ERG's assessment that the departing ICER of £111,858 is fundamentally flawed, the ERG did not proceed to implement further scenario analyses as all the resulting ICERs. The ERG lists below the analyses that would be required to explore further uncertainty in the economic model, once the base case ICER is robust enough to be used to carry sensitivity analysis:

1. Changing the assumption that patients entering the failure state of the economic model receive chemotherapy for the rest of their lives. In the base case model, some patients receive chemotherapy for more than 20 years, which is not clinically plausible. Therefore, the partitioned survival model should be changed to estimate newly progressed patients in both the dinutuximab beta and isotretinoin arms of the model. Once newly progressed patients are estimated, an assumption needs to be made for treatment duration. For example, it could be assumed that relapsed patients would stay on treatment for a maximum of one year. An assumption should also be made for the resource use required to manage relapsed patients who have gone off chemotherapy treatment, but are still alive and in the failure state;

2. The cost estimations regarding the chemotherapy regimens used in the failure state should include wastage;

3. The cost of treatment administration in the failure state should use the cost of an inpatient stay (£4,670 for five days), instead of procurement cost for chemotherapy drugs, which is used in the base case model (£2,620.54);

4. Concomitant medication costs in the stable state should include wastage for gabapentin;

5. The proportion of patients receiving IL-2 in the dinutuximab beta arm of the model should be explored. Instead of assuming that 51% of patients received IL-2 (as per APN311-302), the assumption that 41% of patients would receive IL-2 should also be explored. This is to reflect the fact that 41% of children in APN311-302 had residual disease at baseline and therefore would require IL-2 as a concomitant medication, as per dinutuximab beta's licence;

6. The previous STA for dinutuximab alpha (GID-TAG507) reported a published algorithm by Ara *et al.* 2010, which was used to estimate mean EQ-5D HSUVs for individuals in the general population, using a multiple regression including gender, age and age^2 as covariates. The ERG considers this method to be more appropriate than using a logistic regression, as it produces utility values rather than probabilities and is based on a published, peer-reviewed methodology. Therefore, the ERG recommends that the logistic regression in replaced with the published multiple regression to estimate age-specific UK EQ-5D in the model;

7. Given that BSA is one of the key drivers of costs in the economic model, a weighted analysis of costs taking into consideration the proportion of patients falling into different BSA categories would be advisable (for example, while in patients with an average BSA of 0.63m^2, 4 vials of dinutuximab beta are required, in patients with a BSA greater than 0.83m^2, 6 vials may be required to achieve the recommended dose for dinutuximab beta);

8. A discount rate of 3.5% (instead of 1.5%) for costs and benefits should be used to explore structural uncertainty in the analysis;

9. Probabilistic sensitivity analysis should be undertaken to incorporate the impact of varying relative treatment effectiveness estimates on the final ICER.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

In Section 1.3 of the company submission (CS), the company provides an overview of some of the key aspects of neuroblastoma, including prevalence, a description of the different classifications of risk of the condition (very low, low, intermediate and high risk), which denotes baseline level of risk of recurrence, and the corresponding treatment pathways for the various risk categories. The final scope issued by the National Institute for Health and Care Excellence (NICE) for this Single Technology Appraisal (STA) indicates the population of interest to the decision problem to be people with high-risk neuroblastoma previously treated with myeloablative therapy and autologous stem cell transplant (ASCT).[1] Relapsed and refractory neuroblastoma are listed as subgroups of interest.

Overall, the Evidence Review Group (ERG) considers the CS to present a reasonable overview of neuroblastoma that is relevant to the decision problem. However, the ERG considers that additional information on the impact of neuroblastoma on the quality of life (QoL) of people with the condition and their carers, both in the short- and long-term, together with greater detail on the distinction between newly diagnosed and relapsed or refractory neuroblastoma would aid in understanding the challenges faced in treating the population that is the focus of this STA, and the discussion of clinical effectiveness of dinutuximab beta. Here, the ERG provides a summary of the underlying health problem with supplementary information on the areas outlined.

As stated in the CS, neuroblastoma predominantly affects children, and is the most frequent form of cancer to be diagnosed in the first year of life.[2] Most children diagnosed with neuroblastoma are younger than five years, and the median age of diagnosis is 18 months.[3] Neuroblastoma is the most common solid tumour in children that occurs outside the brain and makes up 8% of the total number of children's cancers.[4] Cancer Research UK reports the annual incidence of neuroblastoma in the UK to be approximately 80 to 100 cases per year.[3] As with many cancers, the exact cause of neuroblastoma is unknown. It is known that a neuroblastoma develops from neuroblasts, which are cells within the embryonic sympathetic nervous system, creating tumours in the adrenal glands and/or the sympathetic ganglia. Neuroblastoma tumours have a high rate of metastatic disease, with nearly 50% of tumours at diagnosis being metastatic, with the most common metastatic sites being bone, bone marrow and the liver.[5]

The most common symptoms experienced by children with neuroblastoma are abdominal pain, distention and discomfort, particularly with the presence of an abdominal mass (summarised in Table 1).[3] The symptoms are largely dependent on the location of the primary tumour and metastatic sites.

Table 1. Neuroblastoma clinical signs and symptoms (adapted from CS, Table 3 [pg. 12])

Common clinical signs & symptoms (depends on the location of primary tumour and locoregional/metastatic sites)			
• Palpable abdominal mass • Abdominal distention • Digestive problems • Discomfort • Pain • Bone pain/limping • Headache • Numbness or weakness	• Fever • Weight loss • Nausea, vomiting • Pallor or bleeding • Renal impairment • Sweating • Paralysis (from spinal cord compression)	• Protruding eyeball (proptosis) • Blindness • Periorbital bruising/swelling • Drooping eyelid (ptosis) • Dizziness • Respiratory distress • Dysphagia	• Circulatory problems • Coagulation disorders • Constipation • Diarrhoea • Problems with urination • Bladder or bowel dysfunction • Hypertension

Neuroblastoma is diagnosed with a combination of radiographic imaging, laboratory tests and pathology.[5] Additionally, in suspected cases of neuroblastoma, a patient's urine is tested for biomarkers known to be secreted by the tumour (catecholamine degradation products, homovanillic acid and vanillylmandelic acid).[2] Biomarkers are often used to monitor the status of the disease, especially in less severe cases, such as very low or low risk neuroblastoma. If the person has an abdominal mass, an ultrasound scan is often performed as an initial step, followed by further imaging, including computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen. Imaging using mIBG (meta-iodobenzylguanidine), a radiolabelled isotope, is often used to identify the spread of metastatic sites and is typically implemented before surgery.[5]

The prognosis of neuroblastoma is related to several factors that are associated with a person's risk of relapse, which have been identified as age at diagnosis, clinical stage of disease, amplification of myelocytomatosis viral-related oncogene (MYCN), tumour cell histology and chromosomal aberrations (e.g., 1p deletion or 11q deletion).[2] MYCN amplification is a particularly important prognostic factor, being associated with more aggressive tumours and a poorer rate of survival:[5] MYCN amplification is detected in 20% of neuroblastoma tumours.[6] Additionally, infants diagnosed before the age of 12 months have a better prognosis than those diagnosed at a later age.[7]

Two common tumour staging systems used to stratify neuroblastoma risk are the International Neuroblastoma Staging System (INSS; Table 2) and the International Neuroblastoma Risk Group Staging System (INRGSS; Table 3). INSS staging is assessed after surgery and is based on the extent of tumour removal, whereas INRGSS staging is based on pre-treatment diagnostic images. As a post-surgery assessment, the INSS is strongly dependent on the approach of the individual surgeon. Consequently, the INRSGG was developed to establish a consensus approach for pre-treatment risk stratification.[2] Based on clinical stage of tumour and other prognostic factors, a person is designated as being at very low, low, intermediate or high risk of relapse: risk as determined by INRGSS in combination with other prognostic factors is presented in Appendix 10.1 of the ERG report. The treatment approach for neuroblastoma, either pre- or post-surgery depending on the staging system used, is predominantly determined by a person's designated risk of relapse.

Table 2. International Neuroblastoma Staging System (adapted from CS, Table 4 [pg. 14])

Stage	Description
1	Localised tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour could be positive)
2A	Localised tumour with incomplete gross excision; representative ipsilateral non-adherent lymph nodes negative for tumour microscopically
2B	Localised tumour with or without complete gross excision, with ipsilateral non-adherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes should be negative microscopically
3	Unresectable unilateral tumour infiltrating across the midline, with or without regional lymph node involvement; or localised unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, or other organs (except as defined by stage 4S)
4S	Localised primary tumour in infants younger than 1 year (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, or bone marrow (<10% malignant cells)
Abbreviations: CS, company submission; pg, page.	

Table 3. International Neuroblastoma Risk Group Staging System (adapted from CS, Table 5 [pg. 14])

Stage	Description
L1	Localised tumour not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment (neck, chest, abdomen, or pelvis)
L2	Locoregional tumour with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS). Non-regional (distant) lymph node involvement is metastatic disease.
MS	Metastatic disease in children <18 months, with metastases confined to skin, liver, and/or bone marrow
Patients with multifocal primary tumours should be staged according to the greatest extent of disease as defined in the table. Abbreviations: CS, company submission; pg, page.	

Most people are diagnosed with high-risk neuroblastoma (Table 4), and their prognosis is poor.[6] Less than 50% of people categorised as high-risk achieve 5-year event-free survival (EFS; Table 4), and, even after myeloablative chemotherapy, 5-year overall survival (OS) in this stratum is only 40%.[8] About 20% of people with high-risk neuroblastoma progress early or are refractory to induction therapy, and 50% of people who achieve remission subsequently relapse.[8,9] Across all strata of risk of relapse, 5-year OS from time of first relapse is only 20%.[10] In those who relapse, irrespective of initial level of risk, time to relapse is a strong predictor of survival. People who relapse at between 6 and 18 months after initial diagnosis have a poorer prognosis than those who relapse at a later time point.[10] A study evaluating the outcome in people with relapsed or refractory neuroblastoma reported a median OS from study entry for refractory and relapsed patients of 27.9 (standard deviation [SD] 20.2) months and 11.0 (SD 1.6) months, respectively ($p = 0.03$).[11] The ERG's clinical experts fed back that those with refractory neuroblastoma have a better prognosis than those experiencing relapse because refractory disease advances at a slower pace and, after additional rounds of treatment, eventually a complete response or a very good partial response to therapy is likely to be achieved, and the person can move

on to receive consolidation therapy. By contrast, neuroblastoma that has returned after remission progresses more rapidly and is more difficult to treat.

Table 4. Proportion of people, together with 5-year event-free survival, in risk strata (adapted from Cohn *et al*. 2009[6])

Pre-treatment risk group	Proportion of people in group (%)	5-Year event-free survival (%)
Very Low	28.2	>85
Low	26.8	>75 to ≤85
Intermediate	9.0	≥50 to ≤75
High	36.1	<50

Research into relapsed and refractory neuroblastoma is confounded by disparity across studies in several areas, including definitions for relapsed and refractory neuroblastoma.[11] Additionally, studies differ in terms of eligibility criteria, with some studies not only including people with measurable soft tissue disease assessed by cross-sectional imaging and defined as per Response Evaluation Criteria in Solid Tumors (RECIST) but also those with evaluable disease assessed by uptake on mIBG scan or bone marrow histology.[11] Criteria implemented to determine response to treatment also vary across studies.[11] The ERG's clinical advisors highlighted that, at this time, there are no universally accepted definitions for relapsed and refractory neuroblastoma. The ERG's clinical advisors emphasised that those with relapsed disease are clinically distinct from those who are refractory to treatment and stressed that they consider it important to consider the two groups as discrete populations. Across studies, relapse is commonly defined as those who experience relapse or progression after achieving a complete or partial response to treatment (response criteria available in Table 5), whereas refractory neuroblastoma is frequently classed as disease not responding to front-line therapy (e.g., no response, mixed response, or insufficient partial response but without relapse or progression).[11]

The ERG's clinical experts additionally advised that the definition of refractory neuroblastoma might differ between a clinical trial and clinical practice. Within a clinical trial, refractory might be defined as not achieving an adequate response to induction therapy (Figure 1), which could include those who have achieved a partial response to treatment. By contrast, in clinical practice, patients with a partial response are unlikely to be classed as refractory and would be eligible for subsequent consolidation chemotherapy. In either setting, patients that have a response to induction therapy that is poorer than desired will typically undergo additional cycles of chemotherapy before proceeding to consolidation therapy: response to treatment is typically categorised as per International Neuroblastoma Response Criteria (Table 5). Based on the clinical expert's feedback, the ERG considers that people with refractory disease as defined in the clinical trial setting could have a better prognosis than those of the same status in clinical practice as the group could include those achieving partial response.

Table 5. International Neuroblastoma Response Criteria[12]

Response	Primary site	Metastatic site(s)
Complete response	No evidence of tumour	No evidence of metastatic disease Catecholamines normal
Very good partial response	Decreased by 90–99%	No evidence of metastatic disease Residual bone scan changes are allowed
Partial response	Decreased by >50%	All measurable sites decreased by >50% Bones and bone marrow: number of positive sites decreased by >50% and no new lesions present; no more than one positive bone marrow site allowed (if this represents a reduction in the number of sites originally positive for tumour at diagnosis)
Mixed response	No new lesions; 50%–90% reduction of any measurable lesion (primary or metastatic) with <50% reduction in other lesions and <25% increase in any existing lesion	
No response or stable disease	No new lesions; <50% reduction but <25% increase in any existing lesion	
Progressive disease	Any new lesion; Increase in any measurable lesion by >25%; previous negative bone marrow now positive for tumour	

The CS did not include a description of the impact of neuroblastoma on the QoL of people with the disease or their families and carers. In the long-term, neuroblastoma has been shown to adversely affect the physical and academic performance,[13,14] activities of daily living, and psychosocial functioning[15] of people with active disease[13] and those who have survived. For parents and families of a person with neuroblastoma, coping with and adapting to a child with the condition is challenging and can put a strain on parents' mental health, with increased reports of post-traumatic stress disorder, anxiety and depression among parents of a child with cancer.[16,17] Healthy siblings of those with neuroblastoma can also suffer from psychological distress that can result in increased risk of experiencing psychological issues later in life.[18]

In addition to the effects of neuroblastoma itself on QoL, exposure to the intensive multiagent multimodal therapies required to treat the disease can potentially lead to physical complications in the long-term (about 5 years after diagnosis). Treatment-related effects are dependent on therapies and doses received, as well as age at start of treatment. Potential complications developing in the long-term associated with treatment include hearing loss, learning difficulties, occurrence of other cancers and heart and lung problems.[19,20] A study comparing people with neuroblastoma with siblings without the disease found that those undergoing treatment for neuroblastoma were at an increased risk of musculoskeletal, neurological, sensory, and endocrine complications.[20] Additionally, people who had received multimodality therapy (surgery with radiotherapy and/or chemotherapy) rather than surgery alone were twice as likely to develop chronic health conditions (Relative Risk of 2.2, 95% Confidence Interval: 1.6 to 3.0).[20] Moreover, neuroblastoma survivors were less likely than siblings to have ever been employed or to be married, and had a lower personal income.[20] It is noted that the survivors of

neuroblastoma included in the study were diagnosed between 1970 and 1986 and so had not been exposed to some of the treatment options available today, including anti-GD2 monoclonal antibodies.

2.2 Critique of company's overview of current service provision

The company presents an appropriate overview of the widely accepted treatment strategies for the different risk strata of neuroblastoma, as well as relapsed and refractory disease, including reporting of the treatment options available at each stage. References cited in support of the treatment strategies are narrative reviews. No clinical guideline published by an organisational body is cited in support of the treatment pathway, and no mention is made of consultation with clinical experts based in England and the wider UK. However, the ERG appreciates that there is a limited number of guidelines on the treatment of neuroblastoma: the ERG identified only one guideline published by the National Cancer Institute.[21]

As the company comments, NICE guidelines or pathways on the management of neuroblastoma are not available. The company identified NICE guidelines advising on how to approach suspected cancer in children, which do not contain specific guidance for neuroblastoma:

- improving outcomes in children and young people with cancer a NICE cancer service guideline (CSG7);[22]
- cancer services for children and young people a NICE quality standard (QS55);[23]
- suspected cancer: recognition and referral a NICE guideline (NG12).[24]

The ERG's clinical advisors highlighted that guidance for clinicians in the UK on the management of neuroblastoma has been published by the Children's Cancer and Leukaemia Group (CCLG). The clinical guideline is not available to non-members of the CCLG.[25] The ERG's clinical advisors outlined the treatment pathway to the ERG, and a patient summary is available on the CCLG website.[4] The pathway outlined by the ERG's clinical advisors aligns with that presented by the company in the CS.

2.2.1 Management of neuroblastoma

People with neuroblastoma that has been categorised as very low, low or intermediate risk of relapse and responds to induction treatment are not relevant to the decision problem that is the focus of this STA.[1] Here, the ERG focuses reporting on treatment of first-line high-risk neuroblastoma, and relapsed and refractory disease.

In brief, treatment options for those with very low- or low-risk neuroblastoma include:[5,21]

- observation without biopsy (particularly for those aged <12 months of age as tumours can spontaneously regress and for perinatal neuroblastoma with small adrenal tumours);
- surgery followed by observation;
- chemotherapy with or without surgery (for symptomatic disease or unresectable progressive disease after surgery);
- radiation therapy (only for emergency therapy).

People with intermediate-risk neuroblastoma undergo a combination of chemotherapy and surgery, if possible, to resect the primary tumour. If people have an unfavourable genomic profile, they might be given more intensive regimens, including radiotherapy.[5] For those with intermediate-risk neuroblastoma, treatment options include:[21]

- chemotherapy with or without surgery;
- surgery and observation (in infants);
- radiation therapy (only for emergency therapy such as progressive disease or life-threatening tumours that have not responded sufficiently rapidly to chemotherapy or surgery).

2.2.1.1 High-risk neuroblastoma

In the CS, the company outlines a three-phase treatment approach for people with high-risk neuroblastoma that consists of induction, consolidation and maintenance stages. The ERG's clinical advisors fed back that the multiphase strategy described by the company accurately reflects the stepwise treatment of high-risk neuroblastoma outlined in the guideline issued by the CCLG (Figure 1).

Intensive induction chemotherapy is given with the goal of reducing the size of the tumour to facilitate removal of as much of the primary tumour as possible during surgery. In the UK, the most common induction chemotherapy regimens are rapid COJEC and modified N7. Rapid COJEC involves an infusion of a combination of five agents (cisplatin, vincristine, carboplatin, etoposide and cyclophosphamide) given for 8 cycles separated by intervals of 10 days, and treatment is completed within 70 days from the first to the last drug administered.[26] The advantage of rapid COJEC compared with standard COJEC is that chemotherapy is administered over a shorter time, which might improve survival.[26] Like rapid COJEC, the modified N7 regimen also comprises five chemotherapy agents, with doxorubicin substituted for carboplatin (modified N7, cyclophosphamide, doxorubicin, vincristine, cisplatin and etoposide). Modified N7 is infused over 3–4 days every 3 weeks for a total of 5 cycles.

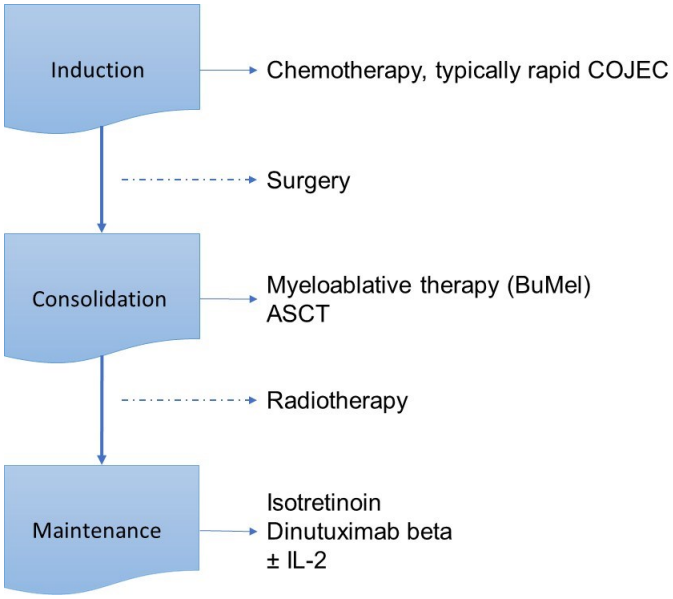
After induction chemotherapy, people might undergo surgical resection to remove any remaining visible tumour.

Next, people undergo consolidation therapy to the site of the primary tumour and residual metastatic sites to eradicate minimal residual disease. Consolidation treatment comprises lethal doses of chemotherapy, known as myeloablative therapy, followed by ASCT of a person's stem cells that were collected during induction: myeloablative chemotherapy depletes blood-producing cells in the bone marrow, and so people undergo ASCT to restore the lost cells. After publication of results from the HR-NBL-1 trial, BuMel (busulfan and melphalan hydrochloride) became the standard myeloablative chemotherapy.[27] After ASCT, people might receive external radiotherapy to remove microscopic tumours at the primary site or at metastatic sites.[28]

The final stage in treatment is the maintenance phase, the goal of which is to reduce the likelihood of growth of new tumours and the return of the neuroblastoma. Standard of care during the maintenance phase involves two types of treatment given in concert, one is a differentiation agent and the second is an immunotherapy. Differentiation therapy is thought to aid the maturation of cancer cells into normal cells, and the standard agent in the UK is isotretinoin (also known as 13-cis-retinoic acid). Immunotherapy is thought to help a person's immune system to recognize and destroy neuroblastoma cells more effectively. In 2010, an RCT comparing an immunotherapy-based regimen versus isotretinoin alone in high-risk neuroblastoma found a statistically significant improvement in EFS at 3 years in the group that received immunotherapy.[29] The immunotherapy assessed in the RCT was dinutuximab (for clarity, hereafter referred to as dinutuximab alpha), an anti-GD2 monoclonal antibody. Publication of the results of the RCT led to immunotherapy becoming a component of standard care in high-risk neuroblastoma, and it was considered unethical to not provide immunotherapy as part of maintenance treatment. The ERG's clinical experts stated that guidance from the CCLG advises that immunotherapy be given in combination with differentiation therapy as a maintenance treatment in high-risk neuroblastoma.

Until recently, in the UK, people with high-risk neuroblastoma had access to immunotherapy in the form of dinutuximab beta through enrolment in the HR-NBL-1 clinical trial, the results of one phase of which form the evidence base in the CS. However, the ERG's clinical experts fed back that recruitment to the study closed in May 2017. Dinutuximab alpha was being assessed in the NICE STA process (GID-TAG507), but the appraisal was suspended when the European marketing authorisation for the monoclonal antibody was withdrawn at the bidding of the holder, who cited production issues and a decision to supply only the US market as reasons for the request.

Figure 1. Treatment pathway for high-risk neuroblastoma



Abbreviations: ASCT, autologous stem cell transplant; BuMel, busulfan and melphalan hydrochloride myeloablative chemotherapy; COJEC, cisplatin, vincristine, carboplatin, etoposide, cyclophosphamide; IL-2, interleukin 2.

2.2.1.2 Relapsed or refractory neuroblastoma

As with high-risk neuroblastoma, guidelines for management of relapsed and refractory neuroblastoma are limited. The ERG's clinical experts indicated that choice of treatment strategy for relapsed or refractory neuroblastoma is, in part, guided by the preferences of the person with neuroblastoma and their families. Treatment options include subsequent cycles of chemotherapy, further radiotherapy or entry into a clinical trial to gain access to novel agents. As with the management of newly diagnosed neuroblastoma, treatment of relapsed or refractory disease is influenced by initial classification of risk, and, in the case of relapse, whether the recurrence is localised or metastatic.[21]

In cases of localised recurrent neuroblastoma initially classified as low or intermediate risk, treatment options include additional surgery followed by observation or chemotherapy, or chemotherapy with or without subsequent surgery.[21] Surgery is not considered suitable for recurrent or refractory neuroblastoma initially identified as high-risk of relapse. Commonly used chemotherapy regimens include topotecan with cyclophosphamide, irinotecan with temozolomide, and topotecan with temozolomide.[5] In people with recurrent neuroblastoma initially designated high-risk, molecular radiotherapy, such as radioactive mIBG, or second ASCT may be considered.[21] In metastatic neuroblastoma of any initial risk classification, novel therapy in a clinical trial might be the only available treatment option.[21]

Currently, there are two ongoing clinical trials involving relapsed and refractory neuroblastoma, the BEACON[30] and LuDO[31] studies. BEACON is a phase II randomised trial comparing the efficacy of various chemotherapy regimens, including the addition of bevacizumab, a monoclonal antibody, to

chemotherapy.[30] LuDO is a phase II single-arm study evaluating the safety and adverse effect profile of 177 lutetium DOTATATE in people with refractory neuroblastoma.[31]

2.2.2 Resource use for implementing treatment with dinutuximab beta

The CS does not explicitly outline the impact of implementation of dinutuximab beta on resource use in the National Health Service. The ERG's clinical experts advised that most of the established oncology units in England that treat neuroblastoma are set up to administer dinutuximab beta due to their participation in the HR-NBL-1 clinical trial.[32] Thus, addition of dinutuximab beta to standard care in neuroblastoma would require minimal changes to existing facilities and resources.

2.2.3 Estimated number of eligible patients

The company proposes that 41 patients per year in the UK would be eligible for treatment with dinutuximab beta, as summarised in Table 6. The ERG notes that the company has categorised those achieving partial response to induction therapy as refractory, which might not be the case in clinical practice (discussed in Section 2.1). The ERG's clinical experts fed back that the company's estimate is reasonable, highlighting that it would be difficult to obtain an accurate estimate of the number of people potentially eligible for treatment with dinutuximab beta.

Table 6. Calculation of number of people in the UK likely to be eligible for treatment with dinutuximab beta (adpated from CS, Table 54 [pg. 113])

Parameter	**Number**		**Reference**	
Total number of neuroblastoma patients in UK	(11,530,789 × 9.1 cases)/10^6 = 105		[33] 9.1 cases per million population (1988–1997) [34] 2015 UK population ages 0–14: 11,530,789	
High-risk neuroblastoma				
	%	Number	Reference	Comments
High-risk patients	36	38	[35]	INRG task force reporting worldwide neuroblastoma data (N=8800)
Rate of MRD patients	52	20	[36]	Complete response and very good partial response
Rate of refractory patients	38	14	[36]	Partial response, mixed response and no response
Very low/low-risk neuroblastoma				
	%	Number	Reference	Comments
Very low/low-risk patients	55	58	[35]	55% (28.2% + 26.8%)
Relapse rate of very low/low-risk patients	10	6	[37]	EFS 90% →10% relapse; EFS includes relapse and refractory patients
Intermediate-risk neuroblastoma patients				
	%	Number	Reference	Comments
Intermediate-risk patients	9	9	[35]	
Relapse rate of intermediate risk patients	12	1	[38]	EFS for all intermediate-risk patients reported is 88.2%

Dinutuximab beta target population				
	%	Number		
High-risk MRD patients	18.7	20		
High-risk refractory patients	13.7	14		
Very low/low-risk R/R patients	5.5	6		
Intermediate-risk R/R patients	1.1	1		
Total	39.0	41		

Abbreviations: EFS, event free survival; INRG, International Neuroblastoma Risk Group; MRD, minimal residual disease; R/R, relapsed or refractory.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the final decision problem issued by the National Institute for Health and Care Excellence (NICE; company submission [CS], Table 1, page 9) together with their rationale for any deviation from the decision problem (Table 7).[1] The company highlighted the CS deviates from the decision problem in terms of non-consideration of dinutuximab alpha as a relevant comparator, and substitution of event-free survival (EFS) for progression-free survival (PFS).

Table 7. Summary of decision problem as outlined in the company's submission (adapted from CS, Table 1 [pg. 9])

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	People with high-risk neuroblastoma who have had myeloablative therapy and autologous stem cell transplant (ASCT)	Patients with high-risk neuroblastoma, who have previously received induction chemotherapy and achieved at least a partial response, followed by MAT and SCT, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease	The appraisal will consider dinutuximab beta within its marketing authorisation
Intervention	Dinutuximab beta EUSA (dinutuximab beta)	As per scope	N/A
Comparator(s)	• Isotretinoin • Dinutuximab alpha (subject to NICE guidance)	Isotretinoin alone (without immunotherapy)	Drug shortage and withdrawal of marketing authorisation in EU for Unituxin (dinutuximab or ch14.18/SP2/0) precludes its use as a comparator in this submission. Furthermore, currently there is no final NICE recommendation for this product or use established within the NHS.
Outcomes	The outcome measures to be considered include: • OS; • PFS; • AEs of treatment; • HRQoL.	The outcome measures to be considered include: • OS; • EFS; • AEs of treatment; • Tumour response rate; • HRQoL.	Event-free survival was tracked in place of progression-free survival in the clinical trials. Tumour response rate was also tracked in the clinical trials.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	As per scope	N/A

	Consideration should be given to alternative standardised and validated preference-based measures of health-related quality of life that have been designed specifically for use in children. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	• Patients with relapsed disease • Patients with refractory disease	No subgroups will be considered in this submission	The final indication from EPAR[39] includes the high-risk neuroblastoma patients, as well as patients with history of relapsed/refractory neuroblastoma, with or without residual disease. Therefore, no subgroups are considered
Special considerations, including issues related to equity or equality			
Abbreviations AE, adverse events; ASCT, autologous stem cell transplant; CS, company submission; EFS, event-free survival; EPAR, European public assessment report; HRQoL, health-related quality of life; MAT, myeloablative therapy; NHS, National Health Service, NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; pg, page.			

3.1 Population

Data submitted in support of the clinical effectiveness of dinutuximab beta are derived from three studies, one RCT (APN311-302) and two observational studies (APN311-202 and APN311-303).

APN311-302 is one phase of the High-Risk Neuroblastoma 1 (HR-NBL-1) study.[40] APN311-302 is a phase III, open label, multinational trial designed to assess the efficacy and safety of adding interleukin 2 (IL-2) to a maintenance treatment regimen of dinutuximab beta and isotretinoin in high-risk neuroblastoma. To be eligible for inclusion in APN311-302, people had to have high-risk neuroblastoma and have achieved at least a partial response to induction therapy, and gone on to undergo consolidation therapy with myeloablative chemotherapy followed by autologous stem cell transplant (ASCT). The ERG notes that the population involved in APN311-302 is narrower than that outlined in the NICE scope but aligns with the marketing authorisation for dinutuximab beta:[39]

"Dinutuximab beta EUSA is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first-line therapy, Dinutuximab beta EUSA should be combined with interleukin 2 (IL-2)."

Recruitment sites for APN311-302 were located in Israel, Australia, and 10 countries across Europe, including Great Britain and Ireland. Of the 406 people randomised to IL-2 or no IL-2, 370 made up the final analysis set, of which [redacted] people ([redacted]%) were recruited from Great Britain and Ireland.[41] Baseline characteristics of the population of APN311-302 are comparable with those of people in the UK likely to be eligible for treatment with dinutuximab beta.

Relapsed and refractory neuroblastoma were listed in the NICE scope as subgroups of interest.[1] In the CS, the company submits evidence from two small observational studies – APN311-202 and APN311-303 – that included only those with relapsed or refractory neuroblastoma, and, based on the NICE scope, are relevant to the decision problem. The primary aim of both studies was to identify a tolerable treatment schedule of dinutuximab beta that reduced the pain-toxicity profile yet maintained the immunomodulatory effect. APN311-202 (N=44) is an ongoing study and so results are based on an interim analysis. APN311-202 is an open-label, single-arm prospective study whereas APN311-303 (N=54) is a retrospective analysis of a compassionate use programme.

Based on the company's response to clarification, [redacted] in APN311-202 or APN311-303 has previously received treatment with dinutuximab beta. In the UK, people with high-risk neuroblastoma are likely have received dinutuximab beta as part of their front-line multimodal treatment because they participated APN311-302. As part of the clarification process, the ERG asked the company to outline whether they envisage dinutuximab beta being used as a re-treatment in relapsed or refractory neuroblastoma in those who had previously received the immunotherapy as part of first-line maintenance treatment. In their response, the company comments that, "*Given the lack of data for the use of Dinutuximab beta EUSA in patients that may have already failed (relapsed) or those that are refractory to Dinutuximab beta EUSA, EUSA Pharma do not support a re-treatment with the drug*". Given that the company does not support re-treatment with dinutuximab beta, and that [redacted] in APN311-202 or APN311-303 has previously received the immunotherapy, the ERG considers that the population experiencing relapse is potentially not relevant to the decision problem because most relapses occur in those categorised as high-risk at initial diagnosis and this group will have received dinutuximab beta as part of their front-line therapy. People experiencing relapse after remission of

neuroblastoma assessed as intermediate risk or lower might be eligible for treatment with dinutuximab beta-based therapy, but the number of people in this category will be small (Table 6). In APN311-303, refractory neuroblastoma was defined as having received ≥2 lines of conventional treatment, and also as

[redacted].[41] APN311-202 focused on those with primary refractory neuroblastoma and included those with stage 4 disease who had received ≥2 lines of treatment before high-dose chemotherapy and ASCT, and for whom repeated lines of induction chemotherapy resulted in a delay from diagnosis to ASCT of over 9 months. Based on the eligibility criteria in APN311-202 and APN311-303, people with refractory neuroblastoma might or might not have previously received dinutuximab beta. Additionally, the ERG's clinical experts highlighted that it is likely that a proportion of those enrolled in APN311-202 and APN311-303 and classified as refractory to treatment are people originally participating in APN311-302 who, rather than being truly refractory, did not achieve an adequate response to induction therapy in APN311-302.

In summary, the ERG considers the evidence submitted for high-risk neuroblastoma, derived from APN311-302, to be representative of people with the condition in England and the wider UK, and to be relevant to the decision problem that is the focus of this STA. However, the ERG has reservations about the comparability of those with relapsed and refractory neuroblastoma in APN311-202 and APN311-303 with people of the same disease status in England, particularly in terms of prior dinutuximab beta treatment and with the company not supporting re-treatment with dinutuximab beta.

3.2 Intervention

As outlined in the CS, dinutuximab beta is a monoclonal chimeric (murine/human) antibody, which is a form of immunotherapy. Dinutuximab beta targets and binds to neuroblastoma cells at carbohydrate sites known as disialoganglioside (GD2) sites, which are overexpressed in neuroblastoma cells. Binding to GD2 sites of neuroblastoma cells triggers complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity resulting in lysis of the cancerous cells (Table 8).[42]

Dinutuximab beta was designated an orphan medicinal product on 8 November 2012[39]. On 23 March 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion of dinutuximab beta, which was followed by approval of the European marketing authorisation under exceptional circumstances on 8 May.[39] A marketing authorisation under exceptional circumstances is awarded when an applicant can demonstrate that they are unable to provide comprehensive data on the efficacy and safety of the agent for which they are seeking authorisation. The approval of dinutuximab beta was granted on the basis that more data informing the efficacy and safety of the treatment be

obtained and submitted for regular review by the European Medicines Agency. Dinutuximab beta is yet to be reviewed by the US Food and Drug Administration.

Dinutuximab beta is administered through intravenous infusion to give a total dose of 100 mg of the agent (Table 8). There are two recommended infusion schedules:

- continuous infusion over the first 10 days of each course at a daily dose of 10 mg/m^2;
- a daily infusion of 20 mg/m^2 infused over 8 hours for the first 5 days of each course.

The marketing authorisation specifies that people with high-risk disease and not achieving a complete response to induction therapy, and those with relapsed or refractory neuroblastoma, should also receive concomitant IL-2.[39] IL-2 is administered through subcutaneous injection at a dose of 6 x 10^6 IU/m^2/day and is given for two periods of five consecutive days (overall dose of 60 x 10^6 IU/m^2 per course (Table 8)): the first 5-day course of IL-2 should start 7 days before the first infusion of dinutuximab beta and the second 5-day course should start concurrently with dinutuximab beta infusion (days 1 to 5 of each dinutuximab beta course).[39] Although not explicitly stated in the marketing authorisation, dinutuximab beta is given concomitantly with the differentiation therapy isotretinoin (given orally at a dose of 160 mg/m^2/day for 14 days per course).[43]

The ERG notes that APN311-302 utilised the short infusion schedule for dinutuximab beta (over 5 days), whereas, in APN311-202 and APN311-303, dinutuximab beta was given as a continuous infusion. In the CS, the company states that, compared with the short infusion schedule, continuous infusion of dinutuximab beta is associated with a reduction in risk of hypersensitivity events, and is the recommended route because of its improved safety profile. The ERG's clinical experts agreed with the company, indicating that continuous infusion of dinutuximab beta would be the preferred schedule in UK clinical practice, for all stages of neuroblastoma. No study comparing the clinical effectiveness of the two infusion rates is available. No dose or infusion schedule was specified in the NICE scope.

Table 8. Summary of the technology, dinutuximab beta (adapted from CS, Section 1.2 [pg. 11])

Area	Details
UK approved name and brand name	Dinutuximab beta EUSA
Mechanism of action	Dinutuximab beta EUSA (ch14.18/CHO) is a monoclonal, chimeric (murine/human) antibody targeting the neuroblastoma tumour-associated carbohydrate, GD2, which is over-expressed by approaching 100% of neuroblastoma cells. By specifically binding GD2, dinutuximab beta triggers CDC (complement dependent cytotoxicity) and ADCC (antibody-dependent cell-mediated cytotoxicity), which leads to target cell lysis.
Marketing authorisation/CE mark status	Dinutuximab beta EUSA received EMA marketing authorisation (centralised procedure) on 8th May 2017 for use in the treatment of high-risk neuroblastoma, as well as in patients with relapsed or refractory neuroblastoma.

Indications and any restriction(s) as described in the summary of product characteristics	Dinutuximab beta EUSA is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first-line therapy, Dinutuximab beta EUSA should be combined with IL-2 (interleukin-2 or aldesleukin).
Method of administration and dosage	Dinutuximab beta EUSA is given by i.v. infusion. Two methods of administration are possible: 1) A continuous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m^2 2) Or five daily infusions of 20 mg/m^2 administered over 8 hours, on the first 5 days of each course When combined with Dinutuximab beta EUSA, IL-2 should be administered as subcutaneous injections of 6×10^6 IU/m^2/day, for 2 periods of 5 consecutive days, resulting in an overall dose of 60×10^6 IU/m^2 per course. The first 5-day course should start 7 days prior to the first infusion of dinutuximab beta and the second 5-day course should start concurrently with dinutuximab beta infusion (days 1 to 5 of each dinutuximab beta course).
Additional tests or investigations	No additional tests or investigations are required for dinutuximab beta beyond those that are already part of current clinical practice to identify the population for whom the technology is indicated in the marketing authorisation
List price and average cost of a course of treatment	Acquisition cost (excluding VAT): £7,610 per vial Average cost of a course of treatment: For an average body surface area of 0.63m^2 for a 3-year-old patient, a full course of treatment costs £152,200 – see Dinutuximab beta EUSA cost-effectiveness analysis (Document B, Section 1.2, page 11).
PAS (if applicable)	Currently, no PAS has been proposed for Dinutuximab beta EUSA
Abbreviations: CS, company submission; EMA, European Medicines Agency; IL-2, interleukin 2; i.v., intravenous; PAS, patient access scheme; pg, page.	

3.3 Comparators

3.3.1 High-risk neuroblastoma

The comparators listed in the NICE final scope as relevant for the appraisal of dinutuximab beta in the treatment of high-risk neuroblastoma are isotretinoin and dinutuximab alpha.[1]

Considering isotretinoin, the company presents evidence from a naïve indirect comparison with a historical control that received only isotretinoin during the maintenance phase after multimodal, multiagent induction and consolidation therapy. The dose of isotretinoin given in APN311-302 and in the historical control is the dose used in UK clinical practice. Isotretinoin is currently the only maintenance phase treatment that is available on the NHS and as such is a relevant comparator to the decision problem.

Within the CS, the company outlines that dinutuximab alpha is not a comparator of interest because the European marketing authorisation is no longer in place, being withdrawn at the request of the holder. The ERG agrees with the company that the withdrawal of the marketing authorisation renders dinutuximab alpha no longer directly relevant to the decision problem. However, within the CS, the

company reports that the two immunotherapies are separate entities, and refers to results on clinical effectiveness of dinutuximab alpha to underscore effect estimates for dinutuximab beta in a narrative comparison (discussed in Section 4.4). To date, there has been no clinical study comparing the two monoclonal antibodies. As described in the CS, the first iteration of dinutuximab, that is dinutuximab alpha, was produced in the SP2/0 cell line. By contrast, dinutuximab beta is produced in the Chinese Hamster Ovary (CHO) cell line. Although the two dinutuximab antibodies have identical amino acid sequences, because they are produced in different cell lines (SP2/0 and CHO), there are marked differences in glycosylation patterns between the two interventions and they are considered distinct from each other, with potential differences in clinical effectiveness and adverse effect profile.[39] Given that the alpha and beta forms of dinutuximab bind to the same target, the ERG considers that, as with other agents belonging to the same drug class, they could potentially elicit similar effects, and, although comparable clinical effectiveness of the two immunotherapies cannot be assumed, results for dinutuximab alpha are an evidence base to help inform the long-term effects of immunotherapy. Thus, the ERG proposes that an indirect comparison of dinutuximab beta versus dinutuximab alpha, although not directly relevant as a comparator in the decision problem, would contribute to understanding of the clinical effectiveness of dinutuximab beta (discussed in greater detail in Section 4.4).

3.3.2 Relapsed or refractory neuroblastoma

No comparators of interest for relapsed or refractory neuroblastoma were listed in the NICE scope, but the populations were highlighted as subgroups of interest. Although the company submitted evidence in support of dinutuximab beta-containing regimens in relapsed or refractory neuroblastoma, they did not discuss appropriate comparators for these groups (Table 7): comparators were listed in the inclusion criteria for the systematic review of the literature (Table 10). As discussed in Section 2.2.1.2, there is no accepted treatment pathway for relapsed or refractory neuroblastoma. The ERG's clinical experts advised that people experiencing relapse of their neuroblastoma or who are refractory to treatment would likely be enrolled into a clinical trial, such as BEACON,[11] in which patients are randomised to receive various chemotherapies. APN311-202 and APN311-303 are single arm studies and, therefore, have no comparator group. In the CS, the company presents a naive indirect assessment of clinical effectiveness of dinutuximab beta in relapsed neuroblastoma using historical cohorts as the comparator group, and the comparator is no dinutuximab beta. People included in the historical cohorts have received a wide variety of treatments at relapse, which possibly reflects the array of interventions used in clinical practice in England.

3.4 Outcomes

The outcomes specified in the NICE final scope are:[1]

- overall survival (OS);

- PFS;
- adverse events;
- health-related quality of life (HRQoL).

The ERG notes that estimates of clinical effectiveness of the dinutuximab beta-containing regimen versus comparators of interest are not derived from head-to-head studies. All reported comparative effect estimates are generated from naïve indirect comparisons utilising outcome data from appropriate historical controls, and only effect estimates of OS are reported.

The ERG notes that the primary objective of both APN311-202 and APN311-303 was to establish a tolerable treatment schedule of dinutuximab beta that reduces the pain–toxicity profile yet maintains the immunomodulatory effect the intervention. However, for APN311-303, OS, and EFS were captured as secondary outcomes. No outcome listed in the NICE scope was a prespecified outcome in APN311-202 (Table 9).

OS and adverse effects were reported for the three studies, but EFS was substituted for PFS across studies. HRQoL was not reported for any included study. In APN311-302, EFS was assessed as the primary outcome and was defined as the time to an event from randomisation until the first occurrence of relapse, disease progression, secondary neoplasm or death from any cause. EFS was captured as a secondary outcome in APN311-303, but was not prespecified in APN311-202 (Table 9). In addition, development of second neoplasm was not counted as an EFS event in APN311-202. The ERG's clinical experts fed back that development of second neoplasm is a rare event, and its omission from EFS in APN311-202 is likely to have minimal impact on estimates of effect. As most events occurring in the studies were relapse, progression or death from any cause, EFS is similar to PFS. As the company acknowledges, and as outlined in the European Public Assessment Report (EPAR) for dinutuximab beta, determination of occurrence of an event can be difficult, and is complicated by exact definition of events and ascertainment of disease status.[39] In APN311-302, no time point for assessment of disease status during or after treatment was pre-specified: potential bias arising from recoding of outcome events is discussed in greater detail in Section 4.1.4.

Data on the adverse effect profile of dinutuximab beta are primarily derived from a safety database comprising 514 people who have undergone treatment with the immunotherapy, with a focus on 98 people who received dinutuximab beta as a continuous infusion over 10 days. Although results on adverse effects are available from APN311-302 and the two observational studies identified, data on safety were not collected consistently across the three studies.

Tumour response was reported for APN311-202 in support of the clinical effectiveness of dinutuximab beta in relapsed and refractory neuroblastoma. The ERG considers it worth mentioning the direction from the US Food and Drug Administration (FDA) on the validity and robustness of data from single-arms studies in oncological conditions.[44] Of particular relevance, the FDA comments that single-arm studies enrolling people with refractory tumours, and for whom there is no available therapy, provide an accurate assessment of overall response rate (ORR). However, given the variability in the natural history of many cancers, single-arm studies, such as APN311-202, do not sufficiently characterise time to event endpoints, such as OS. ORR is considered a direct measure of the antitumor activity of a drug but not as a measure of the stability of disease, and clinical benefit in tumour response does not necessarily lead to benefit in OS. OS is considered the most reliable endpoint in RCTs evaluating interventions in oncological conditions, and is generally the preferred endpoint. However, it is also recognised that long follow-up periods and potential confounding from post-progression therapies can hinder the collection and analysis of survival data.[44]

In summary, the ERG considers the outcomes presented in the submission to be clinically relevant to the decision problem.

Table 9. Relevant outcomes for APN311-202, APN311-302 and APN311-303 (adapted from the CS, Table 11 [pg. 37])

	APN311-302	APN311-202	APN311-303
Primary outcomes	3-year event-free survival	• Pain-toxicity profile • Increase in CD16/CD56 positive activated NK cells	• Pain intensity/morphine use • Incidence, grade and type of adverse event
Secondary outcomes	Overall survival	Anti-tumour response	• Response rate in measurable disease • Overall survival • Event-free survival
Abbreviations: CS, company submission; NK, natural killer; pg, page.			

3.5 Other relevant factors

The NICE final scope specified relapsed and refractory neuroblastoma as subgroups of interest. APN311-202 and APN311-303 involved those with relapsed and refractory neuroblastoma, which allowed consideration of the two disease stages separately from high-risk disease rather than as subgroups of a study. In high-risk neuroblastoma, using APN311-302, the company reported subgroup analyses for those with and without evidence of residual disease prior to treatment with a dinutuximab beta-containing regimen. The ERG's clinical experts outlined that people with minimal residual disease before maintenance therapy have worse prognosis than those who do not. The ERG highlights that it is unclear whether subgroup analyses were prespecified for APN311-302.

For APN311-302, the CS reports estimates of EFS and OS at 1, 2 and 3 years of follow-up. Cut off dates for analyses were not specified. During clarification, the company indicated that mean follow-up

for APN311-302 was [redacted] (SD [redacted]) days, which equates to [redacted] (median follow up was [redacted] days [range of [redacted] to [redacted] days]). Length of follow up for maintenance treatment in high-risk neuroblastoma could be an important consideration. The ERG evaluating the clinical effectiveness of dinutuximab alpha suggested that treatment with the immunomodulatory agent leads to a delay in experiencing an event, and consequently lengthens OS times, but does not prevent recurrence of neuroblastoma in the longer term (up to 10 years) (discussed in more detail in Sections 4.3 and 4.4).[45] The ERG considers the duration of follow-up in APN311-302, and thus the data informing the naïve indirect comparison, to be insufficient to assess clinical effectiveness of dinutuximab beta-containing regimen in the long-term.

4 CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of dinutuximab beta. Details, together with the Evidence Review Group's (ERG's) critique, are provided for:

- the methods implemented by the company to identify relevant evidence;
- clinical efficacy of dinutuximab beta;
- safety profile of dinutuximab beta;
- assessment of comparative clinical effectiveness of dinutuximab beta against relevant comparators (as detailed in Section 4.4).

The ERG notes that the company's search identified one randomised study incorporating dinutuximab beta, APN311-302, which evaluated the effectiveness of adding interleukin-2 (IL-2) to dinutuximab beta given in combination with the differentiation therapy isotretinoin in high-risk neuroblastoma.[41] As outlined in Section 2.2.1, due to ethical considerations, a head-to-head randomised controlled trial (RCT) evaluating dinutuximab beta versus no dinutuximab beta is not, and is unlikely to become, available. Additional data on clinical effectiveness of dinutuximab beta in relapsed and refractory neuroblastoma were derived from a prospective single-arm study, APN311-202, and a retrospective analysis, APN311-303.[41] The identified studies and relevant efficacy data are described in more detail in subsequent sections. Given the lack of RCTs evaluating dinutuximab beta, the company asserted that standard pairwise meta-analyses and indirect treatment comparisons were not possible: the feasibility of carrying out an assessment of comparative clinical effectiveness of dinutuximab beta versus other interventions is discussed in Section 4.4. Data on the adverse effect profile of dinutuximab beta originated from a safety database comprising 514 people who have undergone treatment with the immunotherapy. The ERG considers it important to note that data from APN311-202, APN311-302 and APN311-303 have yet to be published in a peer-reviewed journal.

4.1 Critique of the methods of review

4.1.1 Searches

The company sought to identify studies evaluating the clinical effectiveness of dinutuximab beta and relevant comparator treatments in two distinct groups of people with neuroblastoma:

- as a maintenance treatment for people with high-risk neuroblastoma who had undergone induction chemotherapy and achieved at least a partial response (PR), and then went on to

receive consolidation with myeloablative chemotherapy (MAT) and autologous stem cell transplant (ASCT);

- as a treatment for those with relapsed or refractory neuroblastoma, of any level of risk of relapse.

Searches were carried out in MEDLINE and Education Resource Information Center (ERIC) via PubMed, EMBASE via Elsevier's platform (reported during the clarification process), and the Cochrane Library (Cochrane Database of Systematic Reviews [CDSR], Cochrane Central Register of Controlled Trials [CENTRAL], Database of Abstracts of Reviews of Effects [DARE]). Electronic databases were searched from inception to 4 May 2017 and no restriction was placed on the date of publication of records. There is no mention of searching of the proceedings of key conferences in the clinical area, or searching of clinical trial registries (clinical.trials.gov). It is unclear whether the reference lists of included studies were reviewed as a source of additional potentially relevant evidence. The company provided the search terms and strategies implemented in the company's review of the published literature as an Appendix (Appendix D of the company's submission [CS]).

The two research questions addressed by the company's literature search cover a broader population than that outlined in the scope issued by NICE,[46] which was limited to those with high-risk neuroblastoma and having received myeloablative therapy and ASCT. Although the company indicates that the systematic review was divided into two searches, the ERG notes that one search strategy per database was developed and Boolean operators were implemented to group studies evaluating high-risk versus relapsed or refractory neuroblastoma.

The ERG has some reservations about the validity of the search methods followed to identify relevant evidence. The company's search strategies do not include index terms specific to the individual electronic database. Instead, each search is limited to the use of free-text terms for population, intervention, comparator, outcomes and study design, with the same terms implemented in all searches. The CS does not outline the rationale for the omission of index terms from the search strategies. The ERG considers that not incorporating index terms could result in potentially relevant studies being missed by the search. In addition, the supplied search strategies indicate that the terms used were searched in "All fields". Across the databases, the "All fields" option encompasses categories such as author, journal and publication type, as well as the title and abstract of articles in the database. The ERG considers that the search strategies could have been refined using "tags" appropriate for each database to limit records to those with the relevant term in, for example, the title, abstract, or key words. It should be noted that the format of the search strategies as presented in Appendix D precludes the ERG from replicating the company's search.

In all searches, only one free-text term is implemented for neuroblastoma – "neuroblast*". Examination of systematic reviews of treatments for high-risk neuroblastoma identified several other free-text terms for the population of interest (e.g., ganglioneuroblastoma and neuroepithelioma).[26,47] Moreover, only one term per subgroup is implemented to isolate records specific to high-risk ("high-risk") and to relapsed ("relapse") or refractory ("refractory") neuroblastoma, with no adjustment for potential variation in punctuation or spelling (e.g., "high risk" versus "high-risk" and "relapse" versus "relapsed"). The ERG has reservations about the approach of separating studies by status of neuroblastoma at the search stage through free-text terms for high-risk and relapsed or refractory disease. Given the small number of records likely to be retrieved in the clinical area of neuroblastoma, the ERG considers that it could have been more appropriate to evaluate all studies retrieved using general neuroblastoma terms in combination with filters for intervention, comparator and study design, and subsequently classifying population as high-risk or relapsed or refractory at appraisal of full text publications. A comprehensive set of terms has been used to identify records relating to the intervention dinutuximab beta and its comparators.

All search strategies include free-text terms for clinical and safety outcomes of interest to the decision problem. Inclusion of search terms for outcomes could lead to failure to capture all potentially relevant studies. Although a study might measure the outcome of interest, if the outcome is not mentioned prominently enough in the study record, the database being searched is unlikely to retrieve the study.[48] The ERG has reservations about inclusion of terms for clinical and safety outcomes in this project, particularly given the small number of studies likely to be retrieved relating to neuroblastoma.

Free-text terms have been included to retrieve RCTs, controlled clinical trials (CCTs), and systematic reviews. The ERG notes that inclusion of terms for study design in the search strategy for the Cochrane library is unnecessary as the output of searches in the Cochrane library differentiate results by study design (e.g., Cochrane reviews, other reviews and trials).

In summary, the company conducted a search of the key electronic databases, including MEDLINE, EMBASE and The Cochrane Library, for RCT and CCT evidence relevant to the decision problem. The ERG notes that it is stated in the CS that EUSA Pharma has exclusive rights to the clinical study data from all SIOPEN- and Apeiron Biologics-sponsored dinutuximab beta studies, and no additional studies have been performed outside these organisations. As all data for dinutuximab beta are held by EUSA Pharma, the ERG considers that the company is likely to have identified all evidence for dinutuximab beta that is relevant to the decision problem that is the focus of this Single Technology Appraisal (STA). However, given the ERG's reservations about aspects of the search process as outlined above, the ERG considers that some studies evaluating relevant comparators in high-risk or relapsed or refractory neuroblastoma might have been overlooked.

4.1.2 Inclusion criteria

Full eligibility criteria for the review of clinical effectiveness of dinutuximab beta compared with relevant comparators are presented in Table 10. Two sets of criteria are outlined, reflecting the two populations (high-risk versus relapsed or refractory) identified by the company as being relevant to the decision problem.

For the review of the literature relevant to high-risk neuroblastoma, the company specifies that only studies evaluating those who have previously received induction chemotherapy and achieved at least a partial response before undergoing myeloablative therapy and ASCT are relevant to the decision problem. Although restriction of the population to those achieving a partial response to induction therapy renders a narrower population than that defined in the NICE scope,[46] the ERG considers the limitation to be appropriate as it is in line with the marketing authorisation for dinutuximab beta for the treatment of high-risk neuroblastoma.[39] Additionally, those with relapsed or refractory neuroblastoma are specified in the NICE scope as subgroups of interest. Clinical experts advised the ERG that relapsed and refractory disease are relevant to the decision problem, and, moreover, recommended that the two disease states are distinct populations that should be evaluated separately (discussed in more detail in Section 3.1). The ERG's clinical experts also fed back that the comparators listed by the company are predominantly appropriate for comparison against dinutuximab beta in the treatment of relapsed or refractory neuroblastoma: the ERG's clinical experts commented that clinicians in the UK would be unlikely to use isotretinoin alone for those experiencing relapse or refractory disease.

A key exclusion from consideration was studies of dinutuximab alpha antibody derived from alternative cell lines of those of dinutuximab beta (produced in Chinese hamster ovary [CHO] cells). As noted by the company, the marketing authorisation for a second anti-GD2 monoclonal antibody, known as dinutuximab (for clarity, referred to as dinutuximab alpha), that was produced in the SP2/0 hybridoma cell was withdrawn at the request of the holder and so dinutuximab alpha is no longer a relevant comparator.[49]

It is noted that studies not published in English language were excluded, and so some relevant data might not have been included in the CS.

Overall, the ERG considers the eligibility criteria implemented by the company to be reasonable for the decision problem outlined in the NICE final scope.[46]

Table 10. Eligibility criteria for review of clinical effectiveness of dinutuximab beta (adapted from CS, Tables 7 [pg. 23] and 8 [pg. 55])

	High-risk neuroblastoma	Relapsed or refractory neuroblastoma
Factor	**Inclusion criteria**	**Inclusion criteria**
Population	Patients with high-risk neuroblastoma who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation	Patients with relapsed or refractory neuroblastoma at any level of risk
Interventions	Dinutuximab beta in addition to current standard of care	Dinutuximab beta in addition to current standard of care
Comparators (current standard of care)	Isotretinoin	• Isotretinoin • Interleukin-2 • The following (most common) second-line chemotherapies or high dose therapies: o BuMel + ASCT; o TVD; o TEM/IRN; o Topotecan + cyclophosphamide; o Topotecan + cyclophosphamide + etoposide; o mIBG treatment. • Radiotherapy (localised) • Surgery
Outcomes	Efficacy outcomes: • Tumour response; • Survival in terms of overall survival, progression-free survival, or event-free survival. Safety or tolerability outcomes: • Mortality; • Any AEs; • Any toxicity reported.	Efficacy outcomes: • Tumour response; • Survival in terms of overall survival, progression-free survival, or event-free survival. Safety or tolerability outcomes: • Mortality; • Any AEs; • Any toxicity reported.
Study type	RCTs, CCTs, Reviews	RCTs, CCTs, Reviews
Language restrictions	English language	English language
Factor	**Exclusion criteria**	**Exclusion criteria**
Population	Patients without high-risk neuroblastoma aged less than 12 months, as well as patients that have relapsed or are refractory to standard of care	Patients without relapsed or refractory neuroblastoma aged less than 12 months
Intervention	Studies not investigating dinutuximab beta or isotretinoin treatment during maintenance phase in high-risk neuroblastoma patients, or studies utilizing dinutuximab alpha antibody derived from alternative cell lines	Studies not investigating dinutuximab beta (active substance) or any of the standard of care treatments for the relevant population
Comparators (current standard of care for the relevant population)	Studies investigating the use of any other therapy different to the intervention (dinutuximab beta) or the current standard of care (13-cis retinoic acid) during maintenance phase of high-risk neuroblastoma	Studies investigating the use of any other therapy different to the interventions or comparators stated in the inclusion criteria, or studies utilizing dinutuximab alpha antibody derived from alternative cell lines

Outcomes	Studies not reporting the outcomes listed in the final scope	Studies not reporting the outcomes listed in the final scope
Study type	Letters, editorials, comments, opinions, pharmacokinetic studies, pharmacodynamics studies, *in vitro* or animal studies, conference abstracts	Letters, editorials, comments, opinions, pharmacokinetic studies, pharmacodynamics studies, *in vitro* or animal studies, conference abstracts
Language restrictions	Non-English publications	Non-English publications
Abbreviations: AE, adverse effect; ASCT, autologous stem cell transplant; BuMel, busulfan + melphalan; CCT, controlled clinical trial; CS, company submission; mIBG, meta-iodobenzylguanidine; pgs, pages; RCT, randomised clinical trial; TEM/IRN, temozolomide + irinotecan; TVD, topotecan + vincristine + doxorubicin.		

4.1.3 Critique of screening process and data extraction

Methods implemented to screen the studies retrieved by the systematic search of the literature are presented in Appendix D of the CS. Before initial screening of studies based on title and abstract, a single experienced information specialist excluded irrelevant studies (e.g., animal studies, case reports). Screening of titles and abstract was carried out by a single reviewer, with quality control of a sample of records undertaken by a second researcher. If there was uncertainty about the relevance of a record based on the abstract, the study was considered potentially relevant and a full copy of the publication was obtained. Screening of full-text publications was carried out by a single reviewer, with quality control of a sample of records undertaken by a second reviewer. If necessary, differences in opinion were discussed with a third reviewer. The percentage of records reviewed as part of the quality control in each screening step is unclear. As a single reviewer is likely to have reviewed most records, it is possible that some studies have been included or excluded in error.

In brief, the search of the literature on high-risk neuroblastoma retrieved 223 non-duplicate records, of which 47 full-text publications were reviewed. Screening of full-text publications led to the exclusion of all studies as no identified study evaluated dinutuximab beta versus isotretinoin alone. Similarly, after screening 65 full-text articles from an initial 775 non-duplicate records retrieved on relapsed or refractory neuroblastoma, no study compared dinutuximab beta versus a relevant comparator in this population.

As no study was identified to inform the clinical effectiveness of dinutuximab beta, the company next re-appraised the retrieved studies (both RCTs and CCTs) with a focus on those assessing the clinical effectiveness of the specified comparator(s) irrespective of the use of dinutuximab beta: within the search strategies, the terms for intervention and comparator were combined using "or". Re-assessment of the retrieved studies identified 4 publications on 2 studies in high-risk neuroblastoma,[9,29,50,51] and 20 studies evaluating various regimens in relapsed or refractory neuroblastoma.[8,11,52-69] Appropriate PRISMA flow schematics were presented in the CS (available in Appendix 10.2 of the ERG's report), together with reasons for exclusion of studies (Appendix D of the CS) and lists of studies informing the evidence base of the CS. The ERG notes that none of the 20 identified studies was selected to inform

the comparative assessment of dinutuximab beta in relapsed and refractory neuroblastoma, with the CS presenting a narrative review of results for different types of chemotherapy in this setting. Instead, the company used data from a retrospective analysis of registry data of children with relapse or progression of neuroblastoma,[70] the details of which are not available in the list of identified studies. It is unclear how the company identified the record for the retrospective analysis. In response to the ERG's clarification question as to why the company had not used the identified studies to inform the analysis in relapsed and refractory neuroblastoma, the company informed that the publications presented aggregated data for relapsed and refractory neuroblastoma.

Details on the data extraction process are not available within the CS, and so it is unclear whether all pre-specified data have been extracted from identified studies. In addition, it is unclear whether extracted data forming the basis of the CS have been validated independently. For evidence submitted in support of clinical effectiveness of dinutuximab beta, data were extracted across studies on baseline characteristics, overall survival (OS), event-free survival (EFS), and adverse effects, which are in line with the outcomes listed in the NICE scope. EFS is not specified as an outcome of interest in the NICE scope, but, as discussed in Section 3.4, is substituted for progression-free survival (PFS).

In summary, based on the methods reported by the company, the ERG considers it possible that some relevant studies on comparators of interest to the decision problem might have been excluded during the screening of records and full-text publications. The ERG considers it likely that all key data on dinutuximab beta have been identified (as noted in Section 4.1.1), but has some concerns that studies evaluating comparators might have been overlooked, during both search and screening processes.

4.1.4 Quality assessment

The CS presented quality assessments of the one RCT (APN311-302) and two observational studies (APN311-202 and APN311-303) from which evidence is derived in support of the clinical effectiveness of dinutuximab beta. Data on adverse effects are taken from a safety database comprising 514 people who have undergone treatment with the immunotherapy, rather than a specific study, and, therefore, no quality assessment of the evidence source has been carried out.

Although the CS does not specify the risk-of-bias tool used to assess quality of APN311-202, APN311-302, and APN311-303, given the domains appraised, the ERG considers that the company's assessments are based on the Cochrane risk-of-bias approach for RCTs.[71] Quality of the three studies was based on potential presence of:

- selection bias (random sequence generation and allocation concealment);
- performance bias (masking of participants and key trial personnel);

- detection bias (masking of outcome assessment);
- attrition bias (drop-out rate);
- reporting bias (selective reporting of outcomes or analyses).

Considering the RCT APN311-302, the company outlined that the study was appropriately randomised, with randomisation stratified for national group and previous treatment, and that groups were similar in terms of prognostic factors at baseline. The company indicated that there was no evidence of selective reporting bias, that the rate of drop-out was similar between groups, and that an intention-to-treat (ITT) analysis had been performed.

APN311-302 is open-label in design. It is unclear whether there was an independent review of disease status. The clinical study report (CSR) for APN311-302 indicates that a [redacted], and that the anticipated [redacted].[41] The potential bias associated with the open-label design is not discussed in the CS. The ERG notes that potential biases arising from lack of masking to treatment include:

- reporting bias associated with variation in outcome assessment between the two groups;
- performance bias with variation in treatment or other care given in the two groups;
- bias from difference in proportion of people withdrawing from or adhering to allocated regimen, with potentially more frequent early cessation of treatment in the group receiving IL-2 because of associated adverse effects.

The primary objective of APN311-302 was to assess whether addition of IL-2 to dinutuximab beta, when given in combination with isotretinoin, during maintenance treatment after myeloablative therapy and ASCT for high-risk neuroblastoma would improve 3-year EFS. In APN311-302, events were defined as disease progression or relapse, death from any cause and development of second neoplasm. As the company acknowledges, and as outlined in the European Public Assessment Report (EPAR) for dinutuximab beta, determination of occurrence of an event can be difficult, and is complicated by exact definition of events and ascertainment of disease status.[39] In APN311-302, no time point for assessment of disease status during or after treatment was pre-specified. Given the open-label nature of the study, and the potential inconsistencies across patients in time of outcome assessment, the ERG considers that EFS is at risk of performance bias.

The ERG independently carried out a quality assessment of APN311-302. The ERG's views differed from those of the company in some domains. The company's quality assessment, together with that of the ERG and accompanying minor comments, is presented in Appendix 10.3. The ERG agrees with the company that APN311-302 was adequately randomised, with randomisation carried out using a web-based centralized system. It is unclear from reporting in the CS or the CSR for APN311-302 whether methods were implemented in the web-based system to conceal allocation from those responsible for assigning patients to a treatment group, thus preventing prediction or knowledge of the next treatment allocation and minimising selection bias. The company indicates that allocation concealment is not applicable to APN311-302 as the study is open-label. The ERG considers concealment of allocation for recruiters and those allocating patients to a group to be a separate aspect of trial design to masking of key personnel and patients to treatment. In their response to clarification, the company comments that, "*There is no information as to whether or not the web-based system incorporated a method to conceal allocation sequence from those people assigning participants to intervention groups, however the study design was open-label, so perhaps there was no need for concealing allocation*".

The company states that an ITT analysis was carried out. However, the ERG notes that not all people randomised were evaluated in the group to which they were randomised. Of the 406 people randomised, 370 people were included in the analyses presented in the CS: people who were randomised and for whom an electronic case report form (eCRF) was not available (21 people) and those who received no treatment or for whom no treatment data were available (15 people) were excluded from analyses. The ERG considers that the company has carried out the equivalent of a complete case analysis. The company could have performed an IT analysis either by simplistically assuming a best or worst case scenario for people with missing data or by implementing formal statistical techniques. In addition, it is unclear how many people were initially randomised to each group. Although the proportion of people excluded from the analysis is small (9.1%), it is unclear from the CS why an eCRF was not available for all randomised patients, or why some people did not receive any treatment. The ERG queried why analyses were not based on the ITT population, but it remains unclear from the company's response why the 406 people randomised were not analysed in the groups to which they were initially allocated.

It is noted that there is an imbalance between treatment groups in the proportion of people withdrawing from treatment. A larger proportion of people receiving IL-2 discontinued treatment compared with those not receiving IL-2: 17.5% of patients receiving IL-2 experienced a serious adverse event (SAE) leading to withdrawal, compared with 6% of patients not receiving IL-2. Similarly, of those for whom treatment completion status could be determined, the proportion of people allocated to IL-2 who received at least 50% of the planned dose of dinutuximab beta or IL-2 (if applicable) was considerably smaller in those allocated to IL-2 (39.4% with IL-2 vs 78.3% without IL-2 in cycles 1–5). However, it is recognised that IL-2 administration can be associated with severe adverse effects (e.g., capillary leak

syndrome), and so the imbalance in people withdrawing from or receiving fewer doses of IL-2 could be anticipated.

The ERG notes that APN311-202 and APN311-303 are single-arm observational studies, and are, therefore, associated with a high risk of bias that is inherent in such studies. The lack of a comparator group and the awareness of participants, key personnel and assessors to the treatments given should be borne in mind when interpreting results from the prospective study APN311-202. Similarly, as a retrospective analysis, as the company acknowledges, APN311-303 is potentially at risk of selection bias and bias in outcome assessment. In addition, the company reports that a substantial volume of data could not be retrieved for APN311-303, including key data on prognostic factors. Finally, the ERG considers that it is not appropriate to assess the risk-of-bias associated with APN311-202 and APN311-303 with a system that was designed for randomised studies.

Overall, the ERG predominantly agrees with the quality assessment presented in the CS for the APN311-302 study, with a difference in interpretation on the potential bias associated with allocation concealment. The ERG determines that the lack of masking in APN311-302 and the potential disparity in timing of recording of clinical effectiveness outcomes puts the study at a moderate risk of bias. In relation to APN311-202 and APN311-303, the ERG considers that results from the two observational studies should be interpreted with caution due to the lack of a comparator group and the individual risk of bias associated with each study based on its design (prospective versus retrospective).

4.1.5 Evidence synthesis

Only one RCT incorporating dinutuximab beta was identified (APN311-302). Importantly, APN311-302 was designed to evaluate the effectiveness of adding IL-2 to dinutuximab beta given in combination with isotretinoin after consolidation therapy in people with high-risk neuroblastoma, and, therefore, clinical data on the comparative clinical effectiveness of dinutuximab beta versus no dinutuximab beta are not available from a head-to-head study. As only one RCT was identified, standard pair-wise meta-analysis was not possible for clinical effectiveness.

Evidence presented in the CS on the safety of dinutuximab beta is primarily derived from a safety database, with a focus on 98 people who received dinutuximab beta as a continuous infusion over 10 days. Although results on adverse effects are available from APN311-302 and the two observational studies identified, data on safety were not collected consistently across the three studies. In APN311-302, full reporting of adverse effects was limited to SAEs: other adverse effects were reported as per a pre-defined list of 31 specific toxicities.[39] The CSR of APN311-202 indicates that people were [redacted], and adverse effects were [redacted].[41]

APN311-303 is a retrospective analysis and reported adverse effects are derived from patient records. As APN311-202 and APN311-303 are small single-arm studies with no comparator, and because adverse effects were presented differently across studies, the ERG considers that a synthesis of data on adverse effects from the three studies would not have been feasible.

In the CS, the company presents analyses based on comparison of study data versus historical controls for high-risk and relapsed neuroblastoma: the company did not present an analysis for those with refractory neuroblastoma (requested by the ERG as part of the clarification process; please see Section 4.4). Analyses are naïve indirect comparisons evaluating the clinical effectiveness of dinutuximab beta versus no dinutuximab beta, primarily presenting p-values for comparisons but not estimates of effect with accompanying 95% confidence intervals (CIs). In the CS, the company describes an RCT assessing a combination regimen including another anti-GD2 monoclonal antibody (dinutuximab alpha) versus isotretinoin alone in people with high-risk neuroblastoma.[29] The ERG considers that the results of the study for the group receiving isotretinoin alone could form the basis of a matching-adjusted indirect comparison (MAIC) or simulated treatment comparison (STC) of dinutuximab beta versus isotretinoin in high-risk neuroblastoma, which the NICE scope lists as a comparator of interest in that population.[46] As part of the clarification process, the ERG requested that the company carry out an MAIC. The company decided against carrying out the MAIC, and instead provided adjusted hazard ratios (HRs): the company's rationale for not carrying out an MAIC is discussed in Section 4.4.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

As discussed in Section 4.1, the company's systematic review of the literature identified no full text publication reporting a study evaluating dinutuximab beta. Evidence in the CS in support of the clinical effectiveness of dinutuximab beta in the maintenance treatment of high-risk neuroblastoma is derived from an RCT evaluating the effect of adding IL-2 to dinutuximab beta in combination with isotretinoin in high-risk neuroblastoma. That is, everyone in the study received dinutuximab beta. No direct evidence on dinutuximab beta versus isotretinoin alone is available as such a study was considered unethical, based on the results of the study assessing dinutuximab alpha.[29] Evidence in support of the effectiveness of dinutuximab beta in relapsed or refractory neuroblastoma is derived from two single-arm observational studies, one of which is prospective in design (APN311-202) and the other retrospective (APN311-303). EUSA Pharma holds the, "*exclusive rights to the clinical study data from all SIOPEN- and Apeiron Biologics-sponsored studies assessing dinutuximab beta Apeiron*". The company also reports that additional relevant studies have not been carried out by other organisations and, consequently, EUSA Pharma has access to all data on dinutuximab beta pertinent to the decision problem that is the focus of the STA.

To inform the decision problem, the company used historical controls from an earlier phase of the large long-term study comprising APN311-302 (conduct detailed below) and from a retrospective analysis of registry data of children with relapse or progression of neuroblastoma,[70] stating that the historical cohorts were highly comparable with the populations evaluated in the APN311 studies from which evidence is derived. Details of historical controls and the methods used to generate statistical analyses of comparative effectiveness of dinutuximab beta are detailed in Section 4.4. As an alternative to the use of a historical control, the ERG considers that published results from a study evaluating dinutuximab alpha versus isotretinoin in high-risk neuroblastoma could form the basis of an indirect comparison to generate comparative effect estimates for dinutuximab beta versus isotretinoin alone (discussed in more detail in Section 4.4).

The company also briefly described two other studies in support of the submitted evidence in those with relapsed or refractory neuroblastoma (details of the additional studies summarised in Table 11). The company commented that APN311-101 and APN311-201 were not reported in detail because long-term efficacy data are not available. Based on the marketing authorisation that, in relapsed and refractory neuroblastoma, dinutuximab beta be given in combination with isotretinoin and IL-2, the ERG does not consider APN311-101 or APN311-201 to be relevant to the decision problem and the studies are not discussed further in this report.

Table 11. Overview of APN311-101 and APN311-201 (adapted from CS, Table 9, pg. 27)

Study code **Phase**	**Setting**	**Design**	**Dinutuximab beta schedule** **Dose(s) (mg/m^2/cycle)** **No. of cycles**	**Co-treatment**	**Patients treated/planned** **Age**	**Assessments**
APN311-101 Phase I	R/R	Open label, uncontrolled, multi-centre, dose-escalation	8h/5d 50, 100, 150 1-3 (each 28 days)	None	15/12[a] 15 in dossier >1 year to ≤21 years	Safety Efficacy Pharmacology ***Completed***
APN311-201 Phase II	R/R	Open-label, uncontrolled, multi-centre	8h/5d 100 Up to 9 (each 28 days)	None (cycles 1–3), IL-2 (cycles 4–9)	35/35[b] ≤21 years Amended to include a total 60 patients	Safety Efficacy Pharmacodynamics ***Ongoing***

[a] A total of 16 patients were treated in the study. However, since the signed ICF for one patient could not be found at the time of data collection and analysis, only data from 15 patients were collected and are reported.

[b] Data cut-off date 28 Feb 2015 – last update 05 September 2016.

Abbreviations: CS, company submission; IL-2, interleukin-2; pg, page; R/R, relapsed or refractory.

Studies of other anti-GD2 monoclonal antibodies produced in a cell-line different from that of dinutuximab beta were excluded. The only other potentially relevant anti-GD2 monoclonal antibody is

dinutuximab alpha, which the company indicates is not a relevant comparator because the immunotherapy will not be an available treatment to the National Health Service as a result of withdrawal of the European marketing authorisation at the request of the holder. The ERG agrees with the company that dinutuximab alpha is not a relevant comparator. However, the ERG notes that the CS provides a narrative discussion of the results of the key study assessing dinutuximab alpha alongside findings from the APN311-302 study.

Overall, the ERG agrees with the company that the key study of dinutuximab beta relevant to high-risk neuroblastoma is APN311-302. However, for relapsed and refractory neuroblastoma, the ERG considers the prospective study, APN311-202, to provide more robust evidence than the retrospective analysis APN311-303 (please see Sections below for further detail). The ERG provides details on both APN311-202 and APN311-303, with a focus on results from APN311-202 and referring to APN311-303 as supporting evidence.

4.2.1 Trial conduct

4.2.1.1 High-risk neuroblastoma

4.2.1.1.1 APN311-302

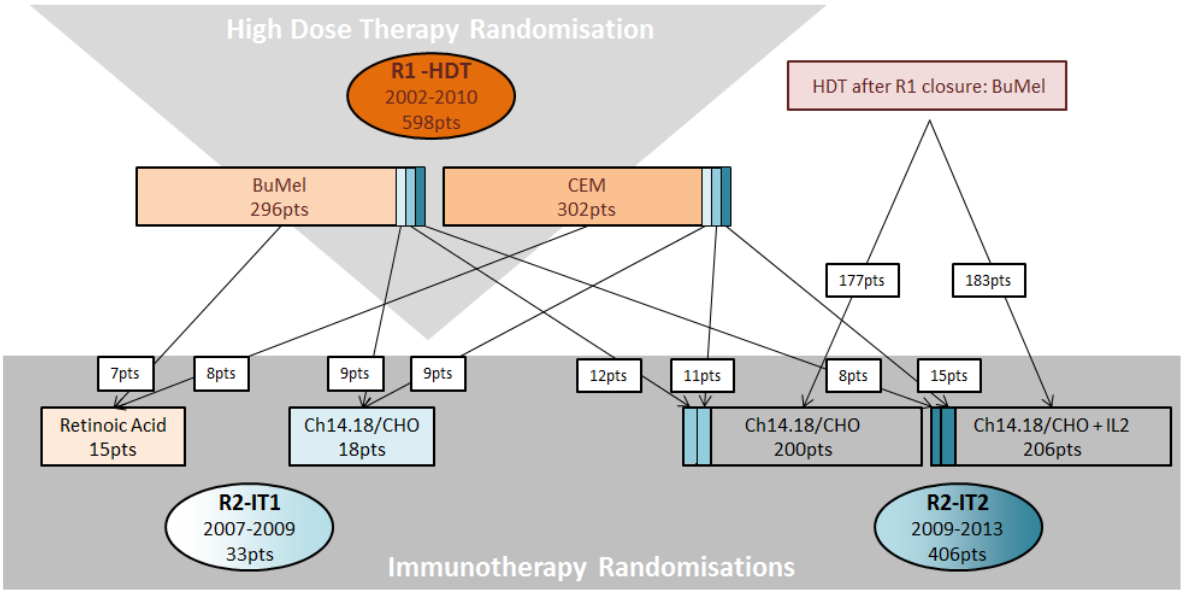
APN311-302 is a segment of the HR-NBL-1 trial established by the Société Internationale D'Oncologie Pédiatrique Europe (SIOPEN).[40] HR-NBL-1 is an investigator-initiated, international, open-label, randomized, phase III trial in people with high-risk neuroblastoma.[41] HR-NBL-1 was set up to test various hypotheses in treating high-risk neuroblastoma and involved several randomisation steps. A schematic of the randomisation stages of the HR-NBL-1 study pertinent to APN311-302 is presented to help illustrate the conduct of the study, and the origin of the treatment groups and historical controls relevant to the decision problem (Figure 2).

In brief, in the randomisation stage referred to as R1 (R1-HDT, Figure 2), the study investigated whether consolidative myeloablative therapy with intravenous busulfan and melphalan (BuMel) would afford a superior EFS at 3 years than myeloablative therapy with continuous infusion of carboplatin, etoposide and melphalan (CEM). BuMel was found to statistically significantly improve EFS at 3 years compared with CEM and is now considered to be the standard myeloablative therapy.[27,41]

The immunotherapy phase of HR-NBL-1 (R2-IT1, Figure 2) was initially designed to assess whether adding dinutuximab beta to isotretinoin after consolidation treatment improved EFS at 3 years compared with isotretinoin alone. In 2010, a phase III trial (ANBL0032) evaluating dinutuximab alpha added to isotretinoin in combination with alternating cycles of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-2 demonstrated an improvement in EFS at 3 years for the dinutuximab alpha-containing regimen compared with isotretinoin alone.[29] Publication of the results of

ANBL0032[29] led to anti-GD2 monoclonal antibody immunotherapy (e.g., dinutuximab alpha) becoming a component of standard care after consolidation therapy in high-risk neuroblastoma. Consequently, the protocol of HR-NBL-1 was amended such that everyone randomised in R2 would receive dinutuximab beta (R2-IT2, Figure 2). The primary hypothesis of the R2 phase became to assess whether adding IL-2 to dinutuximab beta in addition to differentiation therapy with isotretinoin would improve 3-year EFS in those who achieved at least a partial response to prior first-line, multiagent, multimodality therapy. R2-IT2 is the randomisation phase of APN311-302. As can be seen from Figure 2, a small number of people randomised in R2-IT2 came from the R1 phase of the study, with most people randomised in R2-IT2 recruited in a separate process.

Figure 2. The R1 and R2 randomisation stages in the HR-NBL-1 trial[27]



Reprinted from The Lancet Oncology, 18, Ladenstein *et al*., Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. Pages 500–514. Copyright (2017), with permission from Elsevier.

R1–HDT: Randomisation to high-dose myeloablative chemotherapy with either BuMel or CEM.

R2–IT1: Phase that tested the hypothesis that immunotherapy with dinutuximab beta, after high-dose therapy, in addition to differentiation therapy with isotretinoin, would improve 3-year EFS in people with high-risk neuroblastoma (33 people randomised).

R2-IT2: APN311-302 (406 people randomised). Amended HR-NBL-1/SIOPEN protocol that tested the hypothesis that immunotherapy with dinutuximab beta and subcutaneous IL-2 after high-dose therapy, in addition to differentiation therapy with isotretinoin, would improve 3-year EFS in patients with high-risk neuroblastoma.

Abbreviations: BuMel, busulfan and melphalan hydrochloride myeloablative chemotherapy; CEM, carboplatin, etoposide and melphalan myeloablative chemotherapy; Ch14.18/CHO, dinutuximab beta expressed in Chinese hamster ovary cells; EFS, event-free survival; HDT, high-dose therapy; HR-NBL-1, high-risk neuroblastoma-1; IL-2, interleukin 2; no, number; pts, patients.

As part of HR-NBL-1, APN311-302 was also open label and multinational, with recruitment sites in Israel, Australia, and 10 countries across Europe, including Great Britain and Ireland. Initially, 406 people recruited as part of R2-IT2 were randomised to IL-2 or no IL-2. Analyses presented in the CS are based on 370 people for whom an eCRF was available, who received allocated treatment and for whom treatment data were available: patient flow diagram for APN311-302 is presented in Appendix

10.4. Of the 370 people forming the final analysis set in APN311-302, [redacted] people ([redacted]%) were recruited from Great Britain and Ireland.[41] To be eligible for randomisation in APN311-302, people had to:

- have an established diagnosis of neuroblastoma as per the International Neuroblastoma Staging System (INSS);
- be aged below 21 years;
- have high-risk neuroblastoma, which was defined as either;
    - INSS stages 2, 3, 4 or 4s with MYCN amplification of any age below 21 years;

    or

    - INSS stage 4 without MYCN amplification aged ≥12 months at diagnosis and in patients aged 12–18 months only in the presence of segmental chromosomal alterations;
- have tumour cell material available for determination of biological prognostic factors;
- have achieved at least partial remission to induction therapy and undergone consolidation myeloablative therapy followed by ASCT;
    - partial remission or better after induction therapy was defined as achieving at least 50% reduction in skeletal meta-iodobenzylguanidine (mIBG) positivity and no more than three positive but improved spots in mIBG or cytomorphological complete remission in two bone marrow aspirates and no positive bone marrow biopsy.

People who had received [redacted].

Patient recruitment for APN311-302 took place between November 2009 and August 2013. Those eligible for enrolment in APN311-302 were randomised to IL-2 or no IL-2, with both groups receiving dinutuximab beta in addition to differentiation therapy with isotretinoin. Randomisation was carried out using a web-based system and was stratified by national group and by previous treatment (R1-HDT BuMel; R1-HDT CEM; Non R1 people). It is not stated that randomisation was 1:1, but approximately equal numbers of people are included in each group in the final analysis set.

All people randomised were scheduled to receive five 28-day cycles of dinutuximab beta (20 mg/m²/day over 5 days) given as an 8-hour intravenous infusion together with six 28-day cycles of oral isotretinoin (160 mg/m²/day over 14 days). Treatment with isotretinoin was initiated after completion of local irradiation, and no later than Day 120 after peripheral blood stem cell rescue. The first cycle of dinutuximab beta started 3 weeks after the start of treatment with isotretinoin (that is, treatment commenced at week 4 of the schedule). In addition, starting at week 3 of treatment, those randomised to IL-2 also received subcutaneous IL-2 (6 MIU/m^2/day) over 5 days. IL-2 was to be given at least 2 hours after finishing the dinutuximab beta infusion together with prophylactic paracetamol. IL-2 was administered in accordance with the administration schedule:

- weeks 3, 7, 11, 15 and 19, IL-2 was given Monday to Friday;
- weeks 4, 8, 12, 16 and 20, IL-2 was given 2 hours after cessation of the infusion of dinutuximab beta.

Patients who experienced progressive disease during or after induction, or after myeloablative therapy, were discontinued from the study. Treatment with dinutuximab beta was suspended if people experienced the following toxicities:

- Grade 3 (bronchospasm) and 4 (anaphylaxis) allergic reaction;
- Grade 3 serum sickness;
- Grade 4 severe, unrelenting neuropathic pain that was unresponsive to continuous infusion of narcotics and other adjuvant measures including lidocaine infusions.

The primary outcome of the study was EFS at 3 years, which was calculated from the date of the modified R2 randomisation (R2-IT2, Figure 2) and was estimated by the Kaplan–Meier (KM) method. An event within EFS was defined as disease progression or relapse, death from any cause or development of second neoplasm. Definitions for relapse and disease progression as events are not reported in the CS or CSR. The ERG requested a definition for relapsed disease during clarification and, unfortunately, based on the response, it appears that the company interpreted the question as referring to people experiencing relapse and entering APN311-302 rather than relapse as a component of EFS. Disease status was evaluated after myeloablative therapy, radiotherapy and immunotherapy, and at 1-year of follow-up. It is unclear whether people were monitored at regular intervals for relapse, progression or development of second neoplasm after completing 1 year of follow-up: the study had a provisional follow-up of 5 years. In addition, the EMA comments that time points for assessment of disease status were not strictly pre-specified during treatment or follow-up, and, consequently, it is unclear whether the exact time of disease progression has been determined.[39] Disease status of the

[redacted] was evaluated using [redacted].[41] Evaluation of the [redacted].[41] Level of response to treatment [redacted] ([redacted]).

Secondary outcomes included:

- OS, calculated from date of modified randomisation R2 (R2-IT2, Figure 2) to death from any cause;
- cumulative incidence of relapse/progression;
- cumulative incidence of death by disease progression, infection and other reason (definition not available);
- overall response based on the investigator's assessment;
- toxicity;
- relationship of response rates, survival, EFS, and the cumulative incidence of relapse or progressions with potential prognostic factors including MYCN amplification, age by categories (<1 year, 1 to 1.5 years, >1.5 to 5 years and >5 years) and disease status before immunotherapy.

As discussed in Section 4.1, APN311-302 is open label, with investigators and participants aware of the allocated treatment. Clinical effectiveness outcomes (EFS, OS and overall response) were investigator assessed. Non-masking of outcome assessment could lead to performance bias in the assessment of EFS and overall response, but is unlikely to influence OS.

The CS presented data on EFS at 1, 2 and 3 years after randomisation, and also at 5 years for OS, which, in agreement with the report for the suspended STA (GID-TAG507) on dinutuximab alpha,[45] the ERG considers to be an insufficient length of follow-up to assess fully clinical effectiveness in neuroblastoma. In addition, mean follow-up in APN311-302 was [redacted] (SD [redacted]) days, which equates to [redacted]: median follow up was [redacted] days (range of [redacted] to [redacted] days). In the assessment of dinutuximab alpha in high-risk neuroblastoma, it is reported that analyses up to 5 years after randomisation found an improvement in EFS for the dinutuximab alpha-containing regimen, but

longer-term follow-up (up to 10 years) suggested that around half of people would have a cancer-related event, irrespective of treatment received:[45] Additional analyses of clinical effectiveness carried out by the ERG assessing dinutuximab alpha indicated that, "*immunotherapy delays events, and hence lengthens overall survival times, but does not prevent cancer recurrence*".[45] For OS, the ERG assessing dinutuximab alpha noted that the hazard of mortality statistically significantly favoured immunotherapy (HR 0.62, 95% CI: 0.40 to 0.96), from which the ERG suggested that immunotherapy can delay, and possibly prevent, mortality. Clinical effectiveness of dinutuximab alpha is reported in greater detail in Section 4.4.

The study protocol for the HR-NBL-1 study has undergone several amendments. In relation to APN311-302, a key amendment occurred in July 2009 when the treatment regimen of relevance to the decision problem was revised to evaluate the benefit, if any, of adding IL-2 to dinutuximab beta and differentiation therapy with isotretinoin. Other amendments, as reported in the CSR APN311-302, included

[redacted]. [41]

The ERG recognises that APN311-302 represents the best available randomised evidence on the clinical effectiveness of dinutuximab beta, but also notes that the RCT does not inform the decision problem that is the focus of this STA, with everyone randomised having received dinutuximab beta. Moreover, the ERG has some concerns about the conduct of the study, specifically the open label design with apparent absence of independent review of disease status, lack of pre-specified regular follow-up for monitoring for events and potential disparity in recorded time to event, all of which potentially introduce performance bias for the outcomes of EFS and overall response. The lack of long-term follow-up of events (i.e., limited to 5 years) potentially affects the applicability of the results for EFS and OS to the decision problem.

4.2.1.2 Relapsed or refractory neuroblastoma

As part of the clarification process, the ERG asked the company to outline how they envisage dinutuximab beta being used in the treatment of relapsed or refractory neuroblastoma in those who had received the immunotherapy as a first-line maintenance treatment. In the response, the company commented that, "*Given the lack of data for the use of Dinutuximab beta EUSA in patients that may have already failed (relapsed) or those that are refractory to Dinutuximab beta EUSA, EUSA Pharma do not support a re-treatment with the drug*". People in England who relapse are likely to have received dinutuximab beta as part of their multiagent, multimodal first-line therapy through participation in APN311-302, and, thus, on relapse or having refractory disease, would be re-exposed to the immunotherapy. Also, given that [redacted] in APN311-202 or APN311-303 had been treated with dinutuximab beta, the ERG considers that the population experiencing relapse for which evidence is

presented is not representative of people in the UK who would be eligible for treatment with the immunotherapy on relapse and, thus, is potentially not relevant to the decision problem that is the focus of this STA. People experiencing relapse after remission of neuroblastoma assessed as intermediate risk or lower might be eligible for treatment with dinutuximab beta-based therapy, but, as noted earlier, the number of people in this category will be small (Table 6) and, furthermore, evidence is not presented by initial risk categorisation. For completeness, the ERG critiques the quality of the presented evidence in relapsed or refractory neuroblastoma and presents relevant estimates of clinical effect of dinutuximab beta-containing treatment in relapsed and refractory disease.

4.2.1.2.1 APN311-202

Results presented for APN311-202 are derived from an interim analysis of data collected from a prospective SIOPEN study designed with the primary objective of identifying a tolerable treatment schedule of dinutuximab beta that reduced the pain and toxicity profile yet maintained the immunomodulatory effect the intervention: pain, hypersensitivity reactions and capillary leak syndrome are adverse effects associated with administration of dinutuximab beta that warrant a special warning and precaution note in the Summary of Product Characteristics (SmPC).[43] The multinational study has sites in Spain (10), France (9), Italy (9), UK (6), Germany (5), Israel (4), and Austria (1).[39] The first person was enrolled in January 2012 and the data cut off for the interim analysis was February 2015. Key inclusion criteria were:

- neuroblastoma diagnosed according to INSS criteria;
- age >1 to ≤21 years of age (age limit for trial cohorts only);
- received at least one previous high-dose treatment followed by stem cell rescue after conventional therapy to reduce tumour burden;
- fulfilling one of the following criteria:
    - Primary refractory patients with stage 4 disease with at least two lines of treatment prior to high-dose therapy/ASCT, causing a delay from diagnosis to ASCT of over 9 months;
    - Relapse after primary stage 4 disease;
    - Disseminated relapsed neuroblastoma having received ASCT.
- life expectancy of at least 12 weeks.

The study comprised a dose-finding phase (Stage 1) followed by a confirmatory phase (Stage 2). Stage 1 implemented a [redacted].[41] People were to be allocated to a dose regimen of dinutuximab beta in cohorts of 10 people.[39] Planned doses for investigation were 7, 10, or 15 mg/m² given daily with infusion durations varying between 10 and 21 days to give total doses of 100, 150 or 210 mg/m² (e.g. 7 mg/m² for 14 days or 10 mg/m² for 10 days = total 3.3dose of 100 mg/m²).[39] The dose-finding phase was rule-based accounting for the pain and toxicity profile and immunomodulatory (efficacy) capacity. Results on the adverse effect and clinical effectiveness outcomes were to be evaluated after each cohort of 10 people, with the findings of the analysis subsequently determining the next rule-based infusion schedule. The study plan

was to repeat the process until a dose of dinutuximab beta was identified that met all primary endpoint criteria in at least 80% of people.[39] The first cohort of 10 people was allocated to receive 10 mg/m² dinutuximab beta over 10 days (total dose 100 mg/m²) and the total treatment duration in combination with IL-2 and isotretinoin was 35 days. The first allocated dose of dinutuximab beta was subsequently evaluated in an extended group of 24 people in Stage I and was then continued in the confirmatory stage, Stage II, with a planned cohort of 100 people.

All people treated in Stage I and, to date, in Stage II received a total dose of 100 mg/m^2 of dinutuximab beta per cycle given as a continuous long-term infusion over 10 consecutive days: five cycles of dinutuximab beta were given in 5-week intervals, that is, a treatment cycle of 35 days. In addition, people were given subcutaneous IL-2 (6 x 10^6 IU/m^2/day given in two 5-day blocks) and oral isotretinoin (160 mg/m^2 divided into two equal doses given orally twice a day for 14 days after completion of dinutuximab beta infusion).

The interim analysis presented in the CS is based on 44 people with relapsed or refractory neuroblastoma, and comprises 24 people treated in Stage 1 and the first 20 people enrolled during Stage 2. All people included in the analysis have completed study treatment and are therefore eligible for the interim analysis.

Formal hypotheses on clinical effectiveness or adverse effect outcomes relevant to the decision problem were not stated for APN311-202, and no outcome was pre-specified in the protocol.[41] However, EFS and OS were captured and were reported for the final analysis set, which included 44 people. EFS was defined as the time between the first day of IL-2 administration to the date of relapse or progression or death. People without relapse, progression or death at the time of analysis were censored at the last confirmed date of being alive or at the database cut-off date, whichever date came first. The ERG notes that, for APN311-202, development of second neoplasm is not counted as an event, which contrasts with APN311-302. The ERG's clinical experts fed back that development of second neoplasm is a rare event and, thus, its omission from EFS is likely to have minimal impact on any effect estimate generated. In APN311-202, OS was defined as the time between first day of IL-2 administration to death. People not known to have died were censored at the last confirmed date of being alive or at the database cut-off date, whichever date came first. EFS and OS were estimated using KM methods, and EFS and OS at 1 and 2 years' follow-up were reported. Guidance from the US Food and Drug Administration (FDA) indicates that single-arm studies are not appropriate for capturing time-to-event data, such as EFS and OS.[44]

Disease status was assessed by evaluation of urinary catecholamine levels (vanillylmandelic acid, homovanillic acid and dopamine), mIBG scan, CT or MRI scan, and/or ultrasound (if clinically indicated). Evaluation of the bone marrow involved examination of aspirates and trephine biopsy.

Assessments of disease were carried out at screening, mid evaluation and end of treatment. Schedule for follow-up at other time points is unclear.

The ERG considers that data collected for APN311-202 represent the best available evidence on dinutuximab beta in the treatment of relapsed or refractory neuroblastoma but emphasises that results should be interpreted with considerable caution. The study is a single-arm prospective observational study, and as such is associated with a high risk of bias. Moreover, the risk-of-bias in the results is compounded by the lack of pre-specified outcomes and that the results are based on an interim analysis with short-term follow-up.

4.2.1.2.2 APN311-303

APN311-303 was designed to retrospectively evaluate data collected under a compassionate use programme (CU-LTI) carried out in a single site in Germany.[39] People who could not obtain adequate treatment for their neuroblastoma through routine medical treatment or were not eligible for clinical trials were included in the CU-LTI. Data from people enrolled and treated as per the CU-LTI were included in the retrospective analysis. The first person was enrolled in November 2009 and the last person completed treatment in August 2013.[39]

The CU-LTI introduced the treatment approach of a prolonged continuous infusion of dinutuximab beta (rather than a rapid infusion over 8 hours) with the aim of reducing the pain and toxicity profile yet maintaining the immunomodulatory effect in people with high-risk neuroblastoma.[39] In the CU-LTI, dinutuximab beta was administered as a continuous infusion (10 mg/m² for 10 days to give a total dose of 100 mg/m²) in combination with subcutaneous IL-2 (6 x 10^6 IU/m^2/day given in two 5-day blocks) and oral isotretinoin (160 mg/m^2 divided into two equal doses given orally twice a day for 14 days after completion of dinutuximab beta infusion). Treatment was to be given for a maximum of 6 cycles (duration of each cycle was 28 to 35 days) or until there was evidence of disease progression or unacceptable toxicity, whichever occurred first. The first four people enrolled in the CU-LTI were treated with various doses of dinutuximab beta (48–120 mg/m^2/cycle) in combination with different doses of IL-2 (18–60 x 10^6 IU/m^2/cycle): doses of dinutuximab beta and IL-2 were adjusted for the four individuals by the investigator based on safety considerations.

The primary objective of APN311-303 was to assess retrospectively the pain and toxicity profile and safety of prolonged continuous infusion of the dinutuximab beta-containing regimen in high-risk neuroblastoma. Secondary objectives were to evaluate retrospectively:

- response rate in patients with measurable/evaluable disease (skeletal lesions, soft tissue lesions, lymph nodes and/or primary tumour site, bone marrow) as measured by mIBG, CT or MRI

and/or bone marrow examination at the end of cycle 3 and at the end of treatment (after 5th or 6th cycle);

- durability of response;
- OS;
- EFS;
- pharmacodynamic parameters;
- correlation between activated natural killer cells and ch14.18/CHO level with antibody-dependent cell-mediated cytotoxicity;
- pharmacokinetic parameters.

EFS was defined as the number of days from starting treatment in the CU-LTI until relapse or disease progression or as observed and detected by any of CT or MRI, mIBG or bone marrow examination. Again, the ERG notes that the definition of EFS excludes second neoplasm as an event, and, initially, death from any cause. [redacted].[41] A definition of OS is not available within the CS [redacted].

As outlined in the introduction to Section 4.2.1, of APN311-202 and APN311-303, the ERG considers APN311-202 to provide a more robust evidence base for relapsed or refractory neuroblastoma and views APN311-303 as providing data to support the findings from APN311-202. Although data reported for APN311-303 were found to be accurate by Good Clinical Practice inspectors,[39] as a retrospective analysis with no control group, APN311-303 is at increased risk of selection, performance and detection bias, as well as possible lack of standardisation in recording of data, compared with APN311-202. Additionally, the company highlights that a substantial amount of data, particularly for prognostic factors, were not captured and, despite a review of the data, could not be retrieved.[39] Finally, the initial definition of EFS in APN311-303 does not include death, [redacted]. The ERG considers that the definition of EFS applied in APN311-202, and thus the effect estimates generated, is more closely aligned with EFS reported in other studies in neuroblastoma.

4.2.2 Baseline characteristics

4.2.2.1 High-risk neuroblastoma

APN311-302 assesses the effectiveness of adding IL-2 to dinutuximab beta and differentiation therapy with isotretinoin after first-line, multiagent, multimodality therapy, and, thus, the results on comparative clinical effectiveness from the study are not relevant to the decision problem that is the focus of this STA. In the CS, the company combines clinical outcome data from both treatment groups in APN311-302 to form the basis for comparison with historical controls who have not received dinutuximab beta: the ERG considers the company's approach to utilising data for the whole of APN311-302 to be reasonable (discussed in Section 4.4). Therefore, here, the ERG discusses the applicability of the baseline characteristics of the full analysis set (370 people) of APN311-302 to those in England who would likely be eligible for treatment with dinutuximab beta (baseline characteristics summarised in Table 12): similarity of baseline characteristics of APN311-302 and relevant comparator populations is discussed in Section 4.4.1.1. The ERG notes that a [redacted] proportion of people included in APN311-302 were recruited from the UK ([redacted] people [redacted]).

High-risk neuroblastoma typically comprises people who are older than 18 months at diagnosis and with INSS stage 3 or 4 disease, or any INSS stage with amplification of MYCN.[72] Consistent with characteristics of high-risk neuroblastoma, most people in APN311-302 were categorised as INSS stage 4 (88.6%), and many had amplification of MYCN (44.0%): both INSS stage and MYCN status are known to affect prognosis adversely.[72] Mean age at randomisation in APN311-302 was 3.68 (SD 2.63) years, with age of those enrolled ranging from 0.6 to 20 years (Table 12). Most people recruited to APN311-302 were younger than 5 years of age (279 people [75.4%]), which is consistent with the reported typical age at diagnosis of high-risk neuroblastoma.[3]

The ERG's clinical experts fed back that the trial population of APN311-302 is representative of those with high-risk neuroblastoma likely to be eligible for treatment with dinutuximab beta in England.

Table 12. Demographics and baseline characteristics of people in the full analysis set of APN311-302 (adapted from CS, Tables 12 [pg. 39] and 13 [pg. 40])

Parameter	Subgroup/measure	Dinutuximab beta plus isotretinoin (N=180)	Dinutuximab beta + isotretinoin + IL-2 (N=190)	All (N=370)
Gender, n (%)	Male	116 (64.4)	120 (63.2)	236 (63.8)
	Female	64 (35.6)	70 (36.8)	134 (36.2)
Age at randomisation (years)	n	180	189	369
	Mean (SD)	3.55 (2.23)	3.79 (2.97)	3.68 (2.63)
	Median	3.00	3.00	3.00
	Min, Max	0.6, 19.0	0.7, 20.0	0.6, 20.0
Age groups (years), n (%)	<1	5 (2.8)	5 (2.6)	10 (2.7)
	1 to 1.5	8 (4.4)	6 (3.2)	14 (3.8)

	>1.5 to 5	123 (68.3)	132 (69.8)	255 (69.1)
	>5	44 (24.4)	46 (24.3)	90 (24.4)
	Missing	–	1	1
Weight (kg)	n	179	189	369
	Mean (SD)	15.33 (5.24)	16.18 (7.51)	15.77 (6.51)
	Median	14.00	14.30	14.20
	Min, Max	6.4, 55.5	7.0, 54.4	6.4, 55.5
Height (cm)	n	134	152	286
	Mean (SD)	100.46 (16.03)	102.37 (18.80)	101.47 (17.55)
	Median	100.0	98.00	99.00
	Min, Max	71.0, 179.0	70.0, 172.0	70.0, 179.0
Time from diagnosis to randomisation (months)	n	180	190	370
	Mean (SD)	8.36 (1.93)	8.61 (3.23)	8.48 (2.68)
	Median	8.00	8.00	8.00
	Min, Max	6.0, 25.0	6.0, 48.0	6.0, 48.0
MYCN status, n (%)	Amplified	69 (41.6)	83 (46.4)	147 (44.0)
	Not amplified	87 (52.4)	94 (52.5)	178 (53.3)
	Not available	10 (6.0)	2 (1.1)	12 (3.5)
	Missing	14	11	25
INSS stage at initial diagnosis	2[a]	1 (0.6)	–	1 (0.3)
	3[a]	16 (8.9)	18 (9.5)	34 (9.2)
	4	159 (88.3)	169 (88.9)	328 (88.6)
	4S[a]	4 (2.2)	3 (1.6)	7 (1.9)

[a] MYCN amplified.

Abbreviations: cm, centimetre; CS, company submission; FAS, full analysis set; IL-2, interleukin 2; INSS, International Neuroblastoma Staging System; kg, kilogram; MYCN, N-myc proto-oncogene protein; pg, page; SD, standard deviation.

4.2.2.2 Relapsed or refractory neuroblastoma

Here, the ERG reviews the generalisability of the populations enrolled in APN311-202 or APN311-303 to those with relapsed or refractory neuroblastoma likely to be eligible for treatment with dinutuximab beta in England. In Section 4.4.1.2, the ERG critiques the comparability of the populations in APN311-202 and APN311-303 with the historical controls used by the company to generate estimates of comparative clinical effectiveness of dinutuximab beta versus no dinutuximab beta in people with relapsed disease.

APN311-202 is an ongoing prospective study enrolling those with relapsed or primary refractory neuroblastoma, with study sites in the UK: the number of people recruited from the UK to date to APN311-202 is unclear. By contrast, APN311-303 is a retrospective analysis of data collected during the CU-LTI programme administered at a single site in Germany and included those receiving dinutuximab beta at first-line. Baseline characteristics of those recruited and analysed in APN311-202 and APN311-303 are presented in Table 13 to Table 16.

In APN311-202, of the 44 people included to date, 19 people (43.2%) were experiencing relapse and 25 (56.8%) had refractory disease (Table 13). Conversely, in APN311-303, a larger proportion of people

were diagnosed as relapsing (66.7% [30/45]) compared with being refractory (33.3% [15/45]) to treatment (Table 16). Of those diagnosed with relapse, most people in both studies were undergoing their first relapse (16 [69.6%] in APN311-202 and [redacted] in APN311-303; Table 14).

A marginal difference in proportion of people of INSS Stage 4 was noted in people experiencing relapse or refractory neuroblastoma in APN311-202 and in APN311-303 (Stage 4: 93.2% in APN311-202 vs 86.7% [39/45] in APN311-303). However, there was a marked difference between studies in MYCN status at baseline, with a larger proportion of people in APN311-303 having amplified MYCN at baseline (7.1% in APN311-202 vs 17.8% [8/45] in APN311-303). The ERG notes that studies evaluating various chemotherapy regimens in people with relapsed or refractory high-risk neuroblastoma typically report a larger proportion of people with amplified MYCN at baseline than that described in either APN311-202 or APN311-303. A publication of a retrospective analysis of people with first relapse or progression of neuroblastoma (N=2266) identified 33% of people evaluated as having amplified MYCN at baseline:[10] additional publications identified by the ERG reported proportions of people with amplified MYCN ranging from 27.2% to 42.2%.[73])[74,75] Mean age at diagnosis of neuroblastoma for those in APN311-202 (3.2 years, SD 2.0 years) is comparable with that reported for APN311-302 (Table 12). Mean age at diagnosis [redacted] for APN311-303,

[redacted] Table 16).

In relapsed neuroblastoma, time to first relapse is an additional key prognostic factor. In APN311-202 and APN311-303, mean time from diagnosis to most recent relapse is 1,099 days (SD 1,091 days; Table 14) and [redacted] days (SD [redacted] days; Table 14), but the mean value also accounts for those experiencing multiple relapses or disease progression. It is noted that, as discussed in Section 4.2.1.2.2, data on baseline characteristics were not available for all people evaluated in APN311-303.

For most reported baseline characteristics, the ERG considers APN311-202 and APN311-303 to be representative of people with relapsed and refractory neuroblastoma in England. However, the ERG notes considerable disparity across APN311-202, APN311-303 and the published literature in the reported proportions of people with MYCN amplification, which is a key prognostic factor in neuroblastoma. The potential impact of differences in proportion of people with MYCN amplification on clinical effectiveness outcomes is discussed in subsequent sections presenting outcome data for APN311-202 versus historical controls.

The ERG's clinical experts highlighted two issues that should be considered when interpreting results on clinical outcomes from APN311-202 and APN311-303. Firstly, it is likely that a proportion of those enrolled in APN311-202 and APN311-303 and classified as refractory to treatment are people originally

participating in APN311-302 who, rather than being truly refractory, did not achieve an adequate response to induction therapy in APN311-302. In APN311-302, adequate response was defined as at least a partial response, and, thus, some people enrolled in APN311-202 or the CU-LTI of APN311-303 might have achieved a minimal response to induction therapy, which was insufficient to receive further treatment in APN311-302, rather than having no response or experiencing disease progression while on treatment. It is unclear from the CS or CSRs for APN311-202 and APN311-303 whether anyone enrolled in the studies originated from APN311-302. Analysis of data in APN311-303 led to an EFS of 44.8% at 1 year, 31.0% at 2 years and 24.1% at 3 years of follow-up in those with relapsed neuroblastoma compared with EFS of 58.2% at 1 year, 29.1% at 2 years, and 29.1% 3 years (as reported in CS and CSR) in refractory neuroblastoma. Similar results were noted for OS in APN311-303 [redacted] (discussed in greater detail in Section 4.3).

Secondly, since 2009, people diagnosed with high-risk neuroblastoma in England will have been enrolled in APN311-302, and most will have achieved at least a partial response to induction therapy. Consequently, those experiencing relapse of high-risk neuroblastoma today are likely have received dinutuximab beta as part of their first-line multimodal therapy. Based on the company's response to clarification, [redacted] APN311-202 and APN311-303 has received prior dinutuximab beta as part of first-line therapy.

Overall, given the ambiguity around the level of refractoriness to treatment of people in APN311-202 and APN311-303, and whether people with relapse have received prior dinutuximab beta, the ERG considers that there is considerable uncertainty in the extent to which the populations in the two studies are generalisable to those in England with relapsed or refractory neuroblastoma.

Table 13. Demographics and baseline characteristics of people in APN311-202 (adapted from CS, Tables 18 [pg. 44] and 19 [pg. 44])

Parameter	Subgroup/measure	Number of patients (N=44)
Gender	Male	28 (63.6%)
	Female	16 (36.4%)
Ethnicity	White/Caucasian	36 (87.8%)
	Black	–
	Asian	1 (2.4%)
	Unknown	4 (9.8%)
	Missing	3
Age at initial diagnosis (years)	n	44
	Mean (SD)	3.2 (2.0)
	Median	3.0
	Min, Max	0, 9
Age at start of treatment (years)	n	44
	Mean (SD)	6.1 (3.4)
	Median	5.0

	Min, Max	1, 17
MYCN amplification	No	39 (92.9%)
	Yes	3 (7.1%)
	Missing	2
INSS stage at initial diagnosis	1	1 (2.3%)
	4	41 (93.2%)
	4S	2 (4.5%)
Patients with refractory disease, n (%)	–	25 (56.8%)
Disease status at baseline	Measurable by MRI and/or CT	8 (32.0%)
	Evaluable only by mIBG and/or BM histology	13 (52.0%)
	No evidence of disease	4 (16.0%)
Patients with relapsed disease, n (%)	–	19 (43.2%)
Disease status at baseline	Measurable by MRI and/or CT	4 (21.1%)
	Evaluable only by mIBG and/or BM histology	8 (42.1%)
	No evidence of disease	7 (36.8%)

Abbreviations: CS, company submission; INSS, International Neuroblastoma Staging System; MYCN = N-myc proto-oncogene protein; pg, page; SD, standard deviation.

Table 14. Relapse and progression status before receiving dinutuximab beta in APN311-202 and APN311-303 (adapted from CS, Table 20 [pg. 45] and clarification response dated 25 August 2017)

Parameter	**Subgroup/measure**	**APN311-202 (N=44)**	**APN311-303 (N=54)**
Number of relapses/progressions	n	23	[redacted]
	Mean (SD)	1.5 (1.1)	[redacted]
	Median	1.0	[redacted]
	Min, Max	1, 6	[redacted]
Number of relapses/progressions (categories)	1	16 (69.6%)	[redacted]
	2	6 (26.1%)	[redacted]
	5	–	[redacted]
	6	1 (4.3%)	[redacted]
	8	–	[redacted]
Time from initial diagnosis to most recent relapse/progression (days)	n	16	[redacted]
	Mean (SD)	1,099 (1,091)	[redacted]
	Median	618	[redacted]
	Min, Max	253, 4,123	[redacted]
Most recent relapse/progression type	Bone marrow alone	3 (13.0%)	[redacted]
	Combined	13 (56.5%)	[redacted]
	Other metastatic sites alone	1 (4.3%)	[redacted]
	Primary tumour site alone	2 (8.7%)	[redacted]
	Skeleton alone	4 (17.4%)	[redacted]

Abbreviations: CS, company submission; INSS, International Neuroblastoma Staging System; MYCN = N-myc proto-oncogene protein; pg, page; SD, standard deviation.

Table 15. Demographics and baseline characteristics of people enrolled in a compassionate use program (CU-LTI) providing the results for APN311-303 (adapted from CS, Tables 14 [pg. 40] and 16 [pg. 42])

Parameter	Subgroup/measure	Number of patients (N=54)
Gender	Male	33 (61.1%)
	Female	21 (38.9%)
Ethnicity	White/Caucasian	52 (96.3%)
	Black	-
	Asian	2 (3.7%)
Age (years)	n	54
	Mean (SD)	7.3 (4.7)
	Median	6.0
	Min, Max	2, 26
Weight (kg)	n	53
	Mean (SD)	22.33 (12.95)
	Median	17.40
	Min, Max	11.7, 75.1
Height (cm)	n	53
	Mean (SD)	116.1 (22.2)
	Median	110.0
	Min, Max	82, 188
BSA (m^2)	n	53
	Mean (SD)	0.839 (0.307)
	Median	0.730
	Min, Max	0.53, 1.94
Time since first diagnosis to screening visit (months)	n	54
	Mean (SD)	33.1 (25.0)
	Median	25.0
	Min, Max	9, 116
Age at first diagnosis (days)	<547	11 (20.4%)
	≥547	43 (79.6%)
INSS stage	1	1 (1.9%)
	2A	1 (1.9%)
	2B	–
	3	4 (7.5%)
	4	47 (88.7%)
	4S	–
	Missing	1
Baseline status	Relapsed	30 (55.6%)
	Refractory	15 (27.8%)
	Evidence of disease after first-line therapy	3 (5.6%)
	No evidence of disease after first-line therapy	6 (11.1%)

LDH (µkat/L)	n	15
	Mean (SD)	6.80 (5.19)
	Median	5.12
	Min, Max	0.1, 21.0
Serum ferritin (µg/L)	n	12
	Mean (SD)	1,161.34 (1,292.84)
	Median	638.00
	Min, Max	79.1, 4,458.0
Initial treatment	Observation, surgery, or standard chemotherapy	4 (7.4%)
	Intensive multimodality	50 (92.6%)

Abbreviations: BSA, body surface area; cm, centimetre; CS, company submission; INSS, International Neuroblastoma Staging System; LDH, lactate dehydrogenase; m, metre; pg, page; SD, standard deviation.

Table 16. Demographics and baseline characteristics of people enrolled in the compassionate use program (CU-LTI) that provides results for APN311-303 by baseline disease status (adapted from CS, Tables 15 [pg.41] and 17 [pg. 42])

Parameter	**Subgroup/measure**	**Relapse[a] (N=30)**	**Refractory[a] (N=15)**	**First-line[a] (N=9)**
Time since first diagnosis to SCR visit (months)	n	30	15	9
	Mean (SD)	44.6 (27.3)	21.3 (11.7)	14.2 (4.7)
	Median	35.5	16.0	14.0
	Min, Max	21,116	10, 55	9, 23
Age at first diagnosis, n (%)	<547 days	4 (13.3)	6 (40.0)	1 (11.1)
	≥547 days	26 (86.7)	9 (60.0)	8 (88.9)
Disease status at study entry	Measurable by MRI and/or CT	7 (23.3%)	6 (40.0%)	2 (22.2%)
	Evaluable only by mIBG and/or bone marrow histology	16 (53.3%)	7 (46.7%)	1 (11.1%)
	No evidence of disease	7 (23.3%)	2 (13.3%)	6 (66.7%)
INSS stage, n (%)	1	1 (3.4)	–	–
	2[a]	1 (3.4)	–	–
	3	2 (6.9)	1 (6.7)	1 (11.1)
	4	25 (86.2)	14 (93.3)	8 (88.9)
MYCN amplification, n (%)	No	17 (81.0)	9 (69.2)	3 (37.5)
	Yes	4 (19.0)	4 (30.8)	5 (62.5)
Grade NB differentiation, n (%)	Differentiated	6 (46.2)	8 (72.7)	1 (50.0)
	Undifferentiated	7 (53.8)	3 (27.3)	1 (50.0)
MKI, n (%)	Low	1 (33.3)	2 (66.7)	–
	Intermediate	1 (33.3)	–	–
	High	1 (33.3)	1 (33.3%)	–
LDH (µkat/L)	n	8	6	1
	Mean (SD)	7.32 (3.72)	7.21 (6.81)	0.09 (.)
	Median	6.95	4.64	0.09
	Min, Max	2.9, 13.6	3.0, 21.0	0.1, 0.1
Serum ferritin (µg/L)	n	6	5	1
	Mean (SD)	1,237 (1746.77)	1,279.00 (712.55)	159.00 (.)
	Median	341.85	1,287.0	159.00

	Min, Max	79.1, 4,458.0	606.0, 2,369.0	159.0, 159.0
Initial treatment, n (%)	Observation, surgery or standard chemotherapy	4 (13.3%)	–	–
	Intensive multimodality	26 (86.7%)	15 (100.0%)	9 (100.0%)

[a] Note: Missing values are not displayed.

Abbreviations: CS, company submission; CT, computed tomography; INSS, International Neuroblastoma Staging System; LDH, lactate dehydrogenase; mIBG, meta-iodobenzylguanidine; MKI, mitosis-karyorrhexis index; MRI, magnetic resonance imaging; MYCN, N-myc proto-oncogene protein; pg, page; SCR, screening visit; SD, standard deviation.

4.2.3 Description and critique of statistical approach used

4.2.3.1 High-risk neuroblastoma

The primary outcome in APN311-302 was EFS at 3 years, with EFS calculated from the date of the modified R2 randomisation to an event. OS was a secondary outcome. EFS and OS were estimated by the KM method. APN311-302 was powered to detect an improvement of 12.5% in EFS at 3 years with addition of IL-2 to dinutuximab beta and differentiation therapy with isotretinoin, assuming an EFS at 3 years of 55% without IL-2 and using two-sided alpha of 0.05. To achieve 80% power and a difference of 12.5% in EFS, the study required a sample size of 400 people. The company estimated recruitment would occur over a period of 4 years, and that there would be a minimum follow up of 2 years. Patients lost to follow-up without event were censored at the date of their last follow-up evaluation. Statistical significance of differences between treatment regimens in EFS at 3 years, and other time points, and OS was assessed using the log-rank test, adjusted for previous consolidation treatment (BuMel or CEM). As noted earlier, there was no schedule for regular follow-up assessment. Response evaluations were summarised descriptively at baseline, after dinutuximab beta and at 1-year follow-up.[39] The ERG notes that analyses did not follow the ITT principle but were based on 370 people for whom an eCRF was available and who received at least one dose of allocated treatment. The ERG considers that the company has carried out the equivalent of a complete case analysis.

The log-rank test is used to test the null hypothesis that there is no difference between population survival curves at any time point, and, therefore, does not provide information about potential differences at different periods of follow-up.[76] The log-rank test is most likely to detect a difference between treatment groups when the risk of an event is consistently greater for one group than another. As a test of significance alone, the log-rank test does not provide an estimate of the size of the difference between the groups, or an estimate of the uncertainty around the effect of the intervention under investigation.[76] The ERG considers that reporting of HRs and accompanying 95% confidence intervals (95% CIs) at the time points assessed would help reinforce the results of the log-rank test, as well as provide more information about maintenance of clinical effect over time. As noted earlier, the effect of adding IL-2 to dinutuximab beta and isotretinoin therapy is not of interest to the decision problem. The ERG discusses the statistical methods of APN311-302 as the points raised are relevant to the discussion

of the indirect comparisons implemented to generate estimates of comparative effectiveness of dinutuximab beta versus isotretinoin in high-risk neuroblastoma (discussed in Section 4.4).

4.2.3.2 Relapsed or refractory neuroblastoma

No formal statistical hypotheses, statistical analysis methods or power calculations were specified *a priori* for either APN311-202 or APN311-303. The primary objective of APN311-202 and APN311-303, both of which are single-arm studies, was to identify a tolerable treatment schedule for dinutuximab beta that minimised the pain and toxicity profile of the immunotherapy while maintaining the immunomodulatory effect. APN311-202 prospectively collected data on efficacy and safety of dinutuximab beta in people with relapsed or refractory neuroblastoma whereas APN311-303 retrospectively analysed data collated from administration of dinutuximab beta during the CU-LTI.

In APN311-202, the primary outcome was number of CD16/CD56 positive activated natural killer cells. EFS and OS were collected during the study but were not prespecified outcomes. EFS and OS were analysed using KM methods. Data presented in the CS are from an interim analysis of 44 people: APN311-202 is ongoing and the planned recruitment is 100 people.

For APN311-303, as a result of the retrospective nature of the study, all people treated in the CU-LTI were considered for inclusion in analysis of clinical efficacy. The primary endpoint of APN311-303 was the safety and tolerability of dinutuximab beta evaluated by pain intensity and morphine use, adverse effects (type, grade and incidence), vital signs, and changes in clinical laboratory assessments. EFS and OS were secondary endpoints and were analysed using KM methods.

In the CS, the company presents estimates of EFS and OS for dinutuximab beta versus no dinutuximab beta in relapsed neuroblastoma using data from APN311-303 alone, together with a pooled analysis of data from APN311-202 and APN311-303. Significance of differences in EFS and OS as reported in the CS are assessed primarily using the log-rank test.

Given the lack of *a priori* hypotheses and statistical analysis methods for APN311-202 and APN311-303, and the reporting of interim results for APN311-202, the ERG has reservations about the validity and robustness of the data derived from the two studies and advises caution when interpreting reported clinical and safety analyses (additional detail in Section 4.3).

4.2.4 Summary statement

Evidence was not available from a head-to-head study comparing dinutuximab beta versus comparators of interest as set out in the final scope issued by NICE.[46] The company presented naïve indirect comparative assessments in support of the clinical effectiveness of dinutuximab beta in two subgroups

of neuroblastoma – those with high-risk neuroblastoma and those with relapsed or refractory neuroblastoma (discussed in Section 4.4).

Evidence pertaining to the clinical efficacy of dinutuximab beta when added to differentiation therapy with isotretinoin in high-risk neuroblastoma was derived from an open-label, multinational RCT. APN311-302 randomised 406 people to IL-2 or no IL-2 added to dinutuximab beta and isotretinoin in those diagnosed with high-risk neuroblastoma and achieving at least a partial response to first-line, multiagent, multimodality therapy. A large proportion of people analysed in APN311-302 were recruited from the UK ([redacted] people [redacted%]), and baseline characteristics of the trial population are representative of those with high-risk neuroblastoma likely to be eligible for treatment with dinutuximab beta in England.

All people randomised in APN311-302 were scheduled to receive five 28-day cycles of dinutuximab beta (20 mg/m²/day over 5 days) given as an 8-hour intravenous infusion together with six 28-day cycles of oral isotretinoin (160 mg/m²/day over 14 days). The ERG notes that a larger proportion of people receiving IL-2 discontinued treatment compared with those not receiving IL-2: 17.5% of patients receiving IL-2 experienced an SAE leading to withdrawal, compared with 6% of patients not receiving IL-2. Similarly, of those for whom treatment completion status could be determined, the proportion of people allocated to IL-2 who received at least 50% of the planned dose of dinutuximab beta or IL-2 (if applicable) was considerably smaller in those allocated IL-2 (39.4% with IL-2 vs 78.3% without IL-2 in cycles 1–5). IL-2 administration can be associated with severe adverse effects (e.g., difficulty breathing, reduced output of urine, and capillary leak syndrome),[77] and so the imbalance in people withdrawing from or receiving fewer doses of IL-2 could be anticipated.

The primary outcome of APN311-302 was EFS at 3 years, which was estimated by the KM method. OS was captured as a secondary endpoint. All outcomes in APN311-302 were investigator assessed. The open-label nature of APN311-302 could lead to performance bias in the assessment of EFS and overall response, but is unlikely to influence OS. Status of neuroblastoma was evaluated after myeloablative therapy, radiotherapy and immunotherapy, and at 1-year of follow-up. It is unclear whether people were monitored at regular intervals, during treatment or after 1 year, for relapse, progression of disease or development of second neoplasm. The EMA commented that time points for assessment of disease status were not strictly pre-specified during treatment or follow-up, and, consequently, it is unclear whether the exact time of disease progression has been determined.[39] Statistical significance of differences between treatment regimens in EFS and OS was assessed using the log-rank test, adjusted for previous consolidation treatment (BuMel or CEM). The ERG notes that analyses did not follow the ITT principle but were based on 370 people for whom an eCRF was available and who received allocated treatment. The ERG considers that the company has carried out the equivalent of a complete case analysis. The company could have performed an IT analysis either by

simplistically assuming a best or worst case scenario or by implementing formal statistical techniques. Reporting of HRs and accompanying 95% CIs at the time points assessed would help reinforce the results of the log-rank test, as well as provide more information about maintenance of clinical effect over time.

The CS presented data on EFS at 1, 2 and 3 years after randomisation, and at 5 years for OS, which the ERG considers to be an insufficient length of follow-up to assess fully clinical effectiveness in neuroblastoma, [redacted].

The ERG evaluating the clinical effectiveness of dinutuximab alpha suggested that treatment with the immunomodulatory agent leads to a delay in experiencing an event, and consequently lengthens OS times, but does not prevent recurrence of neuroblastoma in the longer term (up to 10 years).

Evidence in support of the effectiveness of dinutuximab beta in relapsed or refractory neuroblastoma is derived from two single-arm observational studies, one of which is prospective in design (APN311-202) and the other retrospective (APN311-303). The primary objective of both APN311-202 and APN311-303 was to identify a tolerable treatment schedule for dinutuximab beta that minimised the pain and toxicity profile of the immunotherapy while maintaining the immunomodulatory effect. APN311-202 prospectively collected data on efficacy and safety of dinutuximab beta in people with relapsed or refractory neuroblastoma whereas APN311-303 retrospectively analysed data collated from administration of dinutuximab beta during a compassionate use program (CU-LTI).

APN311-202 comprises 44 people to date, 19 of whom (43.2%) were experiencing relapse and 25 (56.8%) with refractory disease (Table 13). Conversely, in APN311-303, a larger proportion of people were diagnosed as relapsing (30/45 [66.7%]) compared with being refractory (15/45 [33.3%]) to treatment: APN311-303 also included 9 people receiving dinutuximab beta as first-line treatment. Of those diagnosed with relapse in APN311-202, most people were undergoing their first relapse (84.2%).

In APN311-202 and APN311-303, dinutuximab beta was administered as a continuous long-term infusion over 10 consecutive days to give a total dose of 100 mg/m^2 of dinutuximab beta per cycle. In APN311-202, five cycles of dinutuximab beta were given in 5-week intervals, that is, a treatment cycle of 35 days. In addition, people were given subcutaneous IL-2 (6 x 10^6 IU/m^2/day given in two 5-day blocks) and oral isotretinoin (160 mg/m^2 divided into two equal doses given orally twice a day for 14 days after completion of dinutuximab beta infusion). In APN311-303, the treatment doses were the same as those in APN311-202, with a difference that the cycle duration was 28 to 35 days.

People experiencing relapse or refractory neuroblastoma in APN311-202 and in APN311-303 were similar in INSS stage (Stage 4: 93.2% in APN311-202 vs 86.7% [39/45] in APN311-303). However,

there was a marked difference between studies in MYCN status at baseline, with a larger proportion of people in APN311-303 having amplified MYCN at baseline (7.1% in APN311-202 vs 17.8% [8/45] in APN311-303). For most reported baseline characteristics, the ERG considers APN311-202 and APN311-303 to be representative of people with relapsed and refractory neuroblastoma in England. However, the ERG notes considerable disparity across APN311-202, APN311-303 and the published literature in the reported proportions of people with MYCN amplification, which is a key prognostic factor in neuroblastoma. The company reports that a substantial volume of data could not be retrieved for APN311-303, including key data on prognostic factors.

No formal statistical hypotheses, statistical analysis methods or power calculations were specified *a priori* for either APN311-202 or APN311-303. In APN311-202, the primary outcome was number of CD16/CD56 positive activated natural killer cells. EFS and OS were collected during the study but were not prespecified outcomes. EFS and OS were analysed using KM methods. Data presented in the CS are from an interim analysis of 44 people: APN311-202 is ongoing and the planned recruitment is 100 people. For APN311-303, the primary endpoint was the safety and tolerability of dinutuximab beta evaluated by pain intensity and morphine use, adverse effects (type, grade and incidence), vital signs, and changes in clinical laboratory assessments. EFS and OS were secondary endpoints and were analysed using KM methods. Significance of differences in EFS and OS reported in the CS are assessed using primarily the log-rank test.

The ERG's clinical experts highlighted two issues that should be considered when interpreting results on clinical outcomes from APN311-202 and APN311-303. Firstly, it is likely that a proportion of those enrolled in APN311-202 and APN311-303 and classified as refractory to treatment are people originally participating in APN311-302 who, rather than being truly refractory, did not achieve an adequate response to induction therapy in APN311-302. In APN311-302, adequate response was defined as at least a partial response, and, thus, some people enrolled in APN311-202 or the CU-LTI of APN311-303 might have achieved a minimal response to induction therapy, which was insufficient to receive further treatment in APN311-302, rather than having no response or experiencing disease progression while on treatment. The proposal that those in APN311-202 and APN311-303 might not be truly refractory to treatment is supported by estimates of EFS and OS for the two groups, with higher estimates of EFS for those with refractory compared with relapsed neuroblastoma, which conflicts with expected prognosis for the two disease states.

Secondly, since 2009, people diagnosed with high-risk neuroblastoma in England will have been enrolled in APN311-302, and most will have achieved at least a partial response to induction therapy. Consequently, those experiencing relapse of high-risk neuroblastoma today are likely have received dinutuximab beta as part of their first-line multimodal therapy. Based on the company's response to

clarification, [redacted] in APN311-202 or APN311-303 has previously received treatment with dinutuximab beta.

In summary, considering APN311-302, the ERG has some concerns about the conduct of the study, specifically the open label design with apparent absence of independent review of disease status, lack of pre-specified regular follow-up for monitoring for events and potential disparity in recorded time to event, all of which potentially introduce performance bias for the outcomes of EFS and overall response. In addition, dinutuximab beta was infused over 8 hours for 5 days rather than as a continuous infusion, which would be the preferred administration schedule in UK clinical practice. The lack of long-term follow-up of events (i.e., limited to 5 years) potentially affects the applicability of the results for EFS and OS to the decision problem. Considering APN311-202 and APN311-303, there is ambiguity around the level of refractoriness to treatment of people in the studies, and whether people with relapse have received prior dinutuximab beta. Consequently, the ERG considers there is uncertainty in the extent to which the populations in APN311-202 and APN311-303 are generalisable to those in England with relapsed or refractory neuroblastoma. In addition, the number of people with relapsed and with refractory neuroblastoma in each study is small (44 people in APN311-202 and 45 people in APN311-303). Given the lack of *a priori* hypotheses and statistical analysis methods for APN311-202 and APN311-303, and the reporting of interim results for APN311-202, the ERG has reservations about the validity and robustness of the data derived from the two studies and advises caution when interpreting reported clinical and safety analyses. In addition, the US FDA advises that single-arm studies are not appropriate for capturing time-to-event data, such as EFS and OS.

4.3 Clinical effectiveness results

Direct evidence submitted to NICE in support of dinutuximab beta is derived from one RCT and two observational studies in which dinutuximab beta was given in combination with isotretinoin and, with the exception of one group of the RCT, IL-2. Data presented in this section do not give an indication of the relative clinical effectiveness of dinutuximab beta versus other treatments: results from indirect comparisons are presented in Section 4.4. For completeness, and because these studies are the foundation of the estimates of comparative clinical effectiveness, results for dinutuximab beta generated from APN311-302, APN311-202 and APN311-303 are reported here for the outcomes of EFS and OS.

Within the CS, in high-risk neuroblastoma, the company discusses narratively the clinical effectiveness of dinutuximab beta compared with that of dinutuximab alpha. As outlined in Section 3.3, the ERG considers that an indirect comparison of dinutuximab beta versus dinutuximab alpha would contribute to understanding of the clinical effectiveness of dinutuximab beta (discussed in greater detail in Section 4.4). As there are no direct head-to-head comparative data of dinutuximab alpha and beta, for context, the ERG considers it useful to present EFS and OS for dinutuximab alpha-based treatment and

isotretinoin alone as reported in the full publication of the trial, and for isotretinoin alone from other key publications. The ERG considers that, given the two immunotherapies bind to the same target, the reported clinical effectiveness of dinutuximab alpha can inform on the efficacy of dinutuximab beta through an appropriately adjusted indirect comparison, but emphasises that individual results for the two agents should not be compared naively. Additionally, because of differences in prior myeloablative therapy and concomitant treatments, the ERG cautions that it cannot be assumed that dinutuximab beta-containing regimens are clinically effective because dinutuximab alpha-containing regimens have been shown to be clinically effective when compared with isotretinoin alone.

The company also presents results for tumour response rate from APN311-202 and APN311-303, but not APN311-302. The ERG has decided not to include tumour response rate in its report. Tumour response rate was obtainable for people with measurable disease at the start of treatment with dinutuximab beta and who had one assessment after baseline. Tumour response rate is considered a good measure of anti-tumour activity but does not necessarily relate to disease stability or prognosis. Moreover, as highlighted by the CHMP, best response achieved at any point after initiation of dinutuximab beta was reported, rather than tumour response at end of treatment: best response might not be the most clinically relevant outcome as it encompasses responses of short duration.[39]

The ERG reiterates that no formal primary cut-off date for analysis was specified for APN311-302, APN311-202 or APN311-303. In addition, no formal time period for follow-up assessment of outcomes after treatment was set. In the CS, the company presents data on EFS at 3 years and OS at 2 years for APN311-302, and EFS and OS at 2 years for APN311-303. As part of the clarification process, the company helpfully provided an analysis of EFS and OS at the latest data cut-off for all three studies, together with KM curves for all outcomes requested, including curves adjusted for key prognostic outcomes.

4.3.1 Event-free survival

4.3.1.1 High-risk neuroblastoma

EFS in APN311-302 comprised disease progression or relapse, death from any cause and second neoplasm, and was calculated from the date of randomisation to event occurrence: KM curve for EFS is presented in Figure 3. In the CS, the company presents data on KM estimates of EFS at 3 years, which was the primary outcome for APN311-302, together with EFS at 1 and 2 years of follow-up (Table 17). As part of the clarification process, the company provided an updated analysis of EFS based on time to the last event in each treatment group (Table 17).

In the final analysis set, the CS reports that 79 people (44.1%) randomised to dinutuximab beta and isotretinoin had experienced an event at 3 years compared with 69 people (36.5%) in the group allocated

to receive additionally IL-2: median EFS is not estimable for either group as 50% of people have not experienced an event. The ERG notes [redacted] (Table 17). Based on the company's response to clarification questions, [redacted], which occurred [redacted] follow-up in the group given IL-2 compared with [redacted] for the group not receiving IL-2 (Table 17): data provided in the company's response to clarification indicate that the maximum length of follow-up recorded to date is [redacted] days (equates to [redacted] years). The log-rank test for the difference between groups in EFS, with adjustment for previous induction therapy, was not statistically significant (p = 0.3202; Table 17), indicating that there is no difference in EFS at any time point between dinutuximab beta plus isotretinoin with IL-2 and without IL-2: the ERG notes that the reported log-rank test [redacted]. As the ERG noted, the log-rank test is a test only of significance and gives no indication of size of effect or accompanying uncertainty in estimate of effect.

Although the difference in reported number of events [redacted], the ERG considers the [redacted]. The ERG appreciates that recruitment to APN311-302 took place over 4 years [redacted]. The company helpfully provided adjusted time-to-event data for the two treatment groups in APN311-302 with accompanying KM curves (Appendix 10.5): time-to-event data and curves [redacted].

Using the adjusted time-to-event data supplied by the company (available in Appendix 10.5), the ERG carried out a Cox proportional hazard analysis to generate an effect estimate of IL-2 versus no IL-2 added to dinutuximab beta and differentiation therapy with isotretinoin. However, the ERG notes that [redacted]. Visual inspection of the adjusted KM curve for EFS (Figure 4) suggests that the addition of [redacted]. The ERG considers that one effect modifier that could be influencing the result is

level of response to induction therapy. As noted by the EMA, data indicate that IL-2 confers no benefit when added to dinutuximab beta and isotretinoin in those with high-risk neuroblastoma who achieve complete response to induction therapy, whereas the same could not be concluded for those with evidence of residual disease (discussed in Section 4.3.3).

The ERG carried out the analysis in R version 3.4.1. Given the date of recruitment of the last person to APN311-302 (August 2013), the minimum number of days of follow-up a person can have accrued is 1,461 days. [redacted], in cases of censoring due to lack of an event, [redacted].

[redacted].

Table 17. Summary of event-free survival for APN311-302 (adapted from CS, Tables 23 [pg. 55] and 24 [pg. 56], and from response to clarification dated 10 August 2017, Tables 4 [pg. 9] and 8 [pg. 11], and dated 16 August 2017, Tables 2 [pg. 6] and 4 [pg. 9])

	Dinutuximab beta plus isotretinoin (N=180)	**Dinutuximab beta plus isotretinoin plus IL-2 (N=190)**
KM estimate		
1 year (%)	72.3	72.3
2 years (%)	63.2	66.3
3 years (%)	55.4	61.2
Log-rank test[a]	p = 0.3202[b]	
Cumulated number of events, n (%)		
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
3 years[c]	[redacted]	[redacted]
3 years[d]	79 (44.1)	69 (36.5)
4 years	[redacted]	[redacted]
Last cut off[e]	[redacted]	[redacted]
Censored[f], n (%)	100 (55.9)	120 (63.5)

[a] Log-rank adjusted for previous treatment (busulfan and melphalan vs carboplatin, etoposide and melphalan).

[b] The p-value refers to the analysis based on 3 years' follow-up (stated in CS).

[c,d] On reviewing the company's response to clarification (dated 10 August 2017), the ERG notes [redacted] in the reported number of events at 3 years. Event rate in the row with footnote c [redacted] footnote d presents number of events as reported in the CS.

[e] The [redacted] In the company's response to clarification dated 16 August 2017 [redacted] dinutuximab beta and isotretinoin [redacted] dinutuximab beta plus isotretinoin and IL-2 [redacted].

[f] One person with missing date of death and without progression was excluded from each group.

Abbreviations: CS, company submission; EFS, event-free survival; IL-2, interleukin 2; KM, Kaplan–Meier; pg, page.

Figure 3. Unadjusted KM curve for event-free survival for the full analysis set of APN311-302 (adapted from CS, Figure 4 [pg. 57])

[redacted]

[redacted]Figure 4. Adjusted KM curve for event-free survival for APN311-302 (estimated by ERG)

[redacted]

Curves [redacted] adjusted [redacted] for [redacted]

Abbreviations: [redacted]

[redacted]KM, Kaplan–Meier; pg, page.

As mentioned in the introduction to Section 4.3, because there are no direct head-to-head comparative data of dinutuximab alpha and beta, to highlight the potential longer-term effects of immunotherapy and isotretinoin, the ERG considers it useful to present EFS for dinutuximab alpha-based regimens and isotretinoin alone as reported in the full publication of the trial, and for isotretinoin alone from other key publications. As noted in the CS, in the original research that established the clinical effectiveness of isotretinoin, the differentiation therapy was associated with a 3-year EFS of 46% (SE ±6%)[9] and a 5-year EFS of 42% (SE ±5%; Table 18).[50] In the ANBL0032 RCT, which included isotretinoin as a control group, 2-year EFS in those receiving isotretinoin alone was 46% (SE ±5%).[29] Longer-term follow-up for ANBL0032 is available in the ERG report submitted for the suspended STA (GID-TAG507) of dinutuximab alpha. At 5 years, EFS in the group receiving isotretinoin was 48.3% (95% CI: 38.9% to 57.7%; Table 18).[45] The second group in ANBL0032 received dinutuximab alpha in combination with isotretinoin and alternating IL-2 and GM-CSF.[29] The group receiving immunotherapy had a 2-year EFS of 66% (SE ±6%).[29] In the longer term, EFS at 5 years was reported to be 56.5% (95% CI: 47.3% to 65.7%; Table 18).[45]

Table 18. Reported event-free survival at different time points for dinutuximab alpha and isotretinoin

Year of follow up	Estimate (SE or 95% CI)	
	Dinutuximab alpha plus isotretinoin, IL-2 and GM-CSF	**Isotretinoin alone**
2	66% (SE ±5%)[29]	46% (SE ±5%)[29]
3	62.8% (95% CI: 53.9% to 71.7%)[45]	46% (SE ±6%)[50] 50.9% (95% CI: 41.6% to 60.2%)[45]
4	59.3% (95% CI: 50.3% to 68.4%)[45]	48.3% (95% CI: 38.9% to 57.7%)[45]
5	56.5% (95% CI: 47.3% to 65.7%)[45]	42% (SE ±5%)[50] 48.3% (95% CI: 38.9% to 57.7%)[45]
Abbreviations: CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; IL-2, interleukin 2; SE, standard error.		

4.3.1.2 Relapsed and refractory neuroblastoma

The company presents EFS separately for relapsed and refractory neuroblastoma from APN311-202 and APN311-303 (Table 19), which corresponds to the subgroups of interest set out in the final scope issued by NICE.[46]

As discussed in Section 4.2, EFS was not a primary outcome in either APN311-202 or APN311-303, and was not a secondary outcome in APN311-202. Events captured for EFS in APN311-202 and APN311-303 were relapse or progression, and, in APN311-202, death. For APN311-303, information available in the CSR indicates that [redacted][41]. It is unclear

[redacted]. EFS for people not experiencing an event was censored at their last date of being known to be alive or at their last visit date or at the database cut-off date, whichever came first. KM curves for APN311-202 and APN311-303 supplied by the company as part of the clarification process are presented in Figure 5.

The ERG notes [redacted] (Table 19).[39] EFS for those experiencing relapse of neuroblastoma is similar for people enrolled in APN311-202 and in APN311-303 at 1 and 2 years, with a minor difference noted at 3 years (Table 19). However, differences between studies in EFS for refractory neuroblastoma are more marked, with people in APN311-202 having a better prognosis at 2 years than those in APN311-303 (Table 19). As outlined in Section 4.2, the ERG considers APN311-202 to represent a better evidence base for relapsed and refractory neuroblastoma than APN311-303. However, given the small sample size available for each subgroup, the observational nature of both studies, and the high degree of censoring in each study,[39] the ERG considers that presented EFS results should be interpreted with caution.

Table 19. KM estimates of event-free survival in relapsed and refractory neuroblastoma derived from APN311-202 and APN311-303 (reported from CS [Appendix E] and EPAR[39])

Time	Relapsed neuroblastoma				Refractory neuroblastoma			
	APN311-202 (N=19)		APN311-303 (N=29)		APN311-202 (N=25)		APN311-303 (N=15)	
	EPAR	CS	EPAR	CS	EPAR	CS	EPAR	CS
Number of events, n (%)	NR	[redacted]	NR	[redacted]	NR	[redacted]	NR	[redacted]
Censored	NR	[redacted]	NR	[redacted]	NR	[redacted]	NR	[redacted]
1 year	42.1%	[redacted]	44.8%	[redacted]	60.0%	[redacted]	58.2%	[redacted]
2 years	36.8%	[redacted]	31.0%	[redacted]	55.7%	[redacted]	29.1%	[redacted]
3 years	36.8%	[redacted]	24.1%	[redacted]	44.6%	[redacted]	29.1%	[redacted]

Abbreviations: CS, company submission; EPAR, European Public Assessment Report; KM, Kaplan–Meier; NE, not estimable; NR, not reported.

Figure 5. Adjusted KM curves for event-free survival for APN311-202 and APN311-303 (reproduced from company's clarification response dated 16 August 2017, Figures 28 [pg. 31] and 31 [pg. 44])

[redacted]

[redacted]

Abbreviations:

[redacted]KM, Kaplan–Meier; pg, page.

4.3.2 Overall survival

4.3.2.1 High-risk neuroblastoma

In the CS, the company presents data on KM estimates of OS from APN311-302 at 1, 2 and 3 years of follow-up (Table 20), together with the unadjusted KM curve for OS (Figure 6). As part of the clarification process, the company provided an updated analysis of OS based on time to the last event in each treatment group (Table 20).

In the final analysis set, the CS reports that 60 people (33.5%) randomised to dinutuximab beta and isotretinoin had died by 3 years compared with 56 people (29.8%) in the group allocated to receive additionally IL-2: median OS is not estimable for either group as 50% of people have not experienced an event. As with EFS, the ERG notes [redacted] (Table 20). Based on the company's response to clarification request, [redacted], which occurred [redacted] (Table 17). The log-rank test for the difference between groups in OS, with adjustment for previous induction therapy, was not statistically significant (p = 0.6114; Table 20), indicating that there is no statistically significant difference in OS at any time point between dinutuximab beta plus isotretinoin with IL-2 and without IL-2: the ERG notes that the reported log-rank test [redacted].

Again, the ERG highlights the [redacted]. Using adjusted time-to-event data for OS supplied by the company during the clarification process (available in Appendix 10.6), the ERG generated adjusted KM curves for OS (Figure 7). As with EFS, the ERG notes that [redacted]. Visual inspection of the adjusted KM curves for OS (Figure 7) suggests that the addition of [redacted]

[redacted].

The ERG generated the KM curves using a Cox proportional hazards model as described in the discussion of EFS (Section 4.3.1.1). Of the 370 people in the final analysis set, [redacted]. The ERG has concerns over the large number of people censored from the analysis of OS (Table 20), particularly as the number of people who remain at risk at the time of analysis is unclear: number of people at risk throughout the study was requested by the ERG during clarification but was not supplied by the company.

Table 20. Summary of overall survival for APN311-302 (adapted from CS, Table 25 [pg. 54], and from response to clarification dated 10 August 2017, Tables 2 [pgs 8–9] and 6 [pg. 10], and dated 16 August 2017, Tables 1 [pg. 5] and 3 [pg. 8])

	Dinutuximab beta plus isotretinoin (N=180)	**Dinutuximab beta plus isotretinoin plus IL-2 (N=190)**
KM estimate		
1 year (%)	86.3	87.9
2 years (%)	76.0	75.4
3 years (%)	64.1	69.1
Log-rank test[a]	p = 0.6114[b]	
Cumulated number of events, n (%)		
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
3 years[c]	[redacted]	[redacted]
3 years[d]	60 (33.5)	56 (29.8)
4 years	[redacted]	[redacted]
Last cut off[e]	[redacted]	[redacted]
Censored[f], n (%)	119 (66.5)	132 (70.2)

[a] Log-rank adjusted for previous treatment (busulfan and melphalan vs carboplatin, etoposide and melphalan).

[b] The p-value refers to the analysis based on 3 years' follow-up (stated in CS).

[c,d] On reviewing the company's response to clarification (dated 10 August 2017), the ERG notes [redacted] in the reported number of events at 3 years. Event rate in the row with footnote c [redacted] footnote d presents number of events as reported in the CS.

[e] The [redacted] In the company's response to clarification dated 16 August 2017 [redacted] dinutuximab beta and isotretinoin [redacted] dinutuximab beta plus isotretinoin and IL-2 [redacted].

[f] [redacted].

Abbreviations: CS, company submission; IL-2, interleukin 2; KM, Kaplan–Meier; OS, overall survival; pg, page.

Figure 6. Unadjusted KM curve for overall survival for the full analysis set of APN311-302 (adapted from CS, Figure 5 [pg. 57])

Figure 7. Adjusted KM curve for overall survival for APN311-302 (estimated by ERG)

Abbreviations:

KM, Kaplan–Meier; pg, page.

As mentioned in the introduction to Section 4.3, because there are no direct head-to-head comparative data of dinutuximab alpha and beta, to highlight the potential longer-term effects of immunotherapy and isotretinoin, the ERG considers it useful to present OS for dinutuximab alpha-based regimens and isotretinoin alone as reported in the full publication of the trial, and for isotretinoin alone from other key publications. Isotretinoin alone was associated with a 3-year OS of 56% (SE ±6%; Table 21)[9] and a 5-year OS of 59% (SE ±8%).[50] In ANBL0032, the isotretinoin alone group had a 2-year OS of 75%

(SE ±5%)[29] and a 5-year OS of 57.0% (95% CI: 47.5% to 66.4%; Table 21).[45] In the group receiving dinutuximab alpha in ANBL0032, OS at 2 and 5 years was reported to be 86% (SE ±4%)[29] and 74.2% (95% CI 66.1% to 82.3%), respectively.[45]

Table 21. Reported overall survival at different time points for dinutuximab alpha and isotretinoin

Year of follow up	Estimate (SE or 95% CI)	
	Dinutuximab alpha plus isotretinoin, IL-2 and GM-CSF	**Isotretinoin alone**
2	86% (SE ±4%)[29]	75% (SE ±5%)[29]
3	79.5% (95% CI: 72.1% to 87.0%)[45]	56% (SE ±6%)[50] 67.3% (95% CI: 58.4% to 76.1%)[45]
4	75.1% (95% CI: 67.1% to 83.1%)[45]	61.0% (95% CI: 51.8% to 70.3%)[45]
5	74.2% (95% CI: 66.1% to 82.3%)[45]	59% (SE ±8%)[50] 57.0% (95% CI: 47.5% to 66.4%)[45]
Abbreviations: CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; IL-2, interleukin 2; SE, standard error.		

4.3.2.2 Relapsed or refractory neuroblastoma

OS for relapsed and refractory neuroblastoma from APN311-202 and APN311-303 are presented in Table 22. As discussed in Section 4.2, OS was not a primary outcome in either APN311-202 or APN311-303, and was not a secondary outcome in APN311-202. Mean and median follow-up for the two studies are not available in the CS. KM curves for OS for APN311-202 and APN311-303 supplied by the company as part of the clarification process are presented in Figure 8.

The ERG notes [redacted] (Table 22).[39] OS for those experiencing relapse of or refractory neuroblastoma is similar for people enrolled in APN311-202 and in APN311-303 at the reported time points (Table 22). As highlighted in the description of EFS (Section 0), although the ERG considers APN311-202 to represent the better evidence base, given the small sample size available for each subgroup, the observational nature of both studies, and the high degree of censoring in each study,[39] the ERG reiterates that presented OS results should be interpreted with caution.

Table 22. KM estimates of overall survival in relapsed and refractory neuroblastoma derived from APN311-202 and APN311-303 (reported from CS [Appendix E] and EPAR[39])

Time	Relapsed neuroblastoma				Refractory neuroblastoma			
	APN311-202 (N=19)		APN311-303 (N=29)		APN311-202 (N=25)		APN311-303 (N=15)	
	EPAR	CS	EPAR	CS	EPAR	CS	EPAR	CS
Number of events, n (%)	NR	[redacted]	NR	[redacted]	NR	[redacted]	NR	[redacted]
Censored	NR	[redacted]	NR	[redacted]	NR	[redacted]	NR	[redacted]
KM estimate at 1 year	73.7%	[redacted]	89.7%	[redacted]	100.0%	[redacted]	92.9%	[redacted]
KM estimate at 2 years	42.1%	[redacted]	69.0%	[redacted]	78.3%	[redacted]	69.8%	[redacted]
KM estimate at 3 years	42.1%	[redacted]	54.7%	[redacted]	62.5%	[redacted]	69.8%	[redacted]

Abbreviations: CS, company submission; EPAR, European Public Assessment Report; KM, Kaplan–Meier; NE, not estimable; NR, not reported.

4.3.3 Figure 8. Adjusted KM curves for overall survival for APN311-202 and APN311-303 (reproduced from company's clarification response dated 16 August 2017, Figures 16 [pg. 26] and 19 [pg. 29])[redacted]

[redacted]

4.3.4 [redacted]Subgroup analyses

Subgroups of interest specified by NICE were relapsed and refractory neuroblastoma,[46] and the critique of the clinical effectiveness of dinutuximab beta when given with isotretinoin and with or without IL-2 in the relevant sub-populations is described in Section 4.3. In addition, the company evaluated the potential benefit of adding IL-2 to dinutuximab beta in combination with isotretinoin in the subgroup of those achieving a complete response to prior multimodal, multiagent induction therapy followed by myeloablative chemotherapy and ASCT, and, as a separate subgroup, those who did not: that is, subgroups of those with and without evidence of disease prior to treatment with dinutuximab beta-containing regimen. The CS indicates that the subgroup of people with evidence of disease at baseline encompasses all levels of response, other than complete response, to prior induction therapy: very good partial response; partial response; mixed response; no response; and progressive disease. However, inclusion criteria for APN311-302 restricts eligibility to those achieving at least partial response to multimodal, multiagent induction therapy before receipt of myeloablative therapy and ASCT, and, thus,

the ERG assumes that the 149 people with evidence of disease before administration of a dinutuximab beta-containing regimen achieved a very good partial or partial response to prior treatment.

In those with high-risk neuroblastoma (APN311-302), the company noted a similar trend in EFS in the individual subgroups to that observed in the full analysis population, with a slightly larger proportion of people having EFS in the group receiving IL-2 treatment, irrespective of whether disease was evident at baseline (Table 23): the ERG notes that the number of people reported in the subgroup analysis of APN311-302 is 360 not 370, as is reported for the final analysis set from which EFS and OS for the overall population are derived. The log-rank test for the two subgroups identified no statistically significant differences in EFS or OS between IL-2 and no IL-2 added to dinutuximab beta and isotretinoin (Table 23). Compared with the 3-year EFS for the full trial population (Table 17), the company noted that the proportion of people achieving 3-year EFS was smaller in people with evidence of disease at baseline and larger in those without evidence of disease at baseline (Table 23). The CHMP concluded that the data indicate there is no, or only limited added, benefit of the addition of IL-2 to treatment with dinutuximab beta and isotretinoin as a first-line maintenance treatment in those achieving a complete response to induction therapy (i.e., without residual disease).[39] The CHMP went on to comment that, based on the results from APN311-302, the same conclusion could not be drawn for people with evidence of disease after induction therapy and recommended the inclusion of IL-2 in the dinutuximab beta-containing regimen for those not achieving complete response to induction therapy.[39]

Inferences on the benefit of adding IL-2 to dinutuximab beta and isotretinoin in those with relapsed or refractory neuroblastoma cannot be made as all people in APN311-202 and APN311-303 received IL-2. The CHMP cautioned against extrapolating findings from APN311-302 study to the relapsed or refractory setting.[39]

Table 23. Summary of event-free survival and overall survival from APN311-302 by subgroup of those with or without evidence of disease at baseline (adapted from CS, Appendix E, tables on pages 1–2)

	Evidence of disease at baseline		**Without evidence of disease at baseline**	
	Dinutuximab beta plus isotretinoin (N=73)	**Dinutuximab beta plus isotretinoin plus IL-2 (N=76)[c]**	**Dinutuximab beta plus isotretinoin (N=104)[d]**	**Dinutuximab beta plus isotretinoin plus IL-2 (N=107)**
EFS				
KM estimate				
1 year (%)	66.6%	72.3%	76.5%	72.6%
2 years (%)	58.1%	61.6%	66.7%	69.5%
3 years (%)	45.9%	53.8%	61.7%	66.2%
Log-rank test[a]	p = 0.4944[b]		p = 0.5648[b]	
Events	36 (49.3)	31 (41.3)	41 (39.8)	36 (33.6)

Censored, n (%)	37 (50.7)	44 (58.7)	62 (60.2)	71 (66.4)
OS				
KM estimate				
1 year (%)	82.9%	86.0%	89.2%	88.5%
2 years (%)	73.1%	71.2%	78.2%	77.8%
3 years (%)	54.2%	63.3%	71.0%	72.2%
Log-rank test[a]	p = 0.5710[b]		p = 0.9571[b]	
Events	29 (39.7)	26 (35.1)	30 (29.1)	29 (27.1)
Censored, n (%)	44 (60.3)	48 (64.9)	73 (70.9)	78 (72.9)

[a] Log-rank adjusted for previous treatment (busulfan and melphalan vs carboplatin, etoposide and melphalan).

[b] The p-value refers to the analysis based on 3 years' follow-up.

[c] One person with missing date of death and without progression was excluded from the analysis of EFS and OS.

[d] One person with missing date of death and without progression was excluded from the analysis of EFS and two people with missing date of death were excluded from the analysis of OS.

Abbreviations: CS, company submission; EFS, event-free survival; IL-2, interleukin 2; KM, Kaplan–Meier; OS, overall survival; pg, page.

4.3.5 Adverse effects

The company presents information on adverse effects as detailed in the EPAR,[39] providing data from the three studies from which evidence on clinical effectiveness of dinutuximab beta is derived. The SmPC for dinutuximab beta indicates that there are two options for infusion:[43]

- a continuous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m^2;
- or five daily infusions of 20 mg/m^2 administered over 8 hours, on the first 5 days of each course.

In APN311-302, dinutuximab beta was infused over 5 days. The primary objective of APN311-202 was to identify a tolerable infusion schedule of dinutuximab beta that reduced the pain and toxicity profile yet maintained the immunomodulatory effect. The optimum dose schedule was identified as 100 mg/m^2 infused continuously over 10 days. The safety and pain and toxicity profile of the continuous infusion regimen was retrospectively assessed in APN311-303.

In the section of the CS detailing adverse effects potentially associated with dinutuximab beta (Section 2.10, page 85 of the CS), the company highlights that the method of collection of data on adverse effects varied across the three studies. In APN311-302, only serious adverse effects were fully reported, whereas other adverse events were reported in accordance with a pre-defined list of 31 specific toxicities. Additionally, data were retrospectively evaluated in APN311-303. The company outlines that their reporting of adverse effects in the CS, other than serious adverse effects and adverse drug reactions of interest, focuses on the 98 people from APN311-202 and APN311-303 who received dinutuximab beta as a continuous infusion. In the section discussing the economic model (Section 3.3.1, page 117 of

the CS), the company comments that, "*... based on expert opinion, all UK patients will receive the product with a continuous infusion over the first 10 days to decrease cost for NHS and improve the safety profile (supposed reduced risk of hypersensitivity events)*". The ERG's clinical experts agree with the company that, in UK clinical practice, the preference would be to give dinutuximab beta as a continuous infusion.

The company presents a narrative discussion around the adverse effects experienced across the three studies, based, in a large part, on the adverse effects reported in the EPAR.[39] Here, the ERG briefly reports on treatment-emergent adverse effects and key adverse effects as emphasised in the SmPC, presenting data from APN311-202 and APN311-303, with additional data on adverse effects provided in Appendix 10.7. In APN311-202 and APN311-303, 68 people (69%) completed the planned 5–6 cycles of treatment (Table 24). Only 6 people stopped treatment due to an adverse drug reaction, either as the only reason for cessation or in association with progressive disease.

In APN311-302, dose reductions or premature discontinuations of dinutuximab beta or IL-2 (if applicable) were [redacted] in patients receiving concomitant treatment with IL-2.[41] Mean [redacted] of dinutuximab beta was [redacted], as was the total amount of dinutuximab beta [redacted] of the study ([redacted]).[41] In addition, [redacted] of dinutuximab beta occurred [redacted] treatment ([redacted]). Changes in dinutuximab beta treatment in both groups were predominantly because of toxicity. Of those receiving IL-2, [redacted] had a [redacted]. Exposure to [redacted] the two groups ([redacted]).

Table 24. Summary of completed number of treatment cycles for APN311-202 and APN311-303

Completed cycles	APN311-202 (N=44)	APN311-303 (N=54)
0	–	–
1	3 (6.8%)	1 (1.9%)
2	7 (15.9%)	2 (3.7%)
3	3 (6.8%)	9 (16.7%)
4	2 (4.5%)	3 (5.6%)
5	29 (65.9%)	29 (53.7%)
6	N/A	10 (18.5%)
Abbreviation: N/A, not applicable.		

The SmPC indicates that dinutuximab beta should only be used in a hospital setting and must be administered under the supervision of a physician experienced in the use of oncological therapies.[43] Additionally, dinutuximab beta must be administered by a healthcare professional prepared to manage severe allergic reactions, including anaphylaxis, in an environment in which there is access to full resuscitation services.

If a person receiving dinutuximab beta experiences an adverse drug reaction, the SmPC advises that, based on the clinician's assessment of the severity of the reaction, the dose of dinutuximab beta be reduced by 50% or the infusion temporarily interrupted.[43] Dose reduction of dinutuximab beta should be triggered by any adverse effect of Grade 1 or 2. Adverse effects for which infusion should be interrupted include hypersensitivity reactions (e.g., hypertension and angioedema) and capillary leak syndrome. Treatment with dinutuximab beta should be permanently discontinued if the following toxicities occur:

- grade 3 or 4 anaphylaxis;
- prolonged grade 2 peripheral motor neuropathy;
- grade 3 peripheral neuropathy;
- grade 3 vision eye toxicity;
- grade 4 hyponatremia (<120 mEq/L) despite appropriate fluid management;
- recurrent or grade 4 capillary leak syndrome (requires ventilator support).

Each person in APN311-202 and APN311-303 experienced a treatment-emergent adverse event (TEAE; Table 25). The company reports that, although the number of TEAEs decreased substantially with each treatment cycle, the proportion of people experiencing a TEAE remained high throughout the study (data not presented). Adverse effects noted in the SmPC as special warnings and precautions for use include pain, hypersensitivity reactions and capillary leak syndrome (Table 26).[43] As part of the clarification process, the company provided data on adverse effects experienced by ≥20% of people and thought to be related to treatment with dinutuximab beta (full data set presented in Appendix 10.7). Of the adverse effects of special note in the SmPC, pain and hypotension were each experienced by a similar proportion of people in APN311-202 compared with APN311-303 (Table 26). By contrast, a considerably larger proportion of people experienced capillary leak syndrome in APN311-303 (83.3%) compared with APN311-202 (34.1%; Table 26). The marked difference between APN311-202 and APN311-303 in proportion of people experiencing capillary leak syndrome is attributed to the lack of standardisation in data reporting and emphasis on this particular adverse drug reaction between the

studies.[39] The ERG was unable to ascertain the number of people with peripheral neuropathy, laboratory abnormalities or haematologic toxicities thought to be specifically associated with dinutuximab beta. Other frequently reported treatment-emergent adverse effects possibly related to dinutuximab beta were general disorders and administration site conditions (43/44 [97.7%] in APN311-202 vs 54/54 [100.0%] in APN311-303; Appendix 10.7), and gastrointestinal disorders (33/44 [75.0%] in APN311-202 vs 49/54 [90.7%] in APN311-303).

Table 25. Summary of treatment-emergent adverse events in APN311-202 and APN311-303 (adapted from CS, Table 42 [pg. 87])

Adverse effect	**APN311-202 (N=44)**	**APN311-303 (N=54)**
Any AE	**44 (100.0%)**	**54 (100.0%)**
Any AE possibly related to study drug[a]	44 (100.0%)	54 (100.0%)
Any AE possibly related to IL-2	44 (100.0%)	54 (100.0%)
Any AE possibly related to dinutuximab beta	44 (100.0%)	54 (100.0%)
Any AE possibly related to isotretinoin	N/D	27 (50.0%)
Any serious AE	**26 (59.1%)**	**12 (22.2%)**
Any AE possibly related to study drug[a]	22 (50.0%)	6 (11.1%)
Any AE possibly related to IL-2	18 (40.9%)	4 (7.4%)
Any AE possibly related to dinutuximab beta	20 (45.5%)	6 (11.1%)
Any AE possibly related to isotretinoin	N/D	–
Any AE leading to discontinuation of study drugs[b]	**10 (22.7%)**	**5 (9.3%)**
Maximal NCI CTCAE Grade		
Grade 1 (mild)	–	–
Grade 2 (moderate)	2 (4.5%)	3 (5.6%)
Grade 3 (severe)	20 (45.5%)	32 (59.3%)
Grade 4 (life threatening/disabling)	22 (50.0)	19 (35.2%)
Grade 5 (death)	1 (2.3%)	–
Any AE leading to death	1 (2.3%)	–
Deaths[c]	20 (45.5%)	22 (40.7%)

[a] Depending on the study design refers to dinutuximab beta only or to the combination of dinutuximab beta and IL-2 and isotretinoin. For APN311-202 refers to dinutuximab beta and IL-2 treatment.

[b] Permanent or temporary discontinuation in studies APN311-303 and APN311-202.

[c] All documented deaths, including deaths during follow-up period.

Abbreviations: AE, adverse effect; CS, company submission; IL-2, interleukin 2; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; N/D, not determined; pg, page.

Table 26. Summary of adverse effects of special interest experienced by ≥20% of people and thought to be related to dinutuximab beta (adapted from response to clarification dated 25 August 2017, Table 18 [pgs 24–25])

Adverse effect of special warning or precaution of use[43]	APN311-202 (N=44)	APN311-303 (N=54)
Pain	28 (63.6%)	35 (64.8%)
Hypersensitivity reactions		
Hypotension	22 (50.0%)	32 (59.3%)
Capillary leak syndrome	15 (34.1%)	45 (83.3%)
Eye disorders[a]	10 (22.7%)	13 (24.1%)
Peripheral neuropathy	Unclear	Unclear
Infections and infestations[b]	13 (29.5%)	3 (5.6%)
Haematologic toxicities	Unclear	Unclear
Laboratory abnormalities	Unclear	Unclear

[a] SmPC specifies neurological disorders of the eye as the adverse effect with special warning or precaution for use.

[b] SmPC specifies systemic infections as the adverse effect with special warning or precaution for use.

Abbreviation: SmPC, summary of product characteristics.

Considering adverse effects associated with the combination regimen of dinutuximab beta plus IL-2 plus isotretinoin, the most frequent serious adverse events reported in APN311-202 were infections, pyrexia, hypotension, and thrombocytopaenia (Table 27). Again, there are notable differences between APN311-202 and APN311-303 in proportion of people experiencing individual adverse effects, possibly as a result of prospective versus retrospective collection of data and the lack of standardisation of reporting of adverse effects. The company reports that the occurrence of serious adverse events diminished with increasing number of treatment cycles, decreasing from 39% in cycle 1 to 7% in cycle 5 in APN311-202 and from 15% in cycle 1 to 0% in cycle 5 in APN311-303

In terms of adverse effects, APN311-302 gives data on the adverse effects associated with the addition of IL-2 to dinutuximab beta and isotretinoin. As anticipated based on the known adverse effect profile of IL-2, severe adverse effects occurred more frequently in people receiving IL-2 (46% with IL-2 vs 27% without IL-2; event rate not reported in CS). Capillary leak syndrome, platelet abnormalities, hypotension, infections, nausea or vomiting, fever, and pain related to dinutuximab beta were more common with concomitant administration of IL-2. By contrast, constipation occurred less frequently in those receiving IL-2 (data on adverse effects from APN311-302 presented in Appendix 10.7).

Table 27. Summary of serious adverse events occurring in >1 person in any study (adapted from CS, Table 45 [pg 93 and 94])

System organ class Preferred term	APN311-202 (N=44)	APN311-303 (N=54)
Overall	25 (56.8%)	12 (22.2%)
Blood and lymphatic system disorders	3 (6.8%)	–
Thrombocytopenia	–	–
Anaemia	2 (4.5%)	–

Gastrointestinal disorders	5 (11.4%)	5 (9.3%)
Vomiting	3 (6.8%)	2 (3.7%)
Diarrhoea	3 (6.8%)	1 (1.9%)
General disorders	7 (15.9%)	3 (5.6%)
Pain	2 (4.5%)	1 (1.9%)
Pyrexia	6 (13.6%)	1 (1.9%)
Immune system disorders	2 (4.5%)	–
Anaphylactic reaction	2 (4.5%)	–
Infections and infestations	9 (20.5%)	3 (5.6%)
Bronchitis	–	1 (1.9%)
Gastroenteritis	–	–
Pneumocystis jirovecii pneumonia	–	–
Device related infection	3 (6.8%)	–
Sepsis	4 (9.1%)	–
Investigations	6 (13.6%)	–
Platelet count decreased	2 (4.5%)	–
Metabolism and nutrition disorders	3 (6.8%)	1 (1.9%)
Hyponatremia	2 (4.5%)	–
Nervous system disorders	1 (2.3%)	2 (3.7%)
Convulsion	–	1 (1.9%)
Respiratory disorders	8 (18.2%)	1 (1.9%)
Hypoxia	5 (11.4%)	–
Acute respiratory distress syndrome	2 (4.5%)	1 (1.9%)
Skin disorders	–	–
Vascular disorders	5 (11.4%)	–
Hypotension	3 (6.8%)	–
Abbreviation: CS, company submission.		

4.4 Critique of indirect comparisons

Within the CS, the company presents results for OS derived from naïve indirect comparisons of dinutuximab beta-containing regimens versus historical controls who did not receive dinutuximab beta. In addition to the naïve indirect comparisons, the company presents narrative comparisons of EFS and OS for dinutuximab beta versus dinutuximab alpha and versus isotretinoin alone in the treatment of high-risk neuroblastoma based on results reported by Yu *et al*.[29] and Matthay *et al*.[9,50] (presented in Tables 18 and 21), together with EFS and OS for various regimens implemented in the relapsed and refractory setting. Relevant non-comparative EFS and OS are presented to supplement the reporting of results of the indirect comparisons

In the CS, the company stated that an indirect treatment comparison involving dinutuximab beta was not possible due to the lack of comparable clinical trials. The ERG proposes that an MAIC of the full trial population of APN311-302 versus the group receiving isotretinoin alone in the RCT published by Yu *et al*.[29] is viable, and requested that the company carry out the analysis as part of the clarification

process. In their response to clarification, the company outlined the reasons below in explanation for not carrying out the MAIC:

- "*Like all post hoc analyses, there is the potential for bias, as the comparison does not benefit from the effect of randomisation.*

- *It assumes that the study designs, procedures, treatment pathways and outcome definitions are sufficiently similar to allow rational comparison. Whilst the broad approach to treatment in study 302 and Yu et al.[29] are similar, there are areas of uncertainty around post-progression treatment that may impact the reliability of the OS comparisons.*

- *The selection of prognostic variables is fundamentally dependent on the availability of data from both studies. It is to be expected that there will be undocumented confounders which, were they known, would have a potential impact on the results. As an example, recent work has identified a number of cellular markers that may indicate a greater likelihood of response to dinutuximab beta.[78] As these markers had not been identified at the time study 302 and Yu et al.[29] were designed, no information is available as to whether the patient groups are well matched for this variable*".

The ERG agrees with the company that, as an indirect comparison, the MAIC is associated with potential bias, particularly as it would be an "unanchored" MAIC (i.e., one without a common comparator in the two studies). However, the ERG contends that the naïve indirect comparisons of APN311-302, APN311-202 or APN311-303 versus historical controls are not only potentially at risk from the same type of bias arising from lack of randomisation but also from confounding due to likely differences in effect-modifying factors that will not be adjusted for in a naïve indirect comparison. The ERG also concurs with the company that there are likely differences in post-progression treatments between APN311-302 and the study carried out by Yu et *al*.[29] but considers that these potential differences do not preclude the MAIC and could be discussed as potential sources of bias. Additionally, it is acknowledged that induction therapy and consolidation therapies administered in the study reported by Yu *et al*.[29] differed from those in APN311-302, with a key difference being the sole use of CEM as consolidation therapy in the study by Yu *et al*.[29] The ERG considers that the impact of some of the noted differences between the studies can be investigated through scenario analyses (e.g., use pre-treatment with CEM to identify potential magnitude of discrepancy between groups) and the influence of others be discussed as a potential source of bias.

The company goes on to discuss the presence of unknown baseline confounders, citing a recent publication that identified novel biomarkers potentially associated with improved EFS after long-term infusion of dinutuximab beta.[78] The company indicates that there is a lack of information on

comparability of study populations in terms of the new potential confounders. The ERG considers that the reported research into new biomarkers is in its infancy and the biomarkers have yet to be established as definitive modifiers of response to dinutuximab beta. In addition, the Decision Support Unit guide to carrying out population-adjusted indirect comparisons highlights that, for an unanchored MAIC, as would be the case for dinutuximab beta, it is assumed that all effect modifiers and prognostic factors are accounted for within the analysis, but that it is also recognised that this is typically impossible to do and unanchored comparisons are associated with an unknown level of bias.[79] Thus, the uncertainty around comparability of study populations in baseline biomarkers could be underscored as another potential source of bias.

Given that the historical control R1 is a retrospective collection of data from essentially a non-randomised study, the ERG considers that, despite the differences between APN311-302 and ANBL0032, the study reported by Yu *et al*.[29] provides a more robust evidence base for an indirect comparison, as well as facilitating comparison with both isotretinoin alone and dinutuximab alpha. The major methods outlined in the DSU report on generating comparable effect estimates with individual patient data (IPD) for one study but only summary statistics from another are MAIC and simulated treatment comparison (STC).[79] The assumptions made on the nature of the underlying data being compared (e.g., whether proportional hazards hold) would determine which is most appropriate method of adjustment.

Within the CS, the company discusses narratively the clinical effectiveness of dinutuximab beta compared with that of dinutuximab alpha, stating, "*Clinical study APN311-302 reported the following numbers for the Dinutuximab beta Apeiron with 13-cis-RA arm (without IL-2) in first-line maintenance therapy for OS at 1, 2 and 3 years: 86.3%, 76.0%, 64.1%. Numerically those values are similar for the time point of 2 years OS, while OS at 3 years for Dinutuximab beta Apeiron is higher by 8.1% than dinutuximab. In conclusion, similar 2-year survival rates to those reported in the dinutuximab pivotal study (Yu et al., 2010) were achieved without using GM-CSF and IL-2 cytokines, suggesting the benefit of adopting Dinutuximab beta Apeiron in the treatment of high-risk neuroblastoma patients*". The company indicates that the two immunotherapies are separate entities and potentially afford different clinical benefit. The ERG agrees that dinutuximab alpha and beta are not the same structurally, but considers that, given the two immunotherapies bind to the same target, the reported clinical effectiveness of dinutuximab alpha can help inform the efficacy of dinutuximab beta through an appropriately adjusted indirect comparison, but emphasises that individual results for the two agents should not be compared naively.

4.4.1 Included studies

4.4.1.1 High-risk neuroblastoma

The historical cohort implemented in the naïve indirect comparison was derived from people enrolled in an earlier phase of the HR-NBL-1 study than those enrolled in APN311-302. People forming the historical control R1 were randomised in the R1 phase of HR-NBL-1 (Figure 2), which was designed to compare the effectiveness of BuMel versus CEM as consolidation myeloablative therapy in high-risk neuroblastoma. After induction therapy and myeloablative therapy followed by ASCT, people received only isotretinoin during the maintenance phase. Thus, the company proposes that those treated during the R1 phase of HR-NBL-1 form a valid historical control group for those in APN311-302 who received treatment with dinutuximab beta with or without IL-2 and can be used to generate an estimate of dinutuximab beta plus isotretinoin versus isotretinoin alone.

The company uses the full data set from APN311-302 to inform the indirect comparison, that is, combining data from those who received IL-2 with data from those who did not. The KM curves for OS (Figures 6 and 7) and EFS (Figures 3 and 4) in APN311-302 suggest that addition of IL-2 to dinutuximab beta and isotretinoin [redacted]. The ERG considers it reasonable to combine data from the two groups to give a larger sample size for the indirect comparison. One caveat that should be borne in mind is that subgroup analyses indicate that IL-2 affords greater clinical benefit for those with residual disease at baseline than those without evidence of disease (described in Section 4.3.3), and it is unclear from details available in the CS whether the populations of APN311-302 and the historical control R1 are comparable in terms of this baseline characteristic. The ERG considers that an imbalance between groups in proportion of people without residual disease could perhaps introduce bias into the result, with impact on direction of bias determined by the arm with the larger proportion of those without residual disease.

Comparison of reported baseline characteristics for the full population of APN311-302 and the historical control R1 indicate that the mean age of the groups was similar (Table 28), and the largest proportion of people enrolled were aged between 1.5 and 5 years at first diagnosis in each group (Table 28). For MYCN status and INSS stage, two other key prognostic factors in neuroblastoma, a similar proportion of people in each group were characterised as having amplified MYCN and were diagnosed as INSS stage 4 at baseline (Table 28).

Table 28. Main baseline characteristics for APN311-302 versus historical Control R1 (adapted from CS, Table 35 [pgs 79–80])

Parameter	Isotretinoin alone (N=450)	Dinutuximab beta plus isotretinoin with or without IL-2 (N=370)	Total (N=820)
Gender, n (%)			
Male	275 (61.1)	236 (63.8)	511 (62.3)
Female	175 (38.9)	134 (36.2)	309 (37.7)
Age at initial diagnosis (years)[a]			
Mean (SD)	3.24 (2.18)	2.46 (2.60)	3.34 (2.38)
Median	2.65	2.90	2.70
Min, Max	0.1, 16.8	0.0, 19.5	0.0, 19.5
Missing	0	1	1
Age groups (years), n (%)			
<1	5 (1.1)	28 (7.6)	33 (4.0)
≥1.5[b] to <1.5	56 (12.4)	25 (6.8)	81 (9.9)
>1.5 to ≤5	322 (71.6)	249 (67.3)	571 (69.6)
>5	67 (14.9)	67 (18.1)	134 (16.3)
Missing	0	1 (0.3)	1 (0.1)
MYCN status, n (%)			
Amplified	215 (47.8)	152 (41.1)	367 (44.8)
Not amplified	204 (45.3)	181 (48.9)	385 (47.0)
Missing	31 (6.9)	37 (10.0)	68 (8.3)
INSS stage at initial diagnosis			
Local[c]	59 (13.1)	35 (9.5)	94 (11.5)
4	391 (86.9)	328 (88.6)	719 (87.7)
4S	0	7 (1.9)	7 (0.9)

[a] Age at initial diagnosis was calculated as (date of initial diagnosis – date of birth)/365.25. Half a year was defined as 183 days and a whole year as 365.25 days.

[b] As reported in CSR and EPAR.

[c] Local includes INSS stage 2, 2/3, 2A, 2B, and 3.

Abbreviations: CS, company submission; CSR, clinical study report; EPAR, European Public Assessment Report; IL-2, interleukin 2; INSS, International Neuroblastoma Staging System; Min, minimum; Max, maximum; pgs, pages; SD, standard deviation.

Overall, in terms of the presented baseline characteristics, the ERG considers the full trial population of APN311-302 and the historical control R1 to be comparable. However, the ERG notes that there is an important difference between the populations that should be borne in mind. Most people enrolled in APN311-302 received BuMel as their consolidation myeloablative therapy (383/406; 94.3%). By contrast, as the R1 randomisation phase of HR-NBL-1 was designed to compare the effectiveness of BuMel versus CEM, half of the people in the R1 phase received CEM as their consolidation therapy (302/598; 50.5%). The exact proportion of the 450 people in the historical control R1 who received CEM as consolidation therapy is unclear from the CS, and the ERG did not request this information during the clarification process, but it is likely to be substantially lower than that in APN311-302: the maximum number of people who could have received CEM in the historical control is 71.1% (302/450).

The R1 phase of HR-NBL-1 established that BuMel was the more effective consolidation therapy and the regimen became the standard of care: EFS at 3 years was 50% (95% CI 45% to 56%) in the BuMel group versus 38% (95% CI 32% to 43%; p = 0·0005) in the CEM group.[27] Given the established difference in clinical effectiveness of BuMel over CEM, the ERG considers it important to adjust analyses of EFS and OS for dinutuximab beta for prior consolidation therapy to minimise bias on the effect estimate of maintenance treatment with dinutuximab beta. Alternatively, an analysis could be carried out using a historical control comprising only those who received BuMel as consolidation therapy.

In historical control R1, people received six courses of oral isotretinoin 80 mg/m² twice daily for 14 days every 4 weeks,[27] which is the same schedule of treatment as in APN311-302. The full text publication for the comparison of BuMel versus CEM reports that EFS was calculated from the time of randomisation before high-dose chemotherapy until first occurrence of relapse, progressive disease, secondary malignancy, or death from any cause, or until last contact with patients. It is unclear whether people were assessed at specific stages of the study or at regular intervals after completion of treatment.[27]

4.4.1.2 Relapsed or refractory neuroblastoma

With the company's clarification that they do not envisage people being re-treated with dinutuximab beta, the ERG reiterates that people with relapsed or refractory neuroblastoma in APN311-202 and APN311-303 might not be representative of those in the UK with these stages of disease. People in England who relapse or have refractory disease are likely to have received dinutuximab beta as part of their multiagent, multimodal first-line therapy.

The company presents indirect comparisons of dinutuximab beta plus IL-2 plus isotretinoin versus no dinutuximab beta in people with relapsed neuroblastoma, but not corresponding analyses for refractory neuroblastoma. At clarification, the ERG asked the company to provide clinical and cost effectiveness analyses for refractory neuroblastoma. In their reply, the company agreed that those experiencing relapse and those with refractory neuroblastoma are distinct populations, but went to provide a detailed justification as to why an indirect comparison in those with refractory neuroblastoma was not feasible with the available data. In brief, the company outlined that most of the studies identified in the literature review aggregated data for relapsed and refractory neuroblastoma, and it was not possible to obtain comparative clinical effectiveness data for the subgroup of people with refractory disease (full response to ERG's query available in Appendix 10.8). Based on the company's response, the ERG appreciates that the data available prohibit indirect comparisons in those with refractory neuroblastoma.

The company utilises two historical cohorts derived from people with relapsed or progressed neuroblastoma. One historical cohort was generated from people enrolled in the R1 phase of the HR-

NBL-1 study who experienced relapse during follow-up. People were included who had [redacted]. The historical control R1 (relapsed) comprised 52 people.

The second historical control was based on data from a retrospective study of children with relapse or progression of neuroblastoma and captured in the Italian Neuroblastoma Registry from 1979 to 2006.[70] Hereafter, the second historical control is referred to as Garaventa. People forming the Garaventa cohort had received treatment as per the protocols of the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP). Therapies given in line with AIEOP protocols included tumour resection, chemotherapy, radiotherapy, and myeloablation followed by ASCT, but no immunotherapy, and are therefore representative of treatments used before dinutuximab beta-containing regimens in APN311-202 and APN311-303. In addition, due to changes in neuroblastoma management, for the purposes of comparison with APN311-202 and APN311-303, Garaventa comprised only those with a date of initial diagnosis of 1999 or later, which led to a historical cohort of 29 people.

In addition to having relapsed neuroblastoma, to maximise comparability of populations in the active and control groups, people in the historical controls were limited to those with:[39]

- Age at initial diagnosis of 12 months or older;
- Age at relapse of 12 months or older;
- INSS stage at initial diagnosis of 4 or non-local type of first relapse.

For APN311-202 and APN311-303, the starting point was defined as [redacted] For people forming the historical controls, [redacted] an auxiliary starting point had to be defined for indirect comparisons with people involved in APN311-202 and APN311-303. The auxiliary starting point was equal to the date of first relapse in the historical control plus the median time between first relapse or progression and start of treatment with dinutuximab beta for those in APN311-202 and APN311-303.

Baseline characteristics are not reported consistently for the different cohorts involved in the indirect comparisons in relapsed neuroblastoma (Table 29). Where available, characteristics have been extracted from the CS, the EPAR and the CSRs (Table 29). The ERG notes [redacted] the CS and the CSR in the [redacted] in both

APN311-202 and in APN311-303. For each study, the [redacted]. The CS reports that 19 and 29 people with relapse at baseline were enrolled into APN311-202 and APN311-303, respectively, [redacted].

Based on the available baseline characteristics, with the exception of MYCN status, the ERG considers the populations from APN311-202 and APN311-303 to be mainly comparable with the two historical controls, Garaventa and R1 (relapsed). The ERG notes a larger proportion of people in Garaventa and R1 (relapsed) has an MYCN status of amplified, which is associated with a worse prognosis than those without amplified MYCN. Additionally, a proportion of people in Garaventa (24.1%; Table 29) had progressive disease at baseline, and are likely to have a different outcome to those who are not at this stage of disease.

Additional details helpfully provided by the company in the CS and during clarification indicate that, across APN311-202, APN311-303 and Garaventa, a broad range of treatments were given at first-line treatment in both relapse and refractory neuroblastoma. Details for prior treatments given in R1 (relapsed) were not available from patient data. In the response to clarification, the company highlighted that, based on the protocol for R1, people included in R1 (relapsed) likely received standard first-line treatment of induction therapy, surgery, myeloablative treatment with BuMel followed by ASCT and local radiotherapy, and, finally, differentiation therapy with isotretinoin.

[redacted] (presented in Appendix 10.9). As the company comments, if treatment with anti-GD2 immunotherapy improves OS, [redacted]. [redacted] The ERG considers [redacted].

Table 29. Baseline characteristics for APN311-202 and APN311-303 and the two historical controls referred to as Garaventa and R1 (adapted from CS, Tables 34 [pgs 78–79] and 37 [pg. 82])

Characteristic	APN311-202 + APN311-303 (N=48)[a]	APN311-202 (N=18)[b]	APN311-303 (N=30)[c]	Historical control Garaventa (N=29)	Historical control R1 (N=52)
Gender, n (%)					
Male	25 (52.1)	[redacted]	15 (50.0)	20 (69.0)	33 (63.5)

Female	23 (47.9)	[redacted]	15 (50.0)	9 (31.0)	19 (36.5)
Age at initial diagnosis					
Mean, years (SD)	4.4 (3.6)	[redacted]	4.8 (4.1)	4.3 (2.4)	4.2 (2.4)
Median, years	4.0	[redacted]	3.5	4.0	4.0
Min, max, years	0, 17	[redacted]	1, 17	1, 13	1, 15

MYCN status, n (%)					
Amplified	5 (10.4)	[redacted]	4 (13.3)	8 (27.6)	14 (26.9)
Not amplified	32 (66.7)	[redacted]	17 (56.7)	21 (72.4)	32 (61.5)
Missing	11 (22.9)	[redacted]	9 (30.0)	0	6 (11.5)
INSS stage at initial diagnosis, n (%)					
1	2 (4.2)	1 (5.6)	1 (3.3)	0 (0)	0 (0)
2A	1 (2.1)	0 (0)	1 (3.3)	0 (0)	0 (0)
3	2 (4.2)	0 (0)	2 (6.7)	1 (3.4)	1 (1.9)
4	42 (87.5)	17 (94.4)	25 (83.3)	28 (96.6)	51 (98.1)
Missing	1 (2.1)	0 (0)	1 (3.3)	0 (0)	0 (0)
1p deletion, n (%)					
No loss or aberration	6 (12.5)	6 (33.3)	N/A	11 (37.9)	–
Deletion and imbalance	–	–	N/A	1 (3.4)	–
Deletion	2 (4.2)	2 (11.1)	N/A	6 (20.7)	–
Imbalance	–	–	N/A	6 (20.7)	–
Missing	40 (83.3)	10 (55.6)	30 (100)	5 (17.2)	–
Number of relapses, n (%)					
1	36 (75.0)	N/A	N/A	20 (69.0)	–
2	9 (18.8)	N/A	N/A	7 (24.1)	–
3	–	N/A	N/A	2 (6.9)	–
5	1 (2.1)	N/A	N/A	–	–
6	1 (2.1)	N/A	N/A	–	–
8	1 (2.1)	N/A	N/A	–	–
Type of first relapse, n (%)					
Combined	28 (58.3)	N/A	N/A	10 (34.5%)	–
Disseminated	16 (33.3)	N/A	N/A	17 (58.6%)	–
Local	4 (8.3)	N/A	N/A	2 (6.9%)	–
Time between diagnosis and first relapse					
Mean, years (SD)	2.34 (1.94)	N/A	1.96 (0.85)	1.87 (1.00)	2.26 (1.42)
Median, years	1.65	N/A	1.60	1.70	1.80
Min, max, years	1.0, 11.3	N/A	1.0, 4.3	0.3, 5.8	1.0, 7.4
Missing, n (%)	6 (12.5)	N/A	N/A	0 (0)	0 (0)
Response to treatment of last relapse prior to starting point, n (%)					
CR	14 (29.2)	N/A	N/A	7 (24.1)	–
VGPR/PR/S.D.	34 (70.8)	N/A	N/A	8 (27.6)	–
PD	0 (0)	N/A	N/A	7 (24.1)	–
Missing	–	N/A	N/A	7 (24.1)	–

[a] The EPAR indicates that the combined analysis comprises 19 and 29 people with relapse at baseline from APN311-202 and APN311-303, respectively.

[b] The CSR for the comparison of APN311-202 and APN311-303 versus historical controls [redacted] baseline characteristics presented in the CS for APN311-202 indicate that 19 people were categorised as experiencing relapse at baseline.

[c] The CSR for the comparison of APN311-202 and APN311-303 versus historical controls [redacted] baseline characteristics presented in the CS for APN311-303 indicate that 29 people were categorised as experiencing relapse at baseline.

Abbreviations: CR, complete response; CS, company submission; CSR, clinical study report; EPAR, European Public Assessment Report; INSS, International Neuroblastoma Staging System; N/A, not available; PD, progressive disease; pgs, pages; PR, partial response; SD, standard deviation; S.D., stable disease; VGPR, very good partial response.

4.4.2 Methods

The company evaluated the difference in OS between dinutuximab beta and no dinutuximab beta using the log rank test. Estimates of effect and accompanying 95% CIs were not reported. As part of the clarification process, the ERG requested that, for high-risk neuroblastoma, the company carry out an MAIC using the RCT by Yu *et al*.[80] to inform the comparator group of isotretinoin alone. In case the company considered an MAIC infeasible, as an alternative, the ERG requested HRs and 95% CIs for the indirect comparisons of the relevant APN311 study versus historical control and asked that the HR be adjusted for prior treatment (BuMel vs CEM), MYCN status, and age at diagnosis and INSS stage. As discussed in the paragraph introducing Section 4.4, the company did not carry out the MAIC, instead reporting adjusted HRs, initially adjusted for each individual factor and, after further clarification, adjusted simultaneously for all factors. The company presents p values for chi squared tests for potential association between each prognostic factor and treatment effect. Minimal details on the methods and tools used to generate the HRs are available in the clarification response. Cox proportional hazards regression methods have been implemented to generate multivariate adjusted estimates of effect.

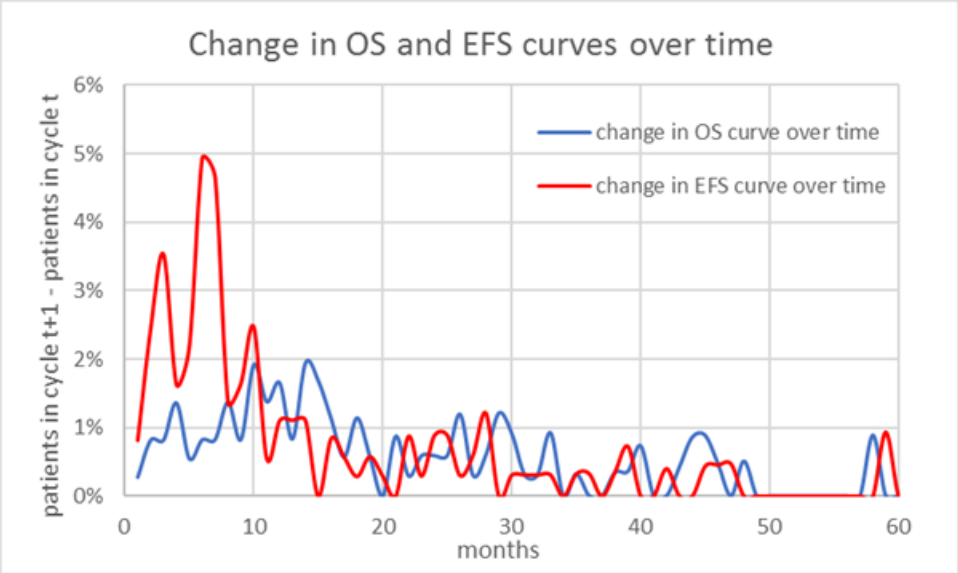
4.4.3 Results

The ERG notes that effect estimates for the indirect comparisons are available for only OS. EFS was not captured during the R1 phase of APN311-302 or in Garaventa, and so evaluation of EFS is not feasible. Given that the ERG evaluating dinutuximab alpha raised the point that the immunotherapy might be delaying rather than preventing events, together with the relatively short length of follow-up available for APN311-302, the ERG considers that the lack of availability of EFS estimates results in an incomplete representation of the short- and long-term clinical effectiveness of dinutuximab beta-containing regimens versus isotretinoin.

Additionally, the ERG has reservations about the validity of the KM data provided by the company. Although EFS and OS KM curves for APN311-302 seem to be valid (Figures 3 and 6, respectively), on investigating the supplied data, the ERG considers that the differences between the curves lack face validity (Figure 9). The ERG noted an inconsistency in the incremental proportion of patients in the OS and EFS curves in APN311-302, which is discussed in greater detail in Section 5.4.5.2. In brief, the ERG observed that the proportion of deaths is larger than the proportion of combined events that make up EFS (death, progression, relapse and second neoplasm), which is the reverse of expected proportions for OS and EFS. As the proportion of patients in the EFS and OS curves decreases over time (because patients progress or die), the difference in the proportion of patients each cycle should always be positive but this does not appear to be true in the results supplied by the company (Figure 9). The change in the EFS curve would be expected to be higher (or the same) as the change in the OS curve, because OS accounts for only death events whereas EFS also encompasses disease progression or relapse, and second neoplasm events. The ERG is unclear how the disparity in incremental events between OS and

EFS has arisen. It might be that the company has made an error in reporting the outcomes included in the KM curves (e.g., if the EFS curve censored death events), or it could be linked with inconsistency in time intervals across the OS and EFS curves.

Figure 9. Change in OS and EFS KM curves over time



4.4.3.1 High-risk neuroblastoma

As the company highlights in the CS, mean OS was substantially longer in those receiving isotretinoin alone (2,447.1 days) compared with those receiving dinutuximab beta plus isotretinoin with or without IL-2 (1,359.4 days; Table 30). Similarly, there was variation between groups in median OS, with a median OS of 1,869 days for those receiving isotretinoin and median OS yet to be reached in the group receiving the dinutuximab beta-containing regimen: estimation of the median OS time was not possible in the group receiving dinutuximab beta-containing regimen as <50% of patients had died at the time of analysis. The company proposes that the large difference in mean OS between the groups is likely due to those in the isotretinoin group being followed for longer. The ERG considers that data from the combined analysis for APN311-302 is immature and has concerns about the disparity in length of follow-up between the two studies.

The company reports that the difference in OS between the two groups was statistically significant when evaluated using the log rank test ($p < 0.0001$; unadjusted HR not available; Table 30) and favoured treatment including dinutuximab beta: unadjusted KM curves for OS are presented in Figure 10. The company reported that Cox regression models had been investigated and that INSS stage at initial diagnosis (combined stage 2 vs stage 4S, stage 3 vs stage 4S and stage 4 vs stage 4S) and prior myeloablative consolidation therapy (BuMel vs CEM) were identified as having statistically significant associations with all-cause mortality ($p = 0.0011$ for INSS stage and $p = 0.001$ for prior myeloablative

therapy). The company went on to report that the difference in OS between groups remained significant when INSS stage and prior myeloablative therapy were added to the OS analysis (p = 0.0139).

Although age at diagnosis and MYCN status were not identified as having a statistically significant association with all-cause mortality in the company's analysis, the ERG notes that it is possible the two risk factors are associated with all-cause mortality and the lack of statistical significance could be due to confounding arising from interactions among the prognostic factors. Thus, the ERG considers it important to adjust for the factors identified by clinical experts and the literature as influencing prognosis of people with high-risk neuroblastoma. The company's multivariate analysis adjusting for requested factors indicated that dinutuximab beta in combination with isotretinoin with or without IL-2 [redacted] compared with isotretinoin alone [redacted]; Table 31). The company cautioned that the results of the multivariate analysis should be interpreted with caution due to, "*the instability of the model arising from overfitting*". Univariate regression analysis [redacted] (Table 31). The ERG agrees with the company that results should be interpreted with caution due to the naïve indirect nature of the analysis.

Table 30. KM estimates for overall survival for the comparison of dinutuximab beta versus no dinutuximab beta (adapted from CS, Table 36 [pg. 81])

Parameter	Measure	Isotretinoin alone (Historical Control R1) (N=450)	Dinutuximab beta plus isotretinoin, with or without IL-2 (APN311-302) (N=367)	All (N=817)
Deaths	n (%)	238 (52.9)	115 (31.3)	353 (43.2)
Censored[b]	n (%)	212 (47.1)	252 (68.7)	464 (56.8)
Overall survival[a] (days)	Mean[c]	2,447.1	1,359.4	2,680.6
	Standard error	90.3	31.4	70.7
	Median	1,869	–[d]	4,448
	95% CI	1,304 to 3,302	–[e]	2,221[f]
Overall survival rate[a] at:	1 year KM estimate	0.83	0.89	0.86
	2 years KM estimate	0.69	0.78	0.73
	3 years KM estimate	0.59	0.71	0.64
	5 years KM estimate	0.5	0.65	0.56
Log-rank test	p-value (two-tailed)	<0.0001		

[a] Overall survival defined as time from the auxiliary starting point to the date of death from any cause.

[b] Patients without an event were censored at the date of their last follow-up evaluation.

[c] The mean survival time and its standard error were underestimated for both group and total because the largest observation was censored and the estimation was restricted to the largest event time.

[d] Estimation of the median survival time was not possible.

[e] Estimation of the upper and lower limits was not possible.

[f] Estimation of the upper limit was not possible.

Abbreviations: CS, company submission; IL-2, interleukin-2; KM, Kaplan–Meier.

Figure 10. KM curves for overall survival curves of isotretinoin alone (labelled as treatment group) versus dinutuximab beta-containing treatment (labelled as MAT and immunotherapy) (adapted from CS, Figure 7 [pg. 81])

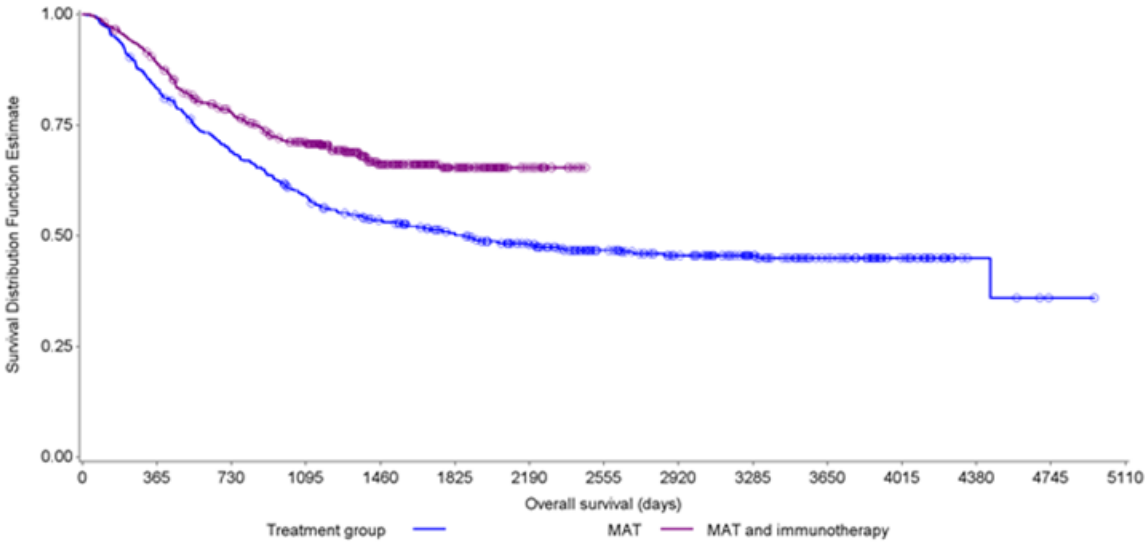


Table 31. Effect estimates generated for isotretinoin alone versus dinutuximab beta plus isotretinoin with or without IL-2 adjusted for various prognostic factors (adapted from clarification responses dated 25 August 2017 and 6 September 2017)

Type 3 tests in Cox model			
Variable	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

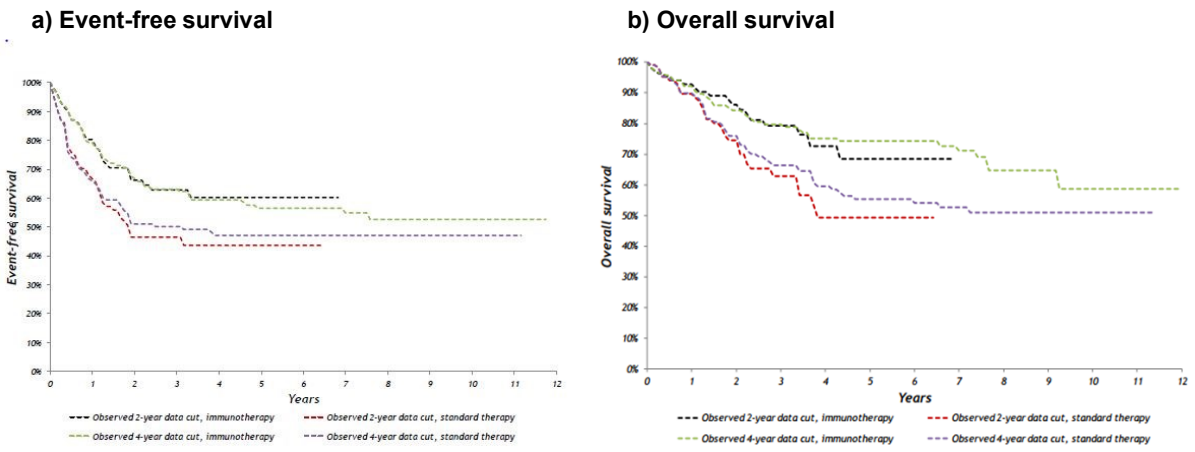
Factors adjusted for	**HR[a]**	**95% CI**
Age and INSS stage at initial diagnosis, MYCN status, and prior myeloablative therapy	[redacted]	[redacted]
Age	[redacted]	[redacted]
INSS stage at initial diagnosis	[redacted]	[redacted]
MYCN status	[redacted]	[redacted]
Prior myeloablative therapy	[redacted]	[redacted]

[a] [redacted].

Abbreviations: CI, confidence interval; HR, hazard ratio; IL-2, interleukin 2; INNS, International Neuroblastoma Staging System.

To expand on the ERG's reservations about the immaturity of the data presented for dinutuximab beta, as discussed in previous sections, the ERG proposes that results on clinical effectiveness of dinutuximab alpha could aid in understanding the clinical effectiveness, particularly in the long term, of dinutuximab beta. Considering OS in ANBL0032, as raised by the ERG assessing dinutuximab alpha in the suspended STA (GID-TAG507), there seems to be an abrupt change in the OS curve for dinutuximab alpha after approximately year 7, as depicted in Figure 11. Importantly, longer-term follow-up available for dinutuximab alpha (12 years) indicate a marked increase in mortality in the dinutuximab alpha group between 6.5 and 9 years (Figure 11) and that the observed data for the immunotherapy-containing regimen and isotretinoin seem to converge between 6.5 and 11 years (Figure 11). The ERG notes that, at 5 years, 65% of people in the dinutuximab alpha group and 47% of people in the isotretinoin group remain at risk of death (Figure 11). OS at 10 years is only marginally higher for those receiving dinutuximab alpha compared with those allocated to isotretinoin alone (approximately 59% with immunotherapy vs 52% with no immunotherapy), but this observation is based on sparse data and it is unclear whether the difference is clinically meaningful (as reported by the ERG assessing dinutuximab alpha).[45] The ERG acknowledges that data from ANBL0032 cannot be used to draw naïve conclusions on the comparative effectiveness of dinutuximab alpha versus dinutuximab beta. However, the ERG highlights the long-term data available for dinutuximab alpha to underscore the ERG's proposal that a formal indirect comparison of dinutuximab beta versus dinutuximab alpha would consolidate understanding of the long-term impact of adding dinutuximab beta, with or without IL-2, to differentiation therapy. Moreover, the ERG also considers it important to bear in mind the potential for diminishing of the clinical benefit of dinutuximab beta-based therapy over no immunotherapy in the long-term.

Figure 11. Observed event-free and overall survival data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis for dinutuximab alpha (Figures 19 and 20 in ERG report for dinutuximab alpha submission, pg. 87)[45]



4.4.3.2 Relapsed or refractory neuroblastoma

In the CS, the company focuses on the indirect comparison of APN311-303 versus Garaventa to support the treatment effect of dinutuximab beta-containing regimens in relapsed neuroblastoma. In support of the presented results, the company also report an analysis of pooled data from APN311-202 and APN311-303 versus each historical control. Given the retrospective nature of APN311-303, during clarification, the ERG requested the company carry out an indirect comparison of APN311-202 alone versus each historical control. Considering the results in totality, the ERG considers it important to summarise effect estimates from all available analyses to [redacted]. In addition, the ERG notes substantial differences between mean and median OS within each cohort, in particular for R1 (relapsed), which, in the ERG's view, suggests that the data are skewed and likely to be influenced by outliers (Table 32).

[redacted] (Table 33): available KM curves for OS are presented in Figures 12 to 16. The ERG has previously outlined concerns around the small sample size of the studies informing the analyses, and the observational nature of the studies. Considering the quality of the studies informing the analysis, together with the naive indirect nature of the comparison, the ERG considers the results of the presented analyses to be unreliable and advises that the results are interpreted with extreme caution.

Table 32. Mean and median overall survival for all groups (adapted from CS, Tables 38 [pg. 82], 39 [pg. 84] and 40 [pg. 85] and from CSR, Tables 3.1.1 [pg. 8145] and 3.1.3 [pg. 8151])

Cohort	Mean OS (SE), days	Median OS (95% CI), days
APN311-202	[redacted]	[redacted]
APN311-303	[redacted]	1,254 (715 to NA)
APN311-202 plus APN311-303	921 (68.5)[a]	1,254 (686 to NA)
Garaventa	541.7 (93.5)[a]	318 (191 to 667)[b]
R1 (relapsed)	911.4 (136.4)[a]	630 (281 to 838)

[a] The company reports that the mean survival time and its SE were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

[b] Table 38 of the CS presents an alternative median OS for the Garaventa population of 287 days (95% CI 160 to 636). The reason for the different reported values is unclear.

Abbreviations: CI, confidence interval; CS, company submission; CSR, clinical study report; NA, not achieved; OS, overall survival; pg, page; SE, standard error.

Table 33. Summary of analyses of overall survival for dinutuximab beta in combination with isotretinoin and IL-2 versus historical control in the treatment of relapsed neuroblastoma (adapted from CS, Tables 37 [pg. 82], 38 [pg. 82] and 39 [pg. 83], CSR for APN311-202 and APN311-303, and clarification response dated 6 September 2017)

Comparison	KM estimate		HR	95% CI
Unadjusted analyses taken from CSR				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]
Unadjusted analyses as reported in CS				
APN311-303 versus R1 (relapsed)	Not available			
APN311-303 versus Garaventa[a]	APN311-303	Control		
KM estimate at 1 year	0.90	0.56	–	–
KM estimate at 2 years	0.69	0.46	–	–
KM estimate at 3 years	0.55	0.28	–	–
APN311-202 + APN311-303 versus R1 (relapsed)[b]	APN311 studies	Control		
KM estimate at 1 year	0.83	0.56	–	–
KM estimate at 2 years	0.60	0.46	–	–
KM estimate at 3 years	0.50	0.28	–	–
APN311-202 + APN311-303 versus Garaventa[c]	APN311 studies	Control		
KM estimate at 1 year	0.83	0.45	–	–
KM estimate at 2 years	0.60	0.31	–	–
KM estimate at 3 years	0.50	0.24	–	–
Adjusted analyses provided during clarification				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]

[a] Log rank p value of 0.0009.

[b] Log rank p value of 0.0302.

[c] Log rank p value of 0.0031.

[d] Adjusted for [redacted].

[e] Adjusted for [redacted].

Abbreviations: CI, confidence interval; CS, company submission; CSR, clinical study report; HR, hazard ratio; KM, Kaplan–Meier; [redacted].

Figure 12. KM curves for overall survival for APN311-202 versus R1 (relapsed) (adapted from CSR, Graph 3.1.3 [pg. 8254])

Figure 13. KM curves for overall survival for APN311-303 versus R1 (relapsed) (adapted from CSR, Graph 3.1.1 [pg. 8250])

Figure 14. KM curves for overall survival for APN311-303 versus Garaventa (adapted from CS, Figure 8 [pg. 83])

Figure 15. KM curves for overall survival for APN311-202 plus APN311-303 versus R1 (relpased) (adapted from CS, Figure 9 [pg. 83])

Figure 16. KM curves for overall survival for APN311-202 plus APN311-303 versus Garaventa (adapted from CS, Figure 10 [pg. 86])

4.5 Summary and conclusions of clinical effectiveness sections

- No direct comparative evidence is available on the clinical effectiveness of dinutuximab beta in high-risk, relapsed or refractory neuroblastoma versus comparators of interest. All effect estimates versus comparators of interest to the decision problem are generated from naïve indirect comparisons.

- Dinutuximab beta has been awarded a European marketing authorisation under exceptional circumstances. The authorisation covers the use of dinutuximab beta in the treatment of high-risk neuroblastoma in people aged 12 months and above, who achieved at least a partial response to induction chemotherapy, and who went on to receive subsequent consolidation treatment with myeloablative therapy and ASCT. Additionally, the authorisation includes people with history of relapsed or refractory neuroblastoma. Dinutuximab beta can be given as a treatment irrespective of presence or absence of residual disease. The marketing authorisation specifies that dinutuximab beta be given in combination with IL-2 in those with high-risk neuroblastoma and not achieving a complete response to induction therapy and those with relapsed or refractory disease.

- In high-risk neuroblastoma, one RCT, APN311-302, provides data on the clinical effectiveness of dinutuximab beta, with or without IL-2, in combination with isotretinoin in the treatment of high-risk neuroblastoma in line with the marketing authorisation. Data from both groups of APN311-302 are combined to inform a naïve indirect comparison versus isotretinoin alone.

- For relapsed and refractory neuroblastoma, evidence on effectiveness of the combination of dinutuximab beta, IL-2 and isotretinoin is derived from two small single-arm observational studies, one prospective in design, APN311-202, and the other retrospective in nature, APN311-303. Again, data are used to inform a naïve indirect comparison, and only for those with relapsed neuroblastoma: available data precluded analysis for those with refractory neuroblastoma.

- APN311-302 is a segment of the HR-NBL-1, which is an investigator-initiated, international, open-label, randomized, phase III trial. The modified primary objective of the APN311-302 phase of HR-NBL-1 was to assess the benefit of adding IL-2, if any, to dinutuximab beta and differentiation therapy with isotretinoin. Outcomes assessed included EFS, OS, and adverse effects of treatment. By contrast, the primary objective of both APN311-202 and APN311-303 was to identify a tolerable treatment schedule for dinutuximab beta that minimised the pain and toxicity profile of the immunotherapy while maintaining the immunomodulatory effect. EFS and OS were captured as secondary outcomes in APN311-303.

- APN311-302 had sites in 10 countries, including the UK. A large proportion of people analysed in APN311-302 were recruited from the UK ([redacted] people [[redacted]%]), and baseline characteristics of the trial population are representative of those with high-risk neuroblastoma likely to be eligible for treatment with dinutuximab beta in England.

- Results presented for APN311-202 are derived from an interim analysis of data collected from a prospective multinational, ongoing study, whereas data from APN311-303 were initially captured under a compassionate use programme (CU-LTI) carried out in a single site in Germany and evaluated retrospectively.

- Comparative estimates of effect are available for only OS. For high-risk neuroblastoma, the historical control for comparison with APN311-302 was derived from an earlier stage of HR-NBL-1 during which people received only isotretinoin as a maintenance therapy after consolidation therapy. The same stage of HR-NBL-1 also forms the basis of a historical cohort of those experiencing relapse. Additionally, published data from a retrospective review of a neuroblastoma registry forms a second historical cohort for comparison in relapsed neuroblastoma. Baseline characteristics for the historical controls are predominantly comparable with those of the populations enrolled in the relevant APN311 study.

- In those with high-risk neuroblastoma achieving a partial response to induction therapy and completing consolidation therapy with myeloablative therapy and ASCT, dinutuximab beta-based treatment, with or without IL-2, was

[redacted] compared with isotretinoin alone [redacted]): the reported HR is adjusted for age, INSS stage at initial diagnosis, MYCN status, and prior myeloablative therapy.

- In relapsed neuroblastoma, [redacted]. For example, OS estimate for [redacted] with dinutuximab beta-based treatment [redacted].

- Data on the adverse effect profile of dinutuximab beta are primarily derived from a safety database comprising 514 people who have undergone treatment with the immunotherapy, with a focus on 98 people who received dinutuximab beta as a continuous infusion over 10 days. Administration of dinutuximab beta is known to be associated with pain, hypersensitivity reactions, and capillary leak syndrome. Each person in APN311-202 and APN311-303 experienced a TEAE. The company reported that, although the number of TEAEs decreased substantially with each treatment cycle, the proportion of people experiencing a TEAE remained high throughout the study (data not presented).

4.5.1 Clinical issues

- Methods implemented to search and appraise the literature for clinical effectiveness undermine the robustness of the company's systematic review process, including omission of index terms for neuroblastoma from the search strategies, review of abstract and full text publications by one reviewer, potential non-validation of data extraction.

- Potential sources of bias associated with design and conduct of APN311-302 include uncertainty around concealment of allocation, open label design of the study and lack of masked independent assessment of EFS, and the possible disparity within the study in timing of follow-up and recording of clinical effectiveness outcomes.

- Investigations carried out by the ERG has led to concerns around the validity of data in APN311-302. Specifically, the ERG noted an inconsistency in the proportion of patients moving out of the OS and EFS KM curves in the APN311-302 study.

- In APN311-302, dinutuximab beta was infused following the short-term schedule of administration over 5 days, whereas preference in UK clinical practice would be to infuse the immunotherapy continuously over 10 days. Evidence assessing whether rate of infusion affects clinical outcomes is not available.

- APN311-202 and APN311-303 are single-arm observational studies and are, by nature, inherently at a high risk of bias. In addition, both studies have a small sample size in each subgroup of relapsed and refractory neuroblastoma, which leads to considerable uncertainty in any estimates of effect.

- Single-arm studies, such as APN311-202 and APN311-303, are not considered appropriate design to capture time to event outcomes, for example, EFS and OS.

- In APN311-303, a substantial amount of data, particularly for prognostic factors, were not captured and, despite a review of the data, could not be retrieved. The retrospective nature of APN311-303 and absence of data could lead to selection bias, and a lack of standardisation in data recording and outcome assessment.

- Population of those experiencing relapse in APN311-202 and APN311-303 might not be representative of those with relapsed neuroblastoma in the UK. Most people experiencing relapse of neuroblastoma are likely to have had an initial diagnosis of high-risk neuroblastoma. In the UK, people with newly diagnosed high-risk neuroblastoma are likely to have received dinutuximab beta as part of their multimodal multiagent front-line treatment through participation in the HR-NBL-1 study. However, based on the company's response to clarification, [redacted] in APN311-202 or APN311-303 had previously received dinutuximab beta, and evidence on re-treatment with the immunotherapy is not available.

- No formal statistical hypotheses, statistical analysis methods or power calculations were specified *a priori* for either APN311-202 or APN311-303. In APN311-202, no clinical outcome was pre-specified as an outcome of interest to the study.

- Data presented for APN311-302 do not adhere to the ITT principle. Initially, 406 people were randomised but analyses are based on the final analysis set, which comprised 370 people for whom for whom an eCRF was available, who received allocated treatment and for whom treatment data were available. An eCRF was not available for 21 people. It is unclear why an

eCRF was not available for all randomised patients, or why some people did not receive any treatment.

- Length of follow-up in APN311-302 might be insufficient to determine fully the clinical effectiveness of dinutuximab beta, particularly whether any clinical benefit is maintained in the longer term. Additionally, there is a substantial [redacted].

- No direct evidence is available on the clinical effectiveness of dinutuximab beta-based regimen versus comparator of interest in high-risk or relapsed neuroblastoma. All comparative estimates of effect are based on naïve indirect comparisons.

- Comparative estimates of clinical effectiveness of dinutuximab beta are available for only OS. EFS was not captured for any of the historical controls. Given that the ERG evaluating dinutuximab alpha raised the point that the immunotherapy might be delaying rather than preventing events, together with the relatively short length of follow-up available for APN311-302, the ERG considers that the lack of availability of EFS estimates results in an incomplete representation of the short- and long-term clinical effectiveness of dinutuximab beta-containing regimens versus no dinutuximab beta.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and the *de novo* economic evaluation submitted by the company. Due to model mistakes and the use of an unsuitable methodological approach identified by the ERG during, and subsequently to, the clarification stage, the company provided two electronic versions of the Microsoft Excel®-based economic model. The focus of the ERG report is therefore on the second, updated, economic model. However, the ERG notes that due to the paramount changes in the updated economic model, which were only accompanied by a brief document as a reply to the ERG's clarification questions, most of the ERG's critique is based on the inspection of the economic model and not on written evidence submitted by the company. The ERG notes that several calculations and assumptions were changed in the updated model, without being reported or justified by the company (or requested by the ERG during the clarification stage). The consequences of this are twofold: the ERG cannot guarantee that some aspects of the economic analysis and/or economic model were not missed; and there were several instances where the ERG had to make assumptions with regards to what was the company's approach.

The ERG identified implementation and formulae errors in the updated economic model (described throughout the report). The ERG is concerned that this reflects a poor level of internal quality assessment of the model by the company.

Furthermore, after the initial clarification stage, NICE decided to extend the deadline of the ERG report to provide the company with more time to address the ERG's requests. This resulted in several rounds of clarification between the ERG and the company, which ended up imposing additional time pressure to the normal timeframe for ERG reviews. Therefore, the ERG could not undertake all the analyses that it considered relevant to improve the quality standard of the methodological approaches in the company's submission. Due to time constraints, the ERG was forced to focus its attention in the aspects deemed more relevant for the analysis. All the changes made, and all the changes that are advisable, in the ERG's opinion, but not undertaken by the ERG, are reported in this document.

5.2 Summary of the company's key results

According to the company's updated base case analysis, the incremental cost-effectiveness ratio (ICER) for dinutuximab beta compared with isotretinoin is £22,338 per QALY gained, for the high-risk population. The company's revised base case ICERs for the high-risk model is reported in Table 34. The ERG does not consider the company's probabilistic sensitivity analysis to be informative, for the reasons discussed in Section 5.5.

Table 34. Company's revised base case results – high-risk population

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£190,521	13.97	-	-	£22,338
Dinutuximab beta + isotretinoin	£311,569	19.39	£121,048	5.42	
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.					

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic literature review to identify studies reporting economic outcomes (i.e. cost-effectiveness, resource use, or costs) for patients with high-risk, relapsed, or refractory neuroblastoma. The company reported carrying out an initial search, restricted on neuroblastoma treatment received, which did not identify any relevant studies. Therefore, an additional search, not restricted by treatment received, was carried out on 21 May 2017.

The company provided the search terms and strategies implemented in its review of the literature as an Appendix (Table 1, Appendix G of the company's submission [CS]). The search terms combined population, intervention, and economic outcome terms. The search was limited to patients with high-risk or relapsed or refractory neuroblastoma aged greater than 12 months, and to English language publications. The company searched the following electronic databases: Medline, Embase, the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects), and the Education Resources Information Centre database. The ERG considers the inclusion and exclusion criteria to be broadly appropriate to capture relevant publication, however, it disagrees with the age restriction applied to the literature search, which was not justified in the CS. Nevertheless, clinical expert opinion provided to the ERG clarified that neuroblastoma cases in patients younger than 12 months are unlikely to be high-risk cases, which reduces the likelihood that the company missed relevant papers by limiting the search to patients older than 12 months.

The company identified two studies[81,82] reporting resource use/costs of neuroblastoma, while no economic evaluations were identified. The company carried out a *post-hoc* manual internet search and identified three additional studies[83-85] reporting costs, which were considered relevant. These studies are described further in Section 5.4.9. The ERG is unsure why the three additional studies identified through the manual search were not identified in the company's initial literature search. Given that the company did not provide any details on excluded studies after full-text appraisal or the reasons for exclusion, the ERG cannot ascertain if the studies were missed from the literature search or excluded during the screening stage. Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases.

Finally, the ERG notes that the company should have searched the NICE website as part of its additional search and included the previous STA of dinutuximab for treating patients with high-risk neuroblastoma as part of the literature base to inform this submission (GID-TAG507).[45]

5.4 Overview and critique of company's economic evaluation

5.4.1 NICE reference case checklist

Table 35 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 3.

Table 35. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The final scope developed by NICE	Yes.
Comparator(s)	Alternative therapies routinely used in the NHS	Unclear. Clinical expert advice sought by the ERG was that in the UK, dinutuximab beta has become standard of care, and therefore clinicians would not treat patients with isotretinoin without dinutuximab beta. The consolidation treatment regimen included in the historical control R1 is unlikely to be reflective of treatment received by UK neuroblastoma patients as half of the people in R1 received CEM as their consolidation therapy. The clinical experts advising the ERG explained that in the UK, BuMel has become standard of care, and CEM is very rarely used given that BuMel has been shown to be a more effective consolidation therapy than CEM. Therefore, it is likely that the clinical outcomes for R1 patients are negatively biased due to half of the patients receiving CEM instead of BuMel as consolidation therapy, before receiving isotretinoin. Furthermore, the company has also included IL-2 as a concomitant drug to isotretinoin. This has not been reported in the CS, and the ERG assumes this was a modelling mistake.
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes, the life time horizon of 90 years is appropriate, considering that the starting age of the model is three years for the high-risk population.
Synthesis of evidence on outcomes	Systematic review	No. A systematic review on clinical effectiveness was conducted. However, no synthesis of evidence was implemented using the RCT data from the dinutuximab alpha submission, which the ERG considers would have been a more robust approach than carrying a naïve comparison to historical control data R1.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes. Portwine *et al*. 2016[86] and Barr *et al*.1999[87] included the HUI2 and HUI3 instruments.
Benefit valuation	Time-trade off or standard gamble	Yes. The HUI intrinsically uses the standard gamble approach to measure preferences
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Unclear. The company uses a mix of HUI2 and HUI3 measures.
Discount rate	An annual rate of 3.5% on both costs and health effects	No, however the ERG accepts the 1.5% discount for the base case analysis, but advises running an additional scenario analysis with a discount rate of 3.5%.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	No. Neither the deterministic or the probabilistic sensitivity analysis undertaken by the company are fit for assessing uncertainty in the model.
Abbreviations used in the table: EQ-5D, EuroQoL 5-Dimension; HRQoL, health-related quality of life; HUI, health utility index; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SF-36, 36-Item Short Form Survey; TTO, time trade-off.		

5.4.2 Population

The population considered by the company for this STA comprises people with high-risk neuroblastoma, who have previously received induction chemotherapy and achieved at least partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease.

The company built two separate models, one for the high-risk population and the other for the relapsed or refractory population. The two models used different clinical data to estimate treatment effectiveness. While the high-risk model used clinical data from study APN311-302 and data from the historical controls from an earlier phase of APN311-302, the relapsed or refractory model took data from APN311-202 and from the historical control from APN311-302 and from a retrospective analysis of registry data of children with relapse or progression of neuroblastoma.[70] However, for the relapsed or refractory population, the data taken from APN311-202 is limited to the relapsed population in the study, and thus the model does not include the refractory population data from the study. This is also the case for the historical control data and the Garaventa study, which only included relapsed patients. As such, the company's relapsed or refractory model is in fact a model for the relapsed population, and will be referred to as the relapsed model, hereafter.

Overall, the ERG considers that the evidence base for the relapsed model is not reliable enough to inform robust decision-making. Furthermore, the company clearly states that it does not support the use of dinutuximab beta for relapsed or refractory patients. Therefore, while Section 4 of the report presents the clinical results for the relapsed population, the economic section does not explore the relapsed model any further. The justification for the ERG's decision is based on the following:

1) The evidence for the relapsed population is extremely poor and unfit for purpose. Study APN311-202 and APN311-303 are very small studies and APN311-303 is a retrospective study (please see Section 4 for more details on the studies' quality assessment);

2) The analysis provided by the company after the clarification stage, reporting the fully adjusted HRs, produced a HR below 1 for the relapsed population (when using the APN311-202 study), suggesting that dinutuximab is less effective that isotretinoin for this population. Therefore, the results, and thus the model results lack clinical meaningfulness;

3) Clinical expert opinion sought by the ERG reported that in the UK, dinutuximab beta is always given as a first line treatment to patients and added that they would not retreat patients with dinutuximab beta unless there was evidence substantiating the effectiveness of dinutuximab as a retreatment option (given that the company decided to not carry on with studies in the relapsed or refractory population, such studies are not foreseeable);

4) The company, in their reply to the ERG's clarification questions states that, "*given the lack of data for the use of dinutuximab beta EUSA in patients that may have already failed (relapsed) or those that are refractory to dinutuximab beta EUSA, EUSA Pharma does not support re-treatment with the drug*". The company adds that there are no on-going studies that evaluate the effectiveness of dinutuximab beta in relapsed of refractory patients.

With regards to the high-risk population, and based on clinical expert opinion given to the ERG, the ERG considers that the full trial population of APN311-302 and R1 are broadly representative of high-risk neuroblastoma patients likely to be eligible for treatment with dinutuximab beta in England. However, the ERG notes that the full population data needs careful consideration with regards to levels of response to induction therapy at baseline (as discussed in Section 4). Nonetheless, the induction therapy received by patients in R1 is less likely to be reflective of clinical practice in the UK and is likely to introduce some bias in the clinical outcomes of the R1 population. This issue is discussed in the next section.

5.4.3 Interventions and comparators

The intervention set out in the NICE scope is dinutuximab beta. The intervention considered in the economic model, which reflects the treatment regimen in APN311-302 does not entirely reflect the NICE scope. In the economic analysis, patients in the dinutuximab beta arm of the model received dinutuximab beta combined with isotretinoin. Furthermore, even though this is not reported in CS, all patients receiving treatment with dinutuximab beta and isotretinoin in the economic model also received interleukin 2 (IL-2).

According to the SmPC, dinutuximab beta is indicated for the treatment of high-risk neuroblastoma in children aged 12 months and above, who have previously received induction chemotherapy and achieved at least partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first-line therapy, dinutuximab beta should be combined with IL-2.

Even though the SmPC indication and the NICE scope do not referrer isotretinoin as a concomitant drug to dinutuximab beta, clinical expert opinion provided to the ERG indicated that dinutuximab would be given with isotretinoin in UK clinical practice. Furthermore, in the reply to the ERG's clarification questions, the company stated that, "*according to clinical guidelines and clinical expert opinion, isotretinoin is always part of the maintenance regimen and always used concomitantly with dinutuximab beta*". Therefore, the ERG considers the inclusion of concomitant isotretinoin in the intervention arm of the economic model appropriate, and reflective of clinical practice in the UK.

The inclusion of IL-2 in the intervention arm of the model is unjustified by the company. In fact, during the clarification stage the company explained that concomitant administration of IL-2 does not have an impact on event-free survival (EFS) or overall survival (OS) and thus patients will not receive it in clinical practice (as a justification for not including IL-2 in the analysis). However, and even though the company seems to imply that IL-2 costs were not included in the model, all patients in the high-risk model received IL-2 (and were therefore costed as such). The ERG's view is that the proportion of patients receiving IL-2 in the high-risk model should reflect the underlying clinical trial data from APN311-302 used to estimate clinical effectiveness in the model. Additionally, an important scenario to include is the proportion of patients in the UK who would be treated with concomitant IL-2. In this instance, both of these scenarios are fairly similar, as 51% of patients in APN311-302 received IL-2 and 41% of patients had evidence of disease at baseline in APN311-302, which according to the marketing authorisation would make this group of patients eligible to receive IL-2 concomitantly with dinutuximab beta.

All people randomised in APN311-302 were scheduled to receive five 28-day cycles of dinutuximab beta (20 mg/m²/day over five days) given as an 8-hour daily intravenous infusion together with six 28-day cycles of oral isotretinoin (160 mg/m²/day over 14 days). The first cycle of dinutuximab beta started 3 weeks after the start of treatment with isotretinoin (at week 4). In addition, starting at week 3 of treatment, those randomised to IL-2 also received subcutaneous IL-2 (6 MIU/m^2/day) over 5 days (therefore started treatment with IL-2 one week before initiating treatment with dinutuximab beta).

The modelled intervention (dinutuximab beta + isotretinoin + IL-2) does not accurately reflect the treatment regimens included in the APN311-302 study. For treatment with dinutuximab beta, people in the trial received 8-hour daily infusions over five days for five cycles. In the model, patients received 24-hour continuous infusions over 5 days, twice (10 days of treatment in total). Clinical expert opinion sought by the ERG agreed that continuous infusions reflect current practice in the UK. Nonetheless, it is unclear if the method of administration of dinutuximab beta (i.e. daily vs continuous) would have had any impact in terms of treatment effectiveness and the safety profile of the drug. With regards to concomitant isotretinoin, patients in the trial received six cycles of treatment, while people in the model received only five cycles. It is unclear to the ERG why the company modelled five cycles of treatment with isotretinoin instead of six, which is recommended in clinical practice.

The comparators considered in the NICE scope are isotretinoin alone and dinutuximab alpha. The comparator considered in the economic model is isotretinoin alone. The exclusion of dinutuximab alpha, justified by the company with the withdrawal of the drug's marketing authorisation in the EU, is considered reasonable by the ERG. The company has also included IL-2 as a concomitant drug to isotretinoin. This has not been reported in the CS, and the ERG assumes this was a modelling mistake. The ERG removed the IL-2 costs from the comparator arm of the economic model and reports the results in Section 6.

The historical cohort R1 used as the source of clinical effectiveness for treatment with isotretinoin, derived from people enrolled in an earlier phase of the HR-NBL-1 (which later on included APN311-302). People forming the historical control R1 were randomised in the R1 phase of HR-NBL-1 (see Section 4 for more details), which was designed to compare the effectiveness of BuMel versus CEM as consolidation myeloablative therapy in high-risk neuroblastoma. After induction therapy and myeloablative therapy followed by ASCT, people received six courses of oral isotretinoin 80 mg/m² twice daily for 14 days, every 4 weeks (maintenance phase).

In the model, patients received five cycles of treatment with isotretinoin. Again, it is unclear to the ERG why the company modelled five cycles of treatment with isotretinoin instead of six, which is the recommended clinical practice. The ERG ran a scenario analysis including six cycles of isotretinoin in the intervention and comparator arms of the economic model. Not surprisingly, the increase in costs in

both treatment arms cancelled out and the final ICER did not change. Furthermore, clinical expert advice sought by the ERG was that in the UK, dinutuximab beta has become standard of care, and therefore clinicians would not treat patients with isotretinoin without dinutuximab beta.

The consolidation treatment regimen included in the historical control R1 is unlikely to be reflective of treatment received by UK neuroblastoma patients. As the historical control study R1 was designed to compare the effectiveness of BuMel versus CEM, half of the people in the R1 phase, received CEM as their consolidation therapy (302/598; 50.5%). The clinical experts advising the ERG explained that in the UK, BuMel has become standard of care, and CEM is very rarely used given that BuMel has been shown to be a more effective consolidation therapy than CEM.

This means R1 is likely to be a poor reflection of the maintenance treatment regimen for neuroblastoma patients in the UK, and that the clinical outcomes for R1 patients are negatively biased due to half of the patients receiving CEM instead of BuMel as consolidation therapy, before receiving isotretinoin. The implications of the latter are that the baseline health of the population receiving isotretinoin is likely to be poorer than that of the population receiving dinutuximab beta plus isotretinoin. In order to have a valid estimate of relative effectiveness of dinutuximab beta plus isotretinoin compared with isotretinoin, it needs to be adjusted for the type of consolidation therapy. This issue is further explored in Section 4 and in Section 5.4.5 of the report.

5.4.4 Modelling approach and model structure

The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of dinutuximab beta given in combination with isotretinoin, in comparison with isotretinoin. The model includes three health states: the event-free state (EFS), the failure state (FS) and death. The proportion of patients occupying the different health sates from cycle 0 until the point of the cure threshold (hereafter referred to as the short-term model) are estimated in a cohort-based partitioned survival model. The economic outcomes for the first five cycles (i.e. the first five months) of the model are estimated in a decision-tree-based model. The economic model after the cure threshold point (hereafter referred to as long-term model) is a separate structure, and also a cohort-based partitioned survival model.

The cohort is allocated to the EFS state at the beginning of the economic analysis and is assumed to initiate treatment with dinutuximab beta plus isotretinoin or isotretinoin alone for a maximum of five months (in treatment cycles of 10 days per month for dinutuximab beta and 14 days for isotretinoin). The treatment and comparator arms in the model, include IL-2 as a treatment, even though this is not reported in the CS. This issue is further explored in Section 5.4.3 and Section 5.4.9. Patients occupying the EFS state are at risk of disease progression or death. Patients in the FS state are also at risk of death and cannot enter remission in the model. The model includes two possible scenarios for a cure threshold.

While one assumes that patients on the EFS state for five years are cured, the other assumes that only after 10 years of EFS, a patient can be assumed cured. When patients reach the cure threshold, the patients in the EFS and the FS state can only move to the death state, as patients cannot progress in the model anymore. At this point in the model, patients in the EFS and in FS states die at different rates, to simulate that some patients are considered cured while others are relapsed patients. This is further explored in Section 5.4.7 of the report. The partitioned survival (or area under the curve [AUC]) approach means that the proportion of patients modelled in each health state is based on parametric survival curves for each clinical outcome. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 5.4.5.

A life time horizon of 90 years is adopted in the model and time is discretised into monthly cycles for the short-term model and yearly cycles for the long-term model. A half-cycle correction was not applied in the model. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at a non-reference-case discount rate of 1.5%.

The company provided two separate models, one for the high-risk population and the other for the relapsed or refractory population. However, for the reasons explained in Section 5.4.2, the focus of the ERG report is on the high-risk model.

5.4.4.1 ERG critique

Overall, the company's modelling approach and model structure is unnecessarily burdensome and removes transparency from the formulae and calculations within the model. It is the ERG's view that the use of a decision-tree to estimate short-term outcomes was unnecessary, especially when the cohort data populating the decision-tree structure is taken from the cohort-based partitioned survival model. The decision-tree model is extremely difficult to navigate and has several circular references in its data implementation, combined with formulae cells filled with white-font numbers. All this makes the ERG's review unnecessarily complex. This also leads to a higher probability of errors in formulae, and a lower probability of all errors being identified during the ERG's review process. In total, the company's model was structured in three different model engines, the decision-tree model, the short-term partitioned survival model and the long-term partitioned survival model. Given that the company provided two models, one for the high-risk population and the other for the relapsed or refractory population, the Microsoft Excel® - based model ended up having six model engines (nonetheless the ERG only reviewed the high-risk model, as explained in Section 5.4.2). The company could have simplified the model structure, and have a single cohort-based partitioned survival model, which would have been more efficient and transparent, and potentially avoided formulae, and calculation errors.

The life time horizon of 90 years is appropriate, considering that the starting age of the model is three years for the high-risk population. The company did not apply half-cycle corrections to the model

cycles. While for the monthly cycles, this is generally fine, the yearly cycles in the long-term model should have been adjusted. The ERG adjusted the annual cycles in the long-term model and provides the results in Section 6 of the report.

The company did not include the first row of costs and QALYs in the Excel model. Therefore, the sum of all model outcomes, included in the final ICER, excluded the costs and benefits related with the first model cycle. Therefore, the ERG corrected this in the model and results are presented in Section 6. Furthermore, the discounting factor being applied in the model was estimated on a monthly basis instead of an annual basis. For example, at 1.5 years in the model, instead of using an annual discount factor of 1, the company used a discount factor of 1.5. The ERG corrected this to reflect annual discounting in the analysis and presents results in Section 6.

The NICE's guide to the methods of technology appraisal states that, *"In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs."*[88]

As discussed in the next sections of the ERG report, the quantification of the survival benefit associated with dinutuximab beta has a high degree of uncertainty. Furthermore, clinical expert opinion, and the ERG's report for the dinutuximab alpha STA (GID-TA507) expressed the view that it is possible that dinutuximab alpha delays, rather than prevents, disease progression and therefore neuroblastoma-related deaths. Nonetheless, the Appraisal Committee (AC) for the dinutuximab alpha submission decided that a 1.5% discount rate was appropriate as the, "*dinutuximab* [alpha] *regimen could be considered to cure neuroblastoma in a small percentage of patients*". Therefore, the ERG accepts the 1.5% discount for the base case analysis, but advises exploring the impact of the discount in an additional scenario analysis with a discount rate of 3.5%, as indicated in Section 6.

5.4.5 Treatment effectiveness

The company's updated model incorporated survival analysis. However, the company did not submit an accompanying document justifying or explaining the methodology undertaken. Therefore, this section of the ERG report is entirely based on the ERG's interpretation of the economic model, which as a review method, is not without its risks.

5.4.5.1 Short-term model (from first cycle to cure threshold)

Treatment effectiveness within the updated short-term model was implemented through a partitioned survival method, which uses the OS and EFS data from APN311-302 to determine mortality and disease progression for each cycle of the economic model, respectively.

In order to extrapolate OS and EFS data to the model time horizon, the company fitted a variety of parametric curves to APN311-302 Kaplan-Meier (KM) data. Through observation of the economic model, it would appear that the company has undertaken a fitting exercise of clinical data with exponential, Weibull, log-logistic, lognormal and Gompertz models. The use of survival analysis in the model depends on the cure threshold assumed for the analysis. The company originally incorporated two alternative scenarios in the model. One assuming a cure threshold of five years, and another one, following a request from the ERG, to consider a 10-year cure threshold. In the updated analysis, the company considered their base case analysis to be based on the 10-year threshold. The company used the KM curves from APN311-302 for the time period where KM data were available (approximately seven years in APN311-302), and then used a parametric curve to extrapolate the clinical data for the rest of the short-term model's time horizon (three years). The final OS and EFS curves used in the model are therefore based on the respective KM curves available, followed by a parametric tail fitted with Gompertz models for both clinical outcomes.

As far as the ERG can assess, the company's choice of survival model was based on summing, for each model cycle, a measure of deviance from the estimated curve in relation to the KM data through the following formula: [(KM survival estimate – Fitted survival curve estimate)/KM survival estimate]^2. The company then assessed which survival model yielded the lowest measure of deviance, and chose that model, which in this case is the Gompertz.

The survival curves for dinutuximab beta were then used to estimate the proportion of patients in each health state for every cycle of the model. The company's model used the following equations:

- EFS = P(EFS);
- FS = P(OS) – P(EFS);
- Death = 1 – P(OS).

Where P(EFS) is the proportion of event-free patients taken from the EFS curve and P(OS) is proportion of patients alive taken from the OS curve.

To estimate OS in the isotretinoin arm of the model, the company used the unadjusted KM data from the historical control R1. Therefore, the company's approach to estimating treatment effectiveness in

the model was based on a naïve comparison of KM (and fitted) data from unadjusted APN311-302 data with unadjusted R1 data. However, R1 does not report EFS data, therefore the company assumed that the absolute separation between OS and EFS observed in the dinutuximab beta arm of the model at year 5 will be the same difference between OS and EFS in the comparator arm.

Nonetheless, based on an investigation of the economic model, the ERG considers that the approach taken by the company was to estimate EFS KM data for isotretinoin for each cycle by using the following formula: $[OS_{isotretinoin} - (OS_{dinutuximab} - EFS_{isotretinoin})]$. The ERG assumes that these KM data were then used to fit an EFS curve in the comparator arm. A similar approach was taken for the intervention arm, the company seems to have used the OS KM curve from R1 (and estimated KM for EFS) for the time period where KM data were available. However, because there are 10-years' worth of OS KM data in R1, the company model never incorporated the fitted Gompertz curves (which were nonetheless provided in the Excel-based model).

5.4.5.2 ERG critique

The ERG has severe concerns with the estimation of treatment effectiveness in the economic analysis. These are discussed in turn in this section. However, the ERG reinforces the fact that the model and the CS lack sufficient detail and transparency for the ERG to be secure that the review conducted was sufficient to ensure the internal validity of the model.

Even though the ERG requested that the company followed the guidance from the NICE DSU Technical Support Document (TSD) 14[89] when rebuilding their model after the clarification stage, the company only followed the guidance partially. Survival analysis was undertaken in the updated model (as opposed to the simplified analysis ran in the original model) however, the assessment of fit for the parametric models was not done in accordance to the guidance. The company did not use the Akaike Information Criterion (AIC) or the Bayesian Information Criterion (BIC) or provide the fit of each parametric model against the observed KM data. Log-cumulative hazard plots were not generated nor used to assess the appropriateness of using a Gompertz model, through assessment of the presence of monotonic, non-monotonic or a constant hazard rate with respect to time. Log-cumulative hazard plots should have been used to assess the proportional hazard (PH) assumption, and inform the decision to model treatment arms independently or through a hazard ratio (HR) in the model. Finally, the company does not make any mention to having used clinical expert opinion to validate extrapolated curves, which is a fundamental tool to assess the external and clinical validity of survival curves.

The NICE DSU Technical Support Document (TSD) 14[89] also mentions that piecewise modelling should only be considered when the standard parametric models have shown to provide a poor fit to KM data. The ERG is uncertain if the company's approach in the updated model followed a piecewise approach. It seems to the ERG that the company still fitted a survival curve to the entire KM curve

(instead of using just the tail) but decided to use KM data (instead of the fitted curve) for the period of time where KM data were available.

Despite these technical shortcomings, the ERG notes that estimated survival data are only used for a maximum of 3 years in the company's base case model, for the dinutuximab beta arm of the model, when the 10-year cure threshold is used. Nonetheless, the ERG disagrees with the approach of using OS and EFS KM data for dinutuximab beta for seven years, and then using estimated survival data for three years. To note is that this approach was not justified by the company. The ERG discusses the issues related with the KM data for OS and EFS in APN311-302 in the next section.

5.4.5.2.1 Kaplan–Meier data from APN311-302

The ERG is extremely concerned with the lack of face validity of the KM data provided by the company. While visual inspection of the OS and EFS curves for APN311-302 might appear valid (Figure 17

Figure 17), the difference between the curves (which gives the proportion of patients in the failure state) and the between-curve relationship lacks face validity, as seen in Figure 18. The ERG investigated the KM data provided by the company in the model and noted an inexplicable inconsistency in the proportion of patients moving out of the OS and EFS KM curves in the APN311-302 trial.

To illustrate this issue, the ERG produced Figure 19 to show the proportion of patients in cycle t minus the proportion of patients in cycle t+1 in the OS and EFS KM curves in APN311-302. As the proportion of patients in the EFS and OS curves decrease over time (because patients progress or die), the difference in the proportion of patients each cycle are always positive (Figure 19). The red curve in Figure 19 shows the proportion of patients who leave the EFS curve over time (representing the additional number of patients who progressed, relapsed or died that cycle) and the blue curve shows the proportion of patients who leave the OS curve over time (representing the additional number of patients who die that cycle). What would be expected to observe, would be that the change in the EFS curve is always higher (or the same) as the change in the OS curve. This is because the OS curve only takes into account death events, while the EFS curve takes into account disease progression or relapse, second neoplasm and death events (according to the CS).

Therefore, the ERG does not see any possible logical explanation for why the proportion of deaths in in the OS curve are higher than the proportion of deaths, added to the proportion of disease, relapse and neoplasm events (captured in the EFS curve). In Figure 19, this is illustrated where the blue curve is above the red curve. This might be related with the company potentially misreporting the outcomes included in the KM curves (for example, if the EFS curve censored death events), or with the time intervals not being consistent across the OS and EFS curves. Either case is worrying, and removes the validity of the KM curves in APN311-302 provided by the company. The same issue was identified for

the OS curve in R1 and the estimated EFS curve for isotretinoin (also shown in Figure 18). Finally, the ERG is also concerned with the fact that the company did not provide numbers at risk to accompany the unadjusted KM data for APN311-302 and R1, despite the ERG's requests for these data at the clarification stage.

Figure 17. Kaplan-Meier curves for OS and PFS in APN311-302

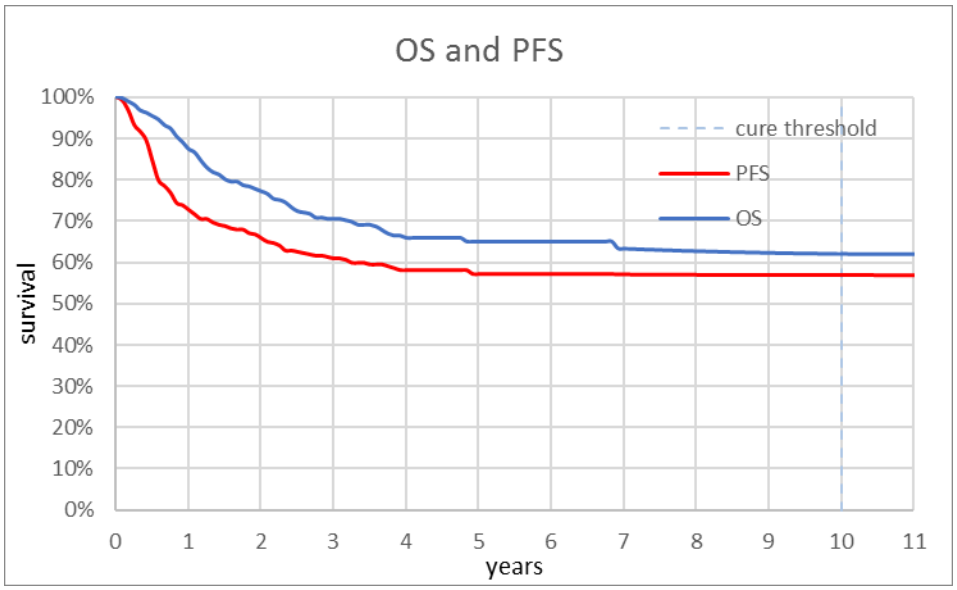


Figure 18. Failure state KM data

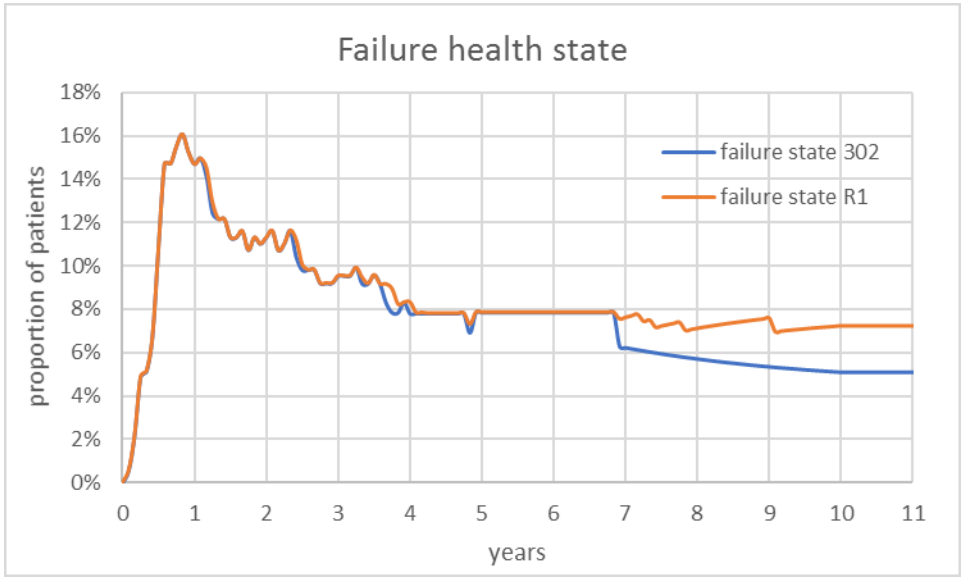
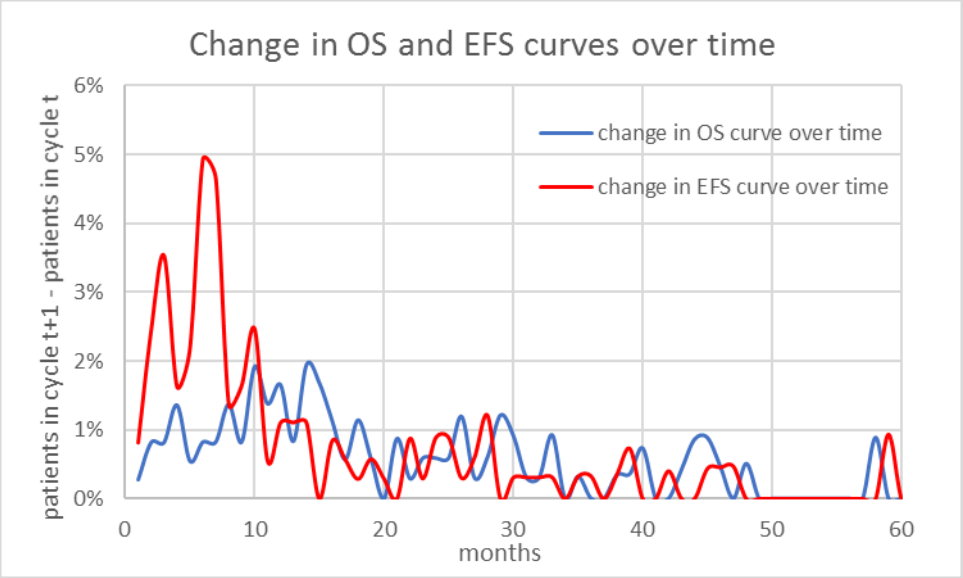


Figure 19. Change in OS and EFS KM curves over time



In conclusion, the ERG considers that the uncertainty and the lack of face validity of the KM data from APN311-302 renders the use of these data inappropriate in the analysis. Using the fitted Gompertz curves to the KM data helps adding some face validity to the OS and EFS curves for dinutuximab beta, however, the fitted and extrapolated curves are still based on the underlying KM data from APN311-302, and are therefore, flawed.

Figure 20 shows the unadjusted OS and EFS KM curves for dinutuximab beta, along with the fitted Gompertz curves, and Figure 21 shows the OS KM curves for isotretinoin taken from R1 and the estimated EFS data for R1 (using APN311-302 data), along with the fitted Gompertz curves. is the ERG notes that using fitted curves instead of the KM data reflects smoother changes in the OS and EFS curves, (Figure 22 compared to Figure 19), however, the red curve crosses the blue curve at approximately month 22, and remains that way for the rest of the short-term model. As explained previously, this reflects an impossible scenario, where the number of deaths in a specific cycle are higher than the number of deaths, summed with the number of progression and relapse events in that same cycle.

In terms of assessment of fit, the ERG can only rely of visual fit and the measure of variance provided by the company. Both seem to suggest that the Gompertz, lognormal and log-logistic models are the more suitable models to fit the KM data for APN311-302. The same is true for the Gompertz curves fitted to the OS data from R1 and the estimated EFS data for isotretinoin.

Figure 20. KM data for OS and EFS for APN311-302

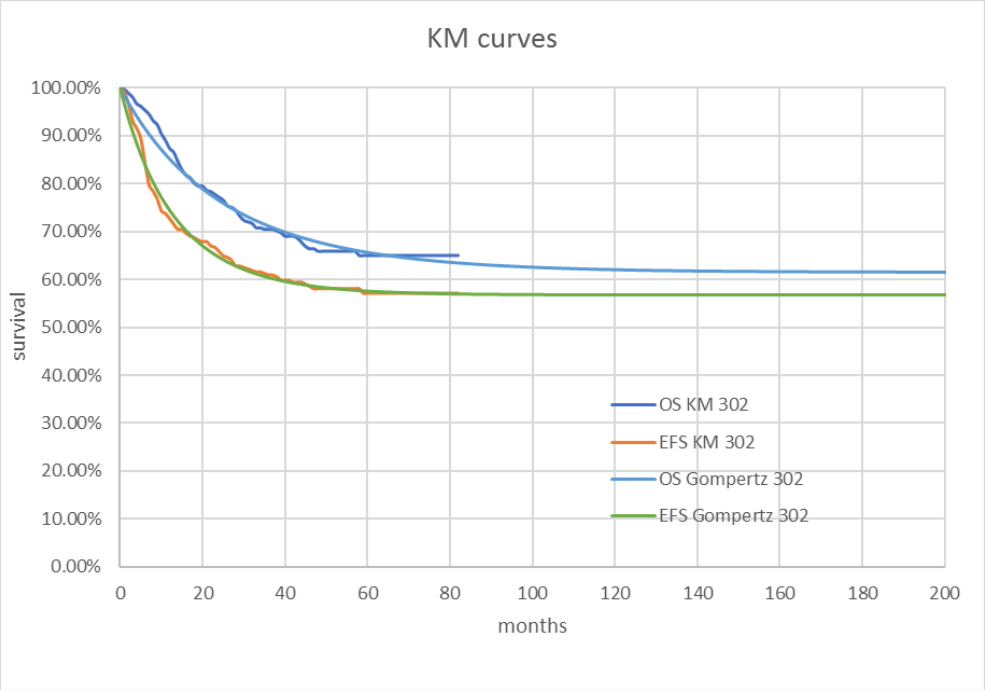


Figure 21. KM data for OS for R1 and estimated KM data for EFS for R1

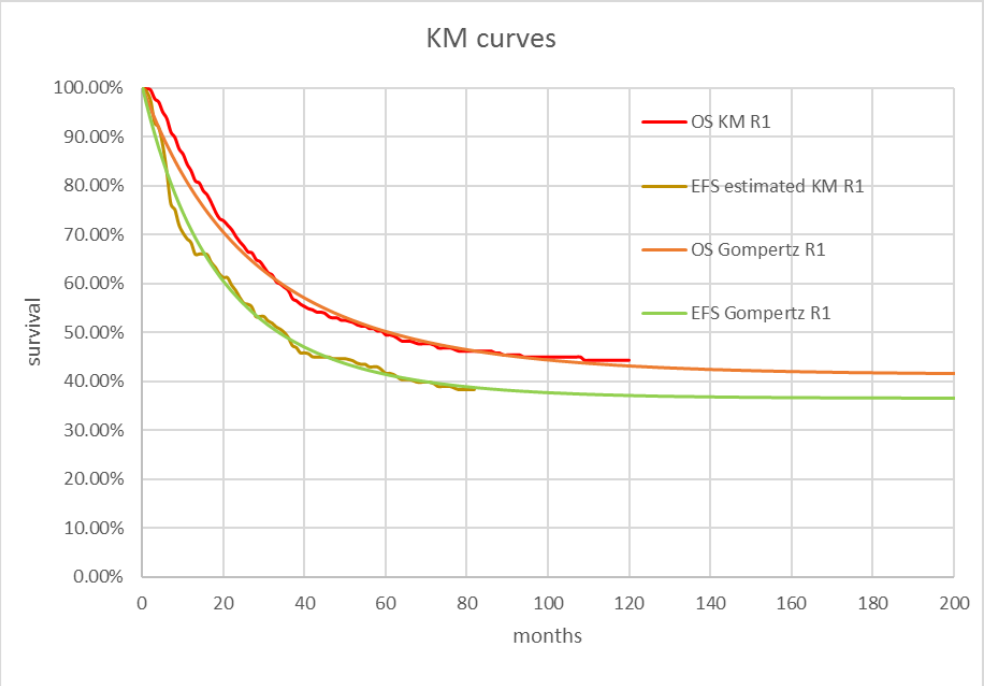
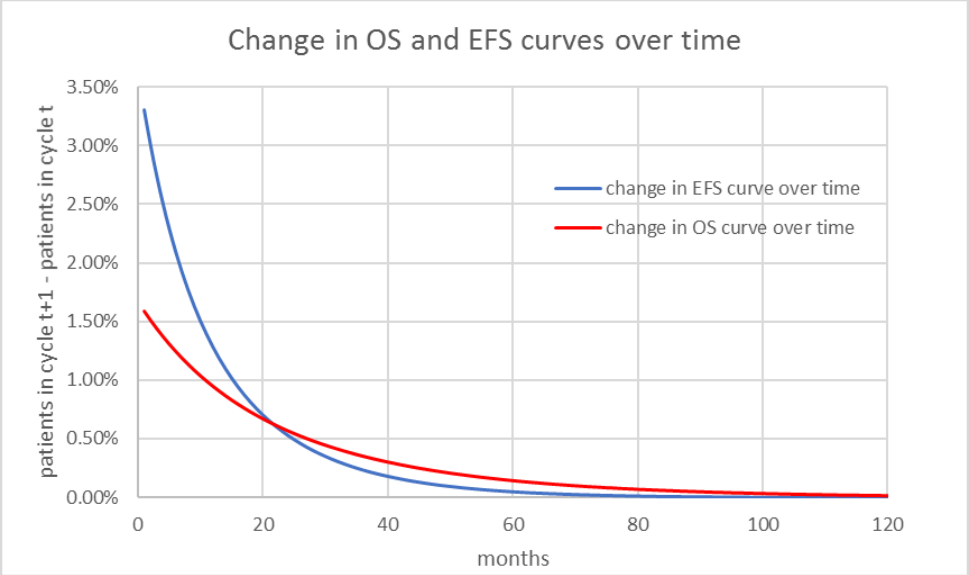


Figure 22. Change in OS and EFS fitted Gompertz curves over time



Equally concerning, is the fact that the company's model relies on the naïve (unadjusted) analysis of dinutuximab beta's effectiveness, compared with isotretinoin. As reported in NICE DSU TSD 18, in the case of a disconnected network of evidence, a naïve (unadjusted) indirect comparison will include sampling error plus systematic error due to the imbalance in both prognostic factors and effect modifiers. The guidance adds that the size of this systematic error can be reduced, and probably substantially, by appropriate use of a matching-adjusted indirect comparison (MAIC).[79]

As part of the clarification process, the ERG requested that the company carry out an MAIC. Furthermore, the ERG proposed that an MAIC of the full trial population in APN311-302 versus the group receiving isotretinoin alone in the RCT published by Yu *et al*.[29] (with the updated follow-up data from the dinutuximab alpha submission) would have constitute a better comparison than using R1 (and would have provided a source EFS data for the comparator arm). The company decided against carrying out an MAIC, and instead provided adjusted HRs. The ERG disagrees with the company's arguments for deciding against an MAIC and considers this to have been a most robust method of analysis in this case (details on the company's justification and ERG's views on the latter can be found in Section 4 of the ERG report).

As an alternative, the company provided HRs and 95% confidence intervals (CIs) for the indirect comparisons of OS in the APN311-302 study versus historical control R1, adjusting for prior treatment (BuMel vs CEM), MYCN status, and age and INSS stage at diagnosis. Hazard ratios were initially adjusted for each individual factor and, after further clarification, adjusted simultaneously for all factors. The company presented p-values for chi-squared tests for potential association between each prognostic factor and treatment effect. Cox proportional hazards regression methods have been implemented to generate multivariate adjusted estimates of effect. These are reported in Table 31 below. However, the

ERG notes that minimal details on the methods and tools used to generate the HRs were provided by the company.

Table 36. Effect estimates for OS generated for isotretinoin alone versus dinutuximab beta plus isotretinoin with or without IL-2 adjusted for various prognostic factors (adapted from clarification responses dated 25th August 2017 and 6th September 2017)

Type 3 tests in Cox model			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Factors adjusted for		**HR[a]**	**95% CI**
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

[a] [redacted].

Abbreviations: CI, confidence interval; HR, hazard ratio; IL-2, interleukin 2; [redacted].

Considering the lack of robustness and appropriateness of the naïve comparison undertaken by the company in their updated analysis, allied to the fact that the company did not carry out an MAIC, the ERG could only use the adjusted OS HR as a means of improving the robustness of the company's naïve analysis. Therefore, the ERG restructured the high-risk economic model to incorporate the use of the OS HR ([redacted]) to estimate an OS curve for isotretinoin. This approach is not without its problems (discussed later), however, it represents an improvement from the company's naïve analysis. Results of this analysis are reported in Section 6.

The ERG notes that effect estimates for the indirect comparisons are available for OS only. Event-free survival was not captured during the R1 phase of APN311-302 and so evaluation of EFS was not feasible. The ERG considers that the lack of availability of EFS estimates results in an incomplete representation of the short- and long-term clinical effectiveness of dinutuximab beta-containing regimens versus no dinutuximab beta.

5.4.5.2.2 Use of HRs in the model

From a methodological point of view, the ERG is uncertain if the use of HRs to estimate OS and EFS in the isotretinoin arm of the model is a robust approach. An investigation of the PH assumption should have been undertaken by the company to substantiate its appropriateness for the analysis. As mentioned

at the beginning of Section 5.4.5.3, the company did not provide log-cumulative hazard plots to demonstrate that it had conducted this assessment, and more concerningly, did not provide the KM data with the respective number of patients at risk, which would have allowed the ERG to carry out its own assessment. Nonetheless, given the possibility that immunotherapy works in a different way from conventional chemotherapy by potentially altering the disease pathway, it might be inappropriate to assume a constant HR between dinutuximab beta and isotretinoin. It is uncertain if the plateau typically observed for immunotherapy agents is likely to be observed for dinutuximab beta, and how this compares to isotretinoin.

Mortality

The ERG is concerned with the process underlying the estimation of the adjusted OS HR. Even though the ERG suggested that the company adjust the OS HR to take into account all the clinically relevant prognostic factors (prior treatment, MYCN status, and age and INSS stage at diagnosis), the ERG assumed that the company would undertake a stepwise approach in order to select the relevant prognostic factors. The company does not seem to have undertaken such an approach, and thus it is unclear if the final OS HR included all the relevant covariates. As shown in Table 31, INSS stage at initial diagnosis (combined stage 2 vs stage 4S, stage 3 vs stage 4S and stage 4 vs stage 4S) and prior myeloablative consolidation therapy (BuMel vs CEM) seem to have statistically significant associations with all-cause mortality. Nonetheless, MYCN status and age are not statistically significant prognostic factors to OS in APN311-302. Therefore, the ERG considers that a stepwise approach, testing for interaction between covariates, and eliminating non-statistically significant variables from the model would have been more appropriate. Nonetheless, considering the lack of a robust alternative, the ERG used the OS [redacted] in the exploratory economic analysis. The company's multivariate analysis indicates that [redacted], however the results of the analysis need to be interpreted with caution, as explained above.

The unadjusted OS KM curves from APN311-302 and R1 are presented in Figure 23. When the ERG used the adjusted OS HR to estimate OS in the isotretinoin arm of the model (by applying the HR to the unadjusted dinutuximab beta curve) obtained the KM curves reported in Figure 24. Given the lack of mature OS data and RCT data, the ERG considers that the discussion around OS data in the dinutuximab alpha STA (GID-TAG507) is relevant for this STA, given the availability of longer-term, RCT data for dinutuximab alpha.

While dinutuximab alpha and dinutuximab beta are not identical in terms of their molecular structure, both drugs could still be considered to belong to the same class of drugs and so potentially have some commonality in terms of outcomes (based on a similar mode of action). Furthermore, the STA considering dinutuximab alpha for high-risk neuroblastoma (GID-TAG507) included isotretinoin alone as the relevant comparator. The isotretinoin data (and the dinutuximab alpha data) in the dinutuximab alpha submission were taken from an RCT from Yu *et al*.[29], but with a longer follow-up period of about 12 years. Therefore, the ERG considers that results from an appropriately adjusted indirect comparison of dinutuximab beta versus isotretinoin and versus dinutuximab alpha would help to inform the decision problem. The major methods outlined in the NICE DSU TSD18 on generating comparable effect estimates with IPD for one study but only summary statistics from another are an MAIC and/or an STC. The ERG considers that, depending on what assumptions are made on the nature of the data being compared (e.g. whether proportional hazards hold), an MAIC or an STC will be the most appropriate method to use in this case.

As can be seen in Figure 25, there seems to be an abrupt change in the OS curve for dinutuximab alpha after approximately year 7. More importantly, Figure 25 provides more insight into the separation of the KM curves when the latest data cut-off point became available for dinutuximab alpha and isotretinoin. The results show that the observed data for immunotherapy and standard therapy appear to converge between 6.5 and 11 years in the updated analysis. This also has implications for the cure threshold, which is discussed in the next subsection.

Equally important is the comparison between the earlier data cut-off in the dinutuximab alpha STA and Figure 23. While this comparison is based on a visual, naïve comparison, it is not unreasonable to hypothesise that the plateau reached at year 5 in the dinutuximab beta curve would progress to reveal an accentuated increase in mortality before reaching another plateau, as seen in Figure 25. The ERG notes that at 5 years, there were still 65% of patients at risk in the dinutuximab alpha arm and 47% of patients in the isotretinoin arm, in the dataset depicted in Figure 25.

This reinforces the ERG's concerns around the lack of mature OS data, especially when it seems plausible that the relative effectiveness of dinutuximab beta might decrease over time. Even though the only source of adjusted data available to the ERG is the adjusted OS HR provided by the company, the ERG is concerned that using it in the analysis leads to an unrealistic clinical scenario, especially in terms of the duration of the effect of dinutuximab beta. Based on a visual inspection of Figure 25, long term survival is only slightly better by 7% among immunotherapy patients (approximately 59% vs 52%) at 10 years. As stated in the dinutuximab alpha ERG report (GID-TAG507), the data for long-term follow-up were too sparse to determine whether the difference in KM curves was meaningful. In the estimated adjusted curves shown in Figure 24, the difference in survival at 10 years is about 12% (50% vs 62%). Even though this difference (7% vs 10%) might not appear large, it is carried through the long-

term model as the survival benefit at 10 years is maintained over the lifetime horizon of the analysis. The long-term model is further discussed in Section 5.4.7.

Finally, the ERG caveats the comparisons here discussed between this STA and the STA for dinutuximab alpha (GID-TAG507), as they are based on naïve unadjusted, visual assessments of survival curves. Nonetheless, and given the richness of the data for dinutuximab alpha (in terms of follow-up period and RCT design), the ERG reinforces its recommendation that an appropriately adjusted indirect comparison of dinutuximab beta versus isotretinoin and versus dinutuximab alpha is carried out to help inform the decision problem, through an MAIC or an STC.

Another important issue is the fact that all patients in the Yu *et al*.[29] study, and therefore in the data used in the dinutuximab alpha submission, received CEM as consolidation therapy instead of BuMel. As discussed in the clinical section and in Section 5.4.3, BuMel is now the standard consolidation treatment in the UK, given its increased effectiveness compared with CEM. Therefore, it is a possibility that patients in the dinutuximab alpha dataset had poorer health at the moment they received dinutuximab alpha, or isotretinoin, and consequently, had worse treatment outcomes. Nonetheless, because the evidence is based on a RCT design, and both the dinutuximab alpha arm and the isotretinoin arm received CEM, the incremental effectiveness of dinutuximab alpha compared with isotretinoin is unlikely to have been affected by the consolidation therapy received. Therefore, it is not unreasonable to assume that the relative benefit between dinutuximab alpha and isotretinoin is unaffected by the consolidation therapy received in Yu *et al.*, and it can be used as a proxy for the relative effectiveness of dinutuximab beta vs isotretinoin.

Figure 23. Unadjusted OS KM curves

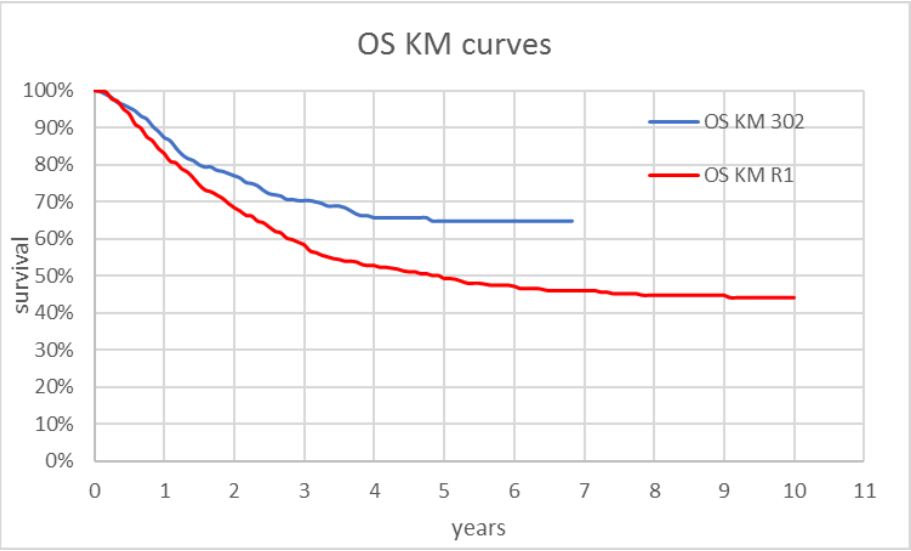


Figure 24. Unadjusted OS curve for dinutuximab beta and estimated isotretinoin OS curve with adjusted HR

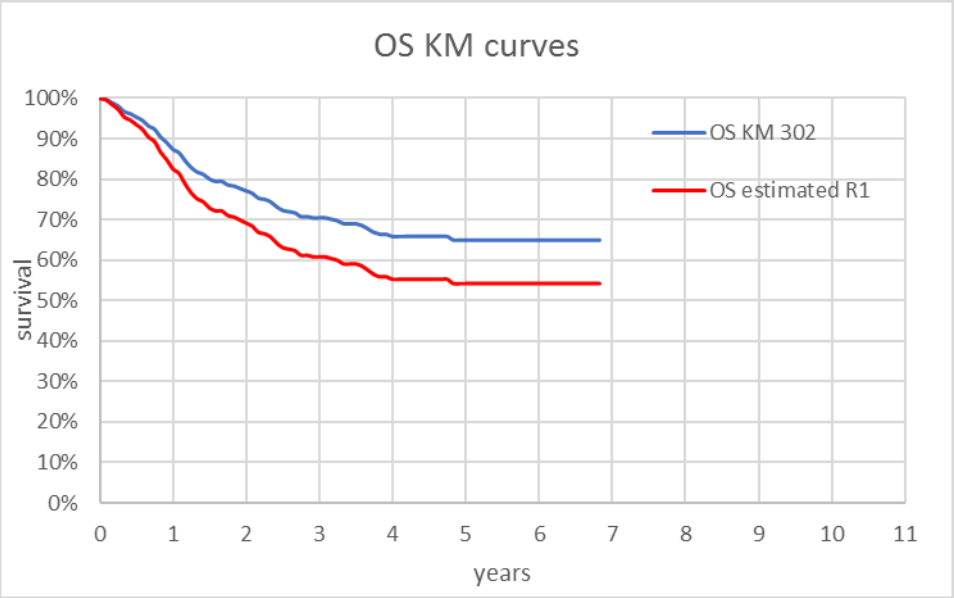
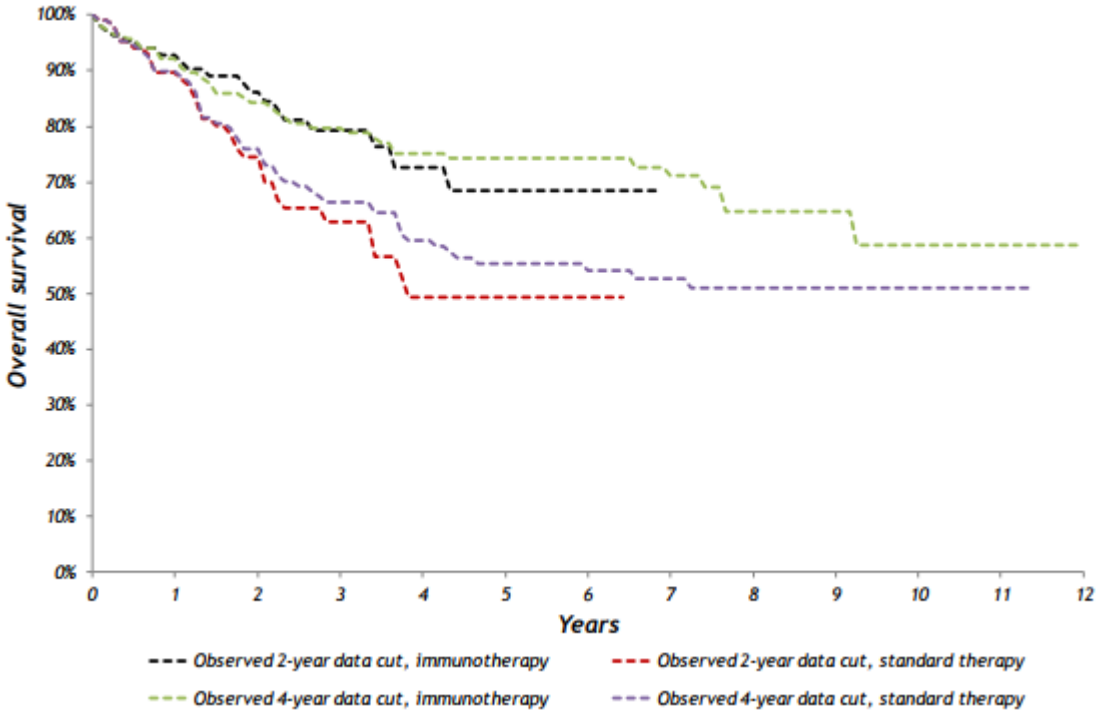


Figure 25. Observed OS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis (Figure 20 in ERG report for dinutuximab alpha [GID-TAG507], page 87)



Event-free survival

Given the lack of EFS data in R1, and the inappropriateness of using a naïve analysis, the ERG had to decide what could be an alternative way of estimating EFS in the isotretinoin arm of the model. As the ERG did not have any other available source of comparator data for EFS, it turned to the previous STA for dinutuximab alpha vs isotretinoin (GID-TAG507).

Figure 27 shows the difference in KM curves when the latest data cut-off point became available for dinutuximab alpha and isotretinoin. The results show that the observed data for immunotherapy and standard therapy appear to converge between 4.5 and 11 years in the updated analysis. Similarly to the conclusion reached for OS data, this has implications for the cure threshold. The ERG notes that the proportion of patients at risk in Figure 27 at five years were 50% in the dinutuximab alpha arm and 40% in the isotretinoin arm.

While this is based on a visual, naïve comparison, the shape of the EFS KM curves for dinutuximab beta from APN311-302 (in orange in Figure 26) seems fairly similar to the shape of the dinutuximab alpha green curve when the longer follow-up data in considered (Figure 27). This could suggest that, had a longer follow-up period been allowed in APN311-302, the EFS curve for dinutuximab beta would eventually drop to be very close to the EFS curve for isotretinoin. However, the unadjusted analysis of dinutuximab beta (Figure 26) shows a substantial separation of EFS curves at around year 7 (approximately 57% vs 38%). The ERG considers this separation to be unsubstantiated as it is based on a naïve comparison and is very likely to represent an overestimation of the effect of dinutuximab beta in terms of preventing disease progression.

This reinforces the ERG concerns around the lack of EFS data for isotretinoin in the current STA, especially when it seems plausible, based on a similar class effect to dinutuximab alpha and reinforced by the opinion of the ERG's clinical experts, that the relative effectiveness of dinutuximab beta might decrease over time. According to Figure 27, long term survival is only slightly better by 7% among immunotherapy patients (approximately 52% vs 45%) at 10 years. Despite the apparent difference between the two curves, this was not found to be statistically significant (p-value for log rank test: 0.153 as stated in the dinutuximab alpha ERG report).

Figure 26. Unadjusted EFS curve for dinutuximab beta and estimated unadjusted EFS curve for isotretinoin

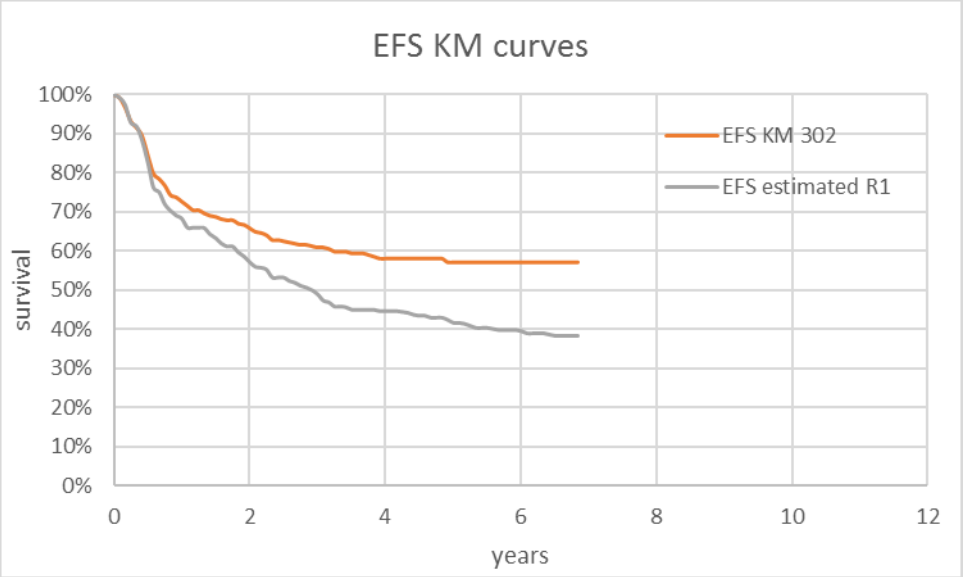
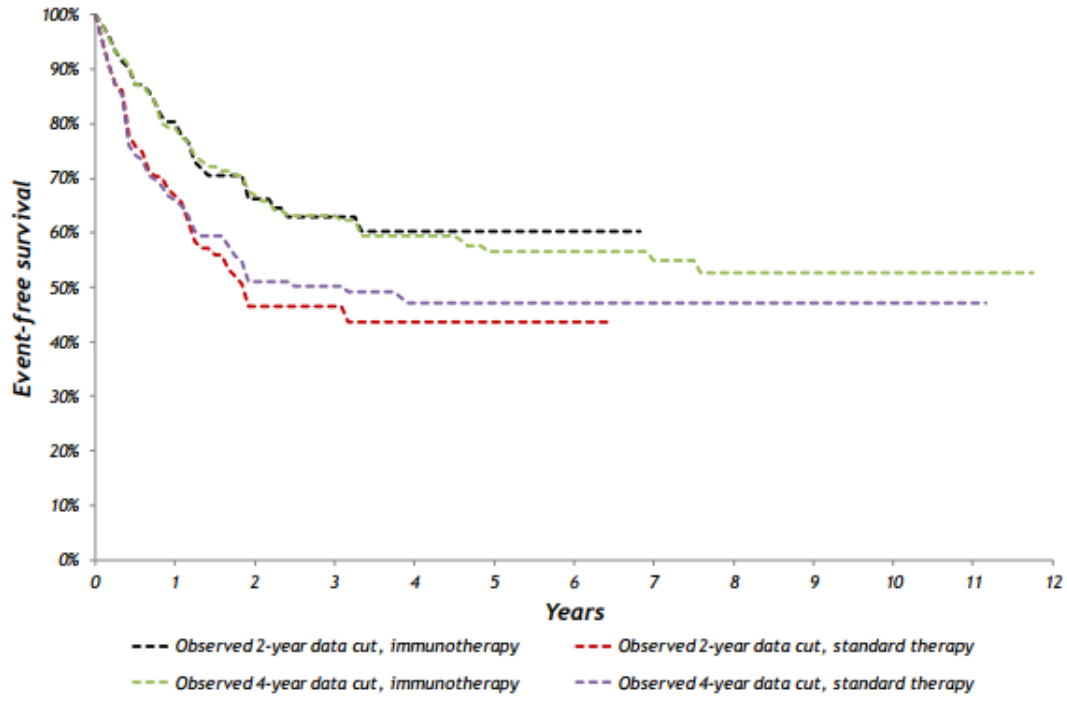


Figure 27. Observed EFS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis (Figure 19 in ERG report for dinutuximab alpha submission, page 86)



While Figure 27 suggests that from year 7.5, dinutuximab alpha is associated with a gain in EFS by 7%, compared with isotretinoin, the unadjusted analysis undertaken by the company and shown in Figure 26, suggests a gain in EFS by approximately 20% for dinutuximab beta compared with isotretinoin.

While the direct comparison between these curves is flawed to some extent, the ERG considers this to be the best available source of data available to the ERG.

Therefore, the ERG took the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission (reported in Table 37) and applied it to the adjusted OS HR estimated for dinutuximab beta. To note is that the EFS HR in Table 37 is not statistically significant, which tallies with the shape of the KM curves reported in Figure 27. The ERG estimated EFS HR for dinutuximab beta compared with isotretinoin is 1.656/1.319* [redacted] = [redacted]. Results of the analysis are reported in Section 6.

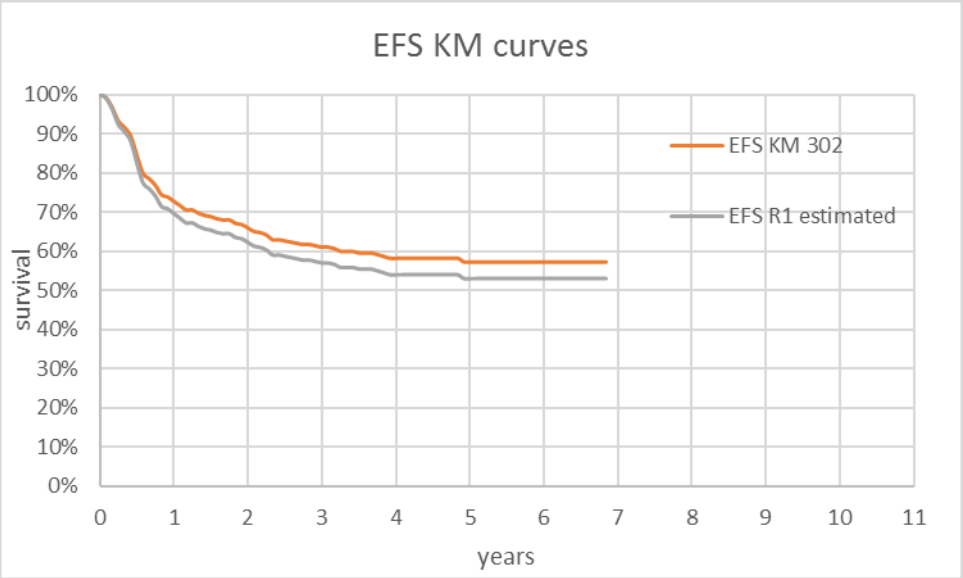
The ERG acknowledges that the underlying assumption in the ERG's approach is that there is a constant relative risk between EFS and OS for dinutuximab alpha, and furthermore, that the latter relationship is also observed for dinutuximab beta vs isotretinoin. This is a caveat to the ERG's approach as not only are these strong assumptions, but also the ERG has no evidence to corroborate them. Howeve,r the ERG notes that these were the best available data to overcome undertaking a naïve analysis of treatment effectiveness in the model.

Table 37. Hazard ratios estimated by the ERG in the dinutuximab alpha STA

Hazard ratio (95% confidence interval)	Event-free survival	Overall survival
Estimated by ERG in the dinutuximab alpha submission	1.319 (0.909, 1.923)	1.656 (1.064, 2.564)

After applying the HR of [redacted] to estimate the EFS curve for isotretinoin, the ERG produced the curves shown in Figure 28. At year 7, the EFS curves seem to be separated by approximately 4% (57% vs 53%). This separation, albeit smaller than the 7% shown in Figure 27, is likely to be a better approximation of the relative effectiveness of dinutuximab beta compared with isotretinoin than the 20%, shown in Figure 26 (resulting from non-evidence based assumptions made by the company, as R1 did not include EFS data). The ERG acknowledges that the separation of the curves shown in Figure 28, maintained throughout the analysis, is smaller than that observed in Figure 27, possibly leading to an underestimation of EFS for dinutuximab beta in the model. However, the ERG notes that the separation between the curves in Figure 27 was found to be not statistically significant, according to the ERG's analysis in the dinutuximab alpha STA (GID-TAG507). Finally, the separation of the curves is also linked to the use of a HR to estimate the EFS curve for isotretinoin. As previously mentioned, although this is unlikely to be the most appropriate methodological approach in this case, the ERG did not have an alternative source of appropriately adjusted data.

Figure 28. Unadjusted EFS curve for dinutuximab beta and estimated isotretinoin EFS curve with adjusted HR



The ERG also notes that about 50% of patients in Figure 27 were event-free at year 11, regardless of having received dinutuximab alpha or not. With regards to the other 50% of patients, who have progressed, it could be hypothesised that dinutuximab alpha delays, rather than prevents a further event. While it would appear that patients receiving isotretinoin experience the majority of their events over the first two years, a considerable number of events experienced by patients on dinutuximab alpha occur between year 2 and year 7. The ERG sought clinical expert opinion with regards to the role of dinutuximab beta in preventing or delaying events. The clinical experts advising the ERG confirmed that dinutuximab beta was expected to delay events, rather than prevent them.

5.4.5.2.3 Methodological synergies in the ERG's approach

As described in the previous sections, the ERG's proposed alternatives to overcome the several methodological shortcomings of the company's analysis are, to some degree, flawed, when considered in isolation. However, when combined and incorporated in the final analysis, the synergies resulting from the individual changes made by the ERG, contribute to an increase in the level of uncertainty in the analysis. The ERG summarises the main methodological changes undertaken in Table 38, but notes that these have been discussed in detail in the previous sections. The overall implications of these changes in the final analysis are explored in this section.

Table 38. Summary of fundamental problems in CS and ERG's ammendments

	Problem in CS	ERG's amendment	Level of mitigation	Proposed approach
	OS and EFS KM curves for dinutuximab beta, taken from APN311-302, are unreliable and unfit for purpose	Use Gompertz curves to predict OS and EFS for dinutuximab beta in the model	Problem not mitigated. While using the Gompertz curves helps increasing the face validity of the curves, the underlying data are flawed rendering the shape of curves equally unreliable (which is illustrated by the EFS curve crossing the OS curve).	The company needs to assess the reason for the problem of the inconsistency in the relationship between the OS and EFS KM curves in APN311-302
	Naïve comparison of OS data	Use of adjusted HR for OS	Problem partially mitigated. Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis. However, the HR estimation method is flawed and it is unlikely that the use of HRs is an appropriate method of analysis.	An indirect comparison of dinutuximab beta versus isotretinoin and versus dinutuximab alpha should be undertaken. The major methods outlined in the DSU applicable in this case are an MAIC and/or an STC. The ERG considers that, depending on what assumptions are made on the nature of the data being compared (e.g. whether proportional hazards hold), an MAIC or an STC will be the most appropriate method to use (please see Section 4 for more details).
	Naïve comparison of EFS data + lack of EFS data for isotretinoin in historical control R1	Taking the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission and applying it to the adjusted OS HR estimated for dinutuximab beta.	Problem partially mitigated. Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis, through the adjusted OS HR. However, the EFS HR carries the same flaws as the OS HR. Furthermore, it relies on the naïve comparison of the relative treatment effectiveness of dinutuximab alpha vs isotretinoin and isotretinoin beta vs isotretinoin.	
Robustness of the final analysis	Economic analysis unfit for purpose. Resulting ICERs are meaningless	Economic analysis unfit for purpose	Problem partially mitigated	As above

When the ERG replaced the OS and EFS KM dinutuximab beta curves by the Gompertz curves in the model, it became apparent that the intrinsic problematic relationship between the OS and the EFS KM curves for dinutuximab beta (Figure 29) were carried to the isotretinoin OS and EFS curves (Figure 30), as HRs were applied to the OS and EFS dinutuximab beta curves to estimate isotretinoin curves.

Using the extrapolated Gompertz curves in the short-term model for OS and EFS, is an attempt to minimise the structural issues found in the KM data from APN311-302. However, given that the underlying KM data is flawed (and the Gompertz curves seems to be a considerable good fit to the shape of the KM curves), the shape of the Gompertz curves carries the same problems as the KM curves. Even though the ERG cannot anticipate the direction or the extent of the error in the shape of the curves, it is known that the OS and EFS curves should have a wider gap, as there is either an underestimation

of events being captured in the EFS curve, or an overestimation of deaths captured in the OS curve. Therefore, the ERG cannot anticipate if the "real" OS curve should sit lower than the one shown in Figure 29, or if the EFS curve should sit higher (or if both curves would move).

When applying the OS and EFS HRs to the dinutuximab beta curves, the ERG obtained the curves shown in Figure 30. The fact that the relative positioning of the dinutuximab beta curves was maintained, allied to the fact that the OS HR and the EFS HR used in the ERG's analysis come from different data sources (thus different populations), leads to the fact that the final relationship between the isotretinoin OS and EFS curves has different and cumulative lawyers of embedded uncertainty. This is illustrated by the EFS curve crossing the OS curve at approximately 70 months. The ERG had to subsequently cap the EFS curve by the OS curve in the isotretinoin arm of the model.

Furthermore, given the possibility that immunotherapy might be delaying rather than preventing events, or simply that immunotherapy works in a different way from isotretinoin, therefore altering the disease pathway, it might be inappropriate to assume a constant HR between immunotherapy and conventional chemotherapy. It is uncertain if the plateau typically observed for immunotherapy agents is likely to be observed for dinutuximab beta, and how this compares to isotretinoin.

Consequently, the ERG considers that while some of the amendments made to the model provided step changes in the right direction, when combined in the final analysis these produce inconsistency and introduce a paramount level of uncertainty in the analysis. In conclusion, the ERG does not consider that the changes made to the company's model are robust enough to produce an economic model fit for robust decision making. Nonetheless, and for inclusiveness, the ERG provides the results of implementing the changes listed in Table 38 in the final ICER in Section 6. However, the ERG emphasises that these results are provided purely for illustrative purposes.

Figure 29. Gomperz OS and EFS curves for dinutuximab beta

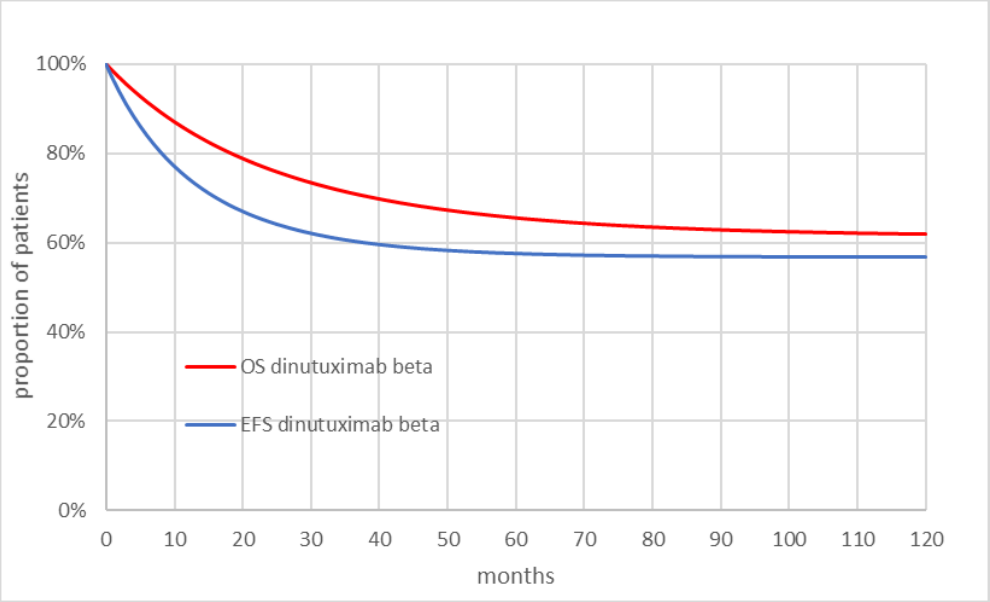
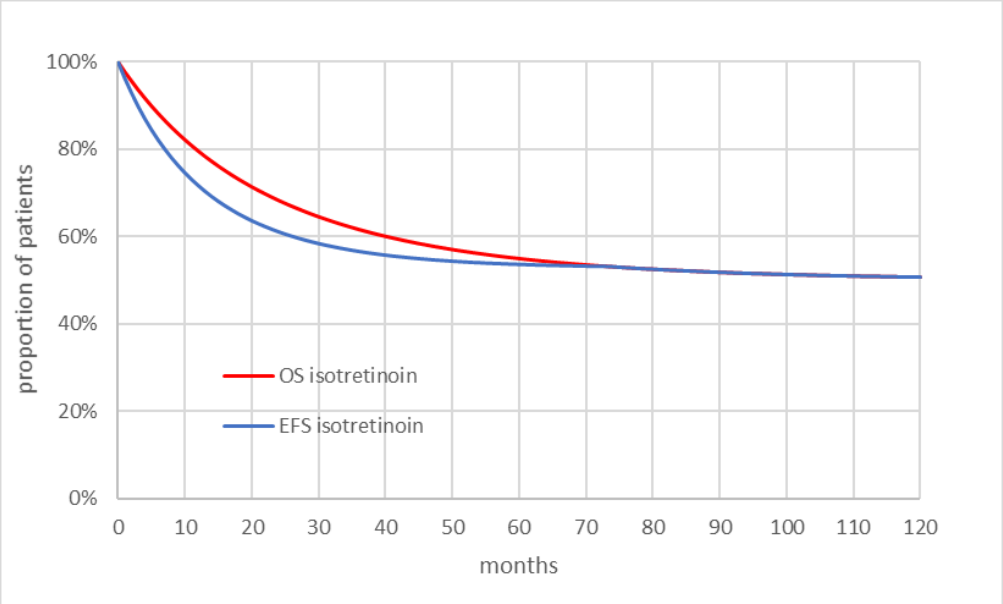


Figure 30. Gomperz OS and EFS curves for isotretinoin



5.4.5.2.4 Cure threshold

As mentioned in Section 5.4.5.1, the company provided two cure threshold scenarios, one assuming that cure would be achieved at five years without an event, and the other assuming that patients without events for 10 years could be considered as potentially cured (as per the ERG request during clarification stage).

The draft final appraisal determination (FAD) document produced by NICE in sequence of the dinutuximab alpha submission reports that, "*The committee heard from the patient experts that it was*

generally accepted that people who had received isotretinoin as standard of care and survived neuroblastoma for 5 years after treatment could expect to live event free. However, the committee heard from the clinical experts that although a relapse after year 5 was rare, in the era of immunotherapy it could occur. The committee heard from clinicians that relapse beyond 10 years is extremely unlikely. It agreed that the evidence showed that there were further events in ANBL0032 after 5 years, especially in the immunotherapy arm. It also agreed that it was implausible that there would be no events after 5 years. The committee noted that the company provided revised analyses using the 10-year cure threshold. It concluded that a cure threshold of 10 years, as used by the company in its revised base-case analyses, was more appropriate than the 5 years used in the company's original base case," it added that, "*The committee heard from the clinical experts that although relapse after 10 years of event-free survival was not impossible it was very unlikely, meaning that patients who remain event free at 10 years are likely to be so for the rest of their lives".*

Given the EFS and OS data reported in Section 5.4.2.1, (Figure 25 and Figure 27), the ERG agrees that five years is unlikely to be the clinical cure threshold for the immunotherapy curves (i.e. dinutuximab alpha and arguably dinutuximab beta), especially for OS. Both figures show that the number of relapses and death events after five years were considerable. Therefore, the ERG considers the 10-year cure threshold the most suitable option for the analysis.

5.4.6 Adverse events

The adverse events (AEs) that have been selected to be included in the model are based on common AE reactions associated with dinutuximab beta listed in the Summary of Product Characteristics (SmPC) document provided in Appendix C of the CS[43]. In the company's clarification response, it was confirmed that all AEs listed in the CS are treatment-emergent. Table 39 presents the AEs used in the high-risk model. Data on the proportions of patients experiencing events are based on the entire safety database of 514 patients with high-risk and relapsed/refractory neuroblastoma, who received dinutuximab beta as a continuous infusion (98 patients) or as repeated daily infusions (416 patients) and patients who were treated in combination with IL-2 (307 patients). The company states that data from the entire safety database were used due to different methods of data collection across studies.

For the isotretinoin arm of the model, data were obtained from the study by Yu *et.al*. 2010[29]. In this study, grade 3 or 4 treatment related adverse events for 108 high-risk neuroblastoma patients on isotretinoin were measured.

Table 39. Adverse events included in the high-risk model (based on Table 56 in the CS)

Adverse event type	First-line Population	Isotretinoin[29]
Pain (including abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia)	77%	6%
Hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release syndrome, serious anaphylactic reactions)	63%	2%
Severe Capillary Leak Syndrome	10%	7%
Eye problems	13%	1%
Peripheral neuropathy	9%	6%
Pyrexia, Infection	88%	22%
Vomiting, Diarrhoea	57%	3%

The impact of AEs on patients' quality of life, and the costs of managing adverse events are described in Section 5.4.8 and Section 5.4.9.

5.4.6.1 ERG critique

The safety data from the SmPC include a mixture of patients who have received dinutuximab beta as a continuous infusion and as daily infusions. Given that the model population received treatment with a continuous infusion, and that it is unclear if the administration method (i.e. continuous infusion vs daily infusion) bears any effect on dinutuximab beta's safety profile, it would have been appropriate to conduct a scenario analysis using the available data on the 98 patients receiving a continuous infusion (obtained from studies APN311-202 and APN311-303 in the SmPC) to estimate the risk of AEs in the model. is the ERG notes that patients in APN311-302 only received daily infusions of dinutuximab beta.

During the clarification stage, the ERG requested that the company perform a scenario analysis for the 98 patients (from study APN311-202 and APN311-303) who received dinutuximab beta as a continuous infusion. However, in their clarification response, the company performed the scenario using only the AE data from APN311-202 (Table 40), with no justification provided. As described in the clinical study report (CSR) for APN311-202, these data are based on more than 10% of patients experiencing the specific AE. However, for severe capillary leak syndrome, the ERG assumes that the company has used the values from the CSR for grade 3+ events, as only 7% of patients experienced the event. Furthermore, the ERG could not confirm the estimate reported by the company for hypersensitivity events. The ERG obtained AE estimates from the CSR for APN311-303 that are based on more than 10% of patients experiencing the AE (grade 3+ for severe capillary leak syndrome) and pooled these with the estimates from APN311-202 and these are presented in Table 40. The ERG performed a scenario analysis using the pooled AE estimates and found that it had a negligible impact on the final ICER.

It should be noted that the majority of patients included in the SmPC safety dataset received IL-2 as part of their treatment (as all patients in APN311-202 and APN311-303 received IL-2). According to the SmPC, when dinutuximab beta is combined with IL-2, the risks of experiencing AEs increases, particular for pyrexia, capillary leak syndrome, pain, hypotension and peripheral neuropathy[43]. Therefore, patients who do not receive IL-2 would have a lower risk of experiencing AEs. The ERG considers that using estimates of AEs derived from treatment with IL-2 is potentially leading to an overestimation of AEs in high-risk patients, given that only 51% of patients in APN311-302 received concomitant IL-2. Adverse events collected in APN311-302 were restricted to serious AEs.

Finally, the ERG notes that it is uncommon for the reporting of AEs to be based on more than 10% of patients experiencing an event. This estimate is usually based on a smaller proportion of patients experiencing the specific event (usually around 2% or 5%). It is therefore likely that the proportion of AEs used in the economic analysis are underestimating some less frequent, but perhaps more serious, AEs.

Table 40. Proportion of adverse events

Adverse event	APN311-202 (events experienced by ≥10% of patients)	APN311-303 (events experienced by ≥10% of patients)	Pooled data (APN311-202 + APN311-303)**	SmPC
Pain (including abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia)	63.6%	74.1%	69%	77%
Hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release syndrome, serious anaphylactic reactions)	50%	n/a	n/a	63%
Severe Capillary Leak Syndrome	6.8%	13%	10%	10%
Eye problems	25%*	40.7%	34%	13%
Peripheral neuropathy	2.3%	1.9%	2%	9%
Pyrexia, Infection	95.5%	98.1%	97%	88%
Vomiting, Diarrhoea	56.8%	74.1%	66%	57%

5.4.7 Mortality and disease progression in the long-term model

This section of the ERG report focuses on the economic model after the cure threshold point (referred to as long-term model). The company made the long-term model flexible enough so that it could start either five or 10 years after the first cycle of the short-term model. However, the company used 10 years as the cure threshold in their base case analysis.

When patients reach the cure threshold in the model, the proportion of patients in the EFS and the FS state can only move to the death state, as patients cannot progress or enter remission in the model

anymore. From this point onwards in the analysis, patients in the EFS and in FS states die at different rates, to translate the fact that some patients are considered cured while others are relapsed patients.

Cured patients do not follow the same mortality rates as those observed in the UK general population. Instead, the company assumes that cured patients (i.e. patients in the EFS state at the cure threshold) will experience a higher standardised annual mortality increased by a factor of 5.6 (95% CI 4.4 to 6.9), compared with the UK general population, based on a report from the Childhood Cancer Survival Study (Laverdiere *et al.* 2009).[20] Therefore, the company applied a 5.6 factor to the age and gender matched mortality in the UK general population. The ERG identified an error in the formulae used by the company, where the 5.6 factor was being applied to female mortality instead of the weighted male and female mortality in the UK general population. The ERG corrected this and presents the results in Section 6.

For patients in the FS state at the cure threshold, the company assumed their mortality to be 90% higher than the mortality assumed for EFS patients (whose mortality is assumed 5.6 times that of the general population matched for age and gender). Resource use and quality of life in the long-term model are explored in Section 5.4.9 and Section 5.4.8 of this report, respectively.

5.4.7.1 ERG critique

As discussed in Section 5.4.5.2.2, the ERG agrees with a cure threshold of 10 years. Furthermore, and as discussed in Section 5.4.5, the cure threshold in the model is extremely important. This is mainly due to the fact that the incremental benefit of dinutuximab beta in terms of OS and EFS at the cure threshold will be maintained throughout the long-term economic analysis. Figure 31 and Figure 32 report the extrapolated benefit in terms of OS and EFS, respectively, over the long-term model. Both figures also compare the ERG's estimated isotretinoin OS and EFS curves and the company's estimated isotretinoin curves. As discussed in Section 5.4.5, the ERG's estimated curves predict a smaller benefit at the cure threshold and thus for the remainder of the economic analysis, compared with the unadjusted OS and EFS curves used by the company. Nonetheless, the ERG is concerned that the OS and EFS benefit at the cure threshold is overestimated with the use of a constant HR in the short-term model. This overestimation would be carried throughout the remainder of the model.

is the EG notes that Figure 31 and Figure 32 portray the ERG's preferred assumption of using fitted survival curves for OS and EFS with a Gompertz model, instead of using KM data for the short-term model, as explained in Section 5.4.5.2.

Figure 31. Long-term OS in the economic analysis

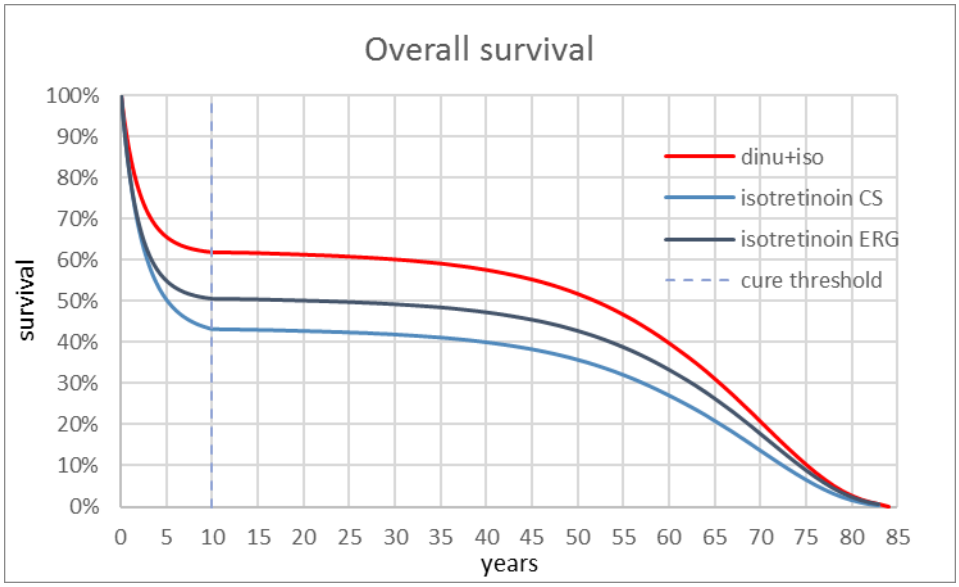
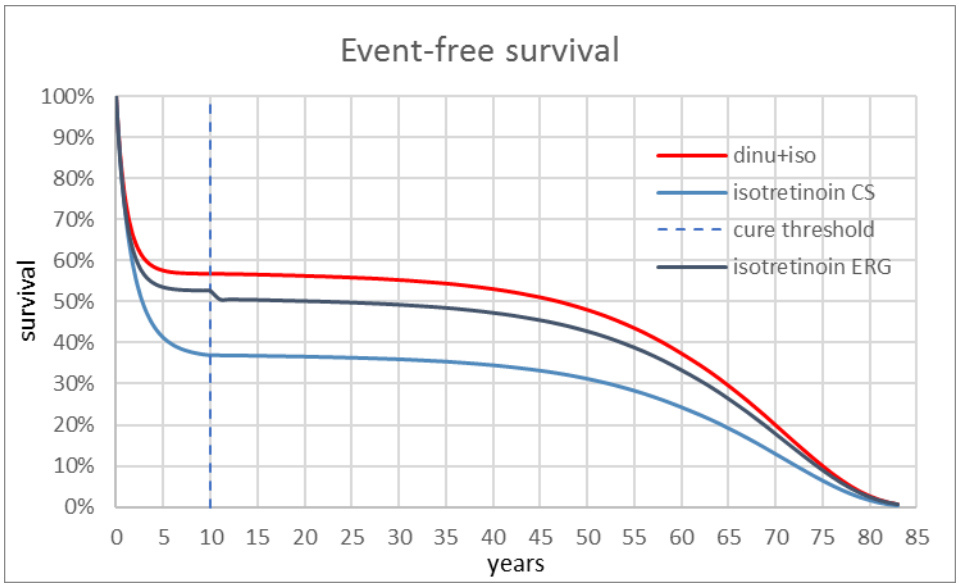


Figure 32. Long-term EFS in the economic analysis



The clinical experts advising the ERG agreed that cured neuroblastoma patients will experience an increase in mortality compared with the general population. They also agreed that relapsed or refractory patients (essentially patients in the FS state) will have a higher mortality, which will increase with every relapse event. Even though the clinical experts were broadly satisfied with the 5.6 factor applied for mortality in the EFS state and the 90% increase in mortality for FS patients, it was mentioned that it is difficult to estimate this increase in mortality, especially for patients in the FS state, as the increase in mortality will be directly related to when/how frequently patients relapse. is the ERG notes that the ACM for the dinutuximab alpha submission (GID-TAG507) concluded that, "*...using an annual standardised mortality ratio of 5.6 for the stable health state as applied by the ERG was a reasonable approach.*"

5.4.8 Health-related quality of life

5.4.8.1 Systematic literature review for HRQoL studies

The company carried out a systematic literature review to identify relevant health-related quality of life (HRQoL) and quality of life studies in patients with high-risk, relapsed, or refractory neuroblastoma. The company searched the following electronic databases: Medline, Embase, the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects), and the Education Resources Information Centre database.

The company reported conducting two searches at different time points. The first search conducted on the 4 May 2017 was restricted to studies reporting specific treatments. This initial search did not identify any relevant studies for any of the populations, therefore the search was amended to exclude restrictions on treatment and run again on the 21 May 2017. The inclusion and exclusion criteria applied in the searches are presented in Table 1, Appendix H of the CS. The second search identified three studies[86,90,91] potentially useful for the HRQoL analysis. The company complemented the database searches with *post-hoc* manual searches on Google and identified five additional studies[87,92-95] and therefore eight studies were included in total.

The systematic literature review conducted by the company included different studies (with the exception of Barr *et al.* 1999[87]) to those identified for inclusion in the previous STA for dinutuximab (GID-TAG507)[45]. However, since the company did not provide a list of excluded papers after full text appraisal, it is unclear whether the studies identified in GID-TAG507 were found by the company's search and excluded or not identified at all. Furthermore, as discussed in Section 5.3, the company's exclusion criteria imposed an age restriction of 12 months in the population searched.

Of the eight included studies, six reported quality of life of survivors of neuroblastoma or other central nervous system (CNS) cancers,[86,87,91,92,94,95] while the remaining two studies reported the quality of life of patients with neuroblastoma. Only two studies (Portwine *et al.* and Barr *et al.*)[86,87] reported health state utility values, which were estimated based on quality of life data collected using the HUI2 and HUI3 instruments. The study by Portwine *et al*. 2016 [86] is a population based survey of HRQoL outcomes in 99 survivors of high-risk neuroblastoma after myeloablative chemotherapy followed by autologous haematopoietic stem cell transplant. The study by Barr *et al.* 1999[87] estimated HRQoL in survivors of CNS tumours and did not include patients with neuroblastoma, yet was considered to be of relevance since it considered survivors of paediatric cancers. Studies included in the review are summarised in Table 41.

Table 41. HRQoL studies identified by the company (CS, pg 123-128, Table 57)

Study	Population	Primary outcome measures	Results	Appropriateness of the study for the cost effectiveness analysis
Jubab *et al.,* 2016[93]	Patients diagnosed with NB, between 2 months and 11 years of age	Wisconsin Quality of Life Questionnaire (WQOLQ)	Mean QoL score was 1.68 ±0.57 (range -0.27 to 3.0) for neuroblastoma and 1.89 ±0.49 (range -0.24 to 2.73) for comparison group, p=0.863. QoL scores and SD by managements approach (mean(SD)) --> Chemotherapy: 1.69(0.51); Radiation: 1.59(0.45); Surgery: 1.62(0.57); Combination: 1.53(0.63) Patients who attended school had higher QOL scores (mean(SD)) than lower-educated patients (2.03(0.33) vs 1.45(0.54), p<0.001). QoL scores and SD by tumour stage (Mean(SD)) --> Stage 1: 1.54(1.01); Stage 2: 1.43 (0.09); Stage 3: 1.73 (0.477); Stage 4: 1.68; 0.54; p=0.90.	QoL data not deemed appropriate for the CEA (not possible to accurately convert to health utility values). WQOLQ not a QoL measure appropriate for childhood cancer
Barr *et al.,* (1999)[87]	Children who have completed therapy for tumours of the CNS and who were attending the neuro-oncology follow-up clinic in the children's Hospital at the Chedoke-McMaster (Hamilton, Ontario, Canada) during the interval from February 1993 to February 1995. Mean time from diagnosis to the time of the study was 3.3 years, and from completion of therapy to the time of the study 2.6 years. The tumour types were	Impact of disease status on global health-related quality of life (utility) expressed as HUI2 and HUI3 scores. ・Impact of site of radiotherapy on global health-related quality of life (utility) expressed as HUI2 and HUI3 scores.	HUI2 by health state (n, mean, SD, median, minimum, maximum) ・Non-evident (28, 0.89, 0.13, 0.93, 0.46, 1.00) ・Residual (10, 0.81, 0.19, 0.89, 0.38, 0.95) ・Recurrent (3, 0.56, 0.41, 0.65, 0.12, 0.92) Children with demonstrable disease (residual or recurrent) had a significantly poorer	The population does NOT include neuroblastoma patients but it has several similarities with the population considered in the CEA: ・Paediatric patients had suffered from cancer ・Patients completed therapy ・Similar health states were studied (residual disease and recurrent disease) Given the lack of data specific

	astrocytoma/glioma (n= 24), primitive neuro-ectodermal tumour/medulloblastoma (n =7), ependymoma (n=3) and others (n= 10)		HRQoL than those whose disease appeared to be in complete remission (P= 0.027 for HUI2) HUI2 utility score for patients with non-evident disease was significantly different (P <0.001) than that for patients with recurrent disease HUI3 by health state (n, mean, SD, median, minimum, maximum) ・Non-evident (28, 0.78, 0.26, 0.82, -0.13, 1.00) ・Residual (10, 0.56, 0.26, 0.66, 0.08, 0.89) ・Recurrent (3, 0.32, 0.57, 0.35, -0.27, 0.88)	to the NB population, the findings from this study were deemed appropriate to be used.
Cai, 2012[90]	Chinese patients, aged between 3 years and 22 years at the time of inclusion into the study with histologically confirmed neuroblastoma, which was refractory to standard treatments.	・Tumour response ・Toxicities ・QoL as measured by Karnofsky or Lansky performance status and face rating pain scale	Only Karnofsky or Lansky PS ≥50 were eligible for this study, almost all the patients got obvious improvement of PS after one course of treatment. The Karnofsky or Lansky PS (% of patients before therapy (BT) and after therapy (AT)) reported were: -Score 50: 28.6% BT, 0% AT -Score 60-70: 42.8% BT, 57.1% AT -Score 80-100: 28.6% BT, 42.8% AT Alleviation of bone pain was the main cause of improvement of quality of life observed. The face rating pain scale (% of patients before therapy (BT) and after therapy (AT)) reported were: - Score 0-1: 42.8% BT, 71.4% AT	QoL data not deemed appropriate for the CEA (not possible to accurately convert to health utility values).

			- Score 2-5: 28.6% BT, 28.6% AT - Score 6-10: 28.6% BT, 0% AT	
Hudson *et al.*, 2003[92]	long-term survivors of childhood cancer who were diagnosed between 1970 and 1986. A randomly selected cohort of the survivors, siblings served as a comparison group	・Six health status domains were assessed: general health', mental health 'functional status, activity limitations, cancer-related pain, and cancer related anxiety/fears. The first 4 domains were assessed in the control group. ・Factors associated with adverse health status in survivors were identified	Compared with siblings, survivors (total population) were significantly more likely to report: -Adverse general health (odds ratio [OR), 2.5; 95% CI, 2.1-3.0; P<.001) -Mental health (OR, 1.8; 95% CI, 1.6-2.1; P<.001) -Activity limitations (OR, 2.7; 95% CI, 2.3-3.3; P<.001) -Functional impairment (OR, 5.2; 95% CI, 4.1-6.6; P<.001) 40% of survivors (total population) reported at least 1 adversely affected health status domain. Compared with siblings, NB survivors were more likely to report: -Adverse general health (odds ratio [OR), 2.1; 95% CI, 1.3-3.2) -Mental health (OR, 1.4; 95% CI, 1.0-2.0) -Activity limitations (OR, 2.7; 95% CI, 1.9-4.0) -Functional impairment (OR, 3.8; 95% CI, 2.3-6.2) Percentage of NB survivors with adverse health status general health: 8.6%, mental health: 15.6%, functional impairment: 8.3%, activity limitations: 11.7%, pain: 7.6%, anxiety: 10.7%, any domain: 41.2%.	QoL data not deemed appropriate for the CEA (not possible to accurately convert to health utility values).

Mort *et al.*, 2011[94]	Young survivors of childhood cancer aged 11-18 years, who had been treated for extracranial malignancies ≤ 16 years of age, had survived ≥ 4 years after the diagnosis, and were currently free of cancer.	Self-assessment of HRQoL was measured using age appropriate and pre-validated standard measures: ・16D was used for 12- to 18-year-old survivors and their controls ・17D was used only for 11-year-old survivors and their controls. ・Pediatric QoL Inventory (PedsQL™)	Survivors estimated with PedsQL instrument their physical health (mean 88.43) as significantly higher (P<0.001) than their psychosocial health (mean 83.74). They gave total 16D scores and all PedsQL scores higher than their controls, but the only statistically significantly (P<0.05) higher score was the PedsQL physical health mean score: - PedsQL total score in survivors (n=203), mean 86.08, SD 11.23. - PedsQLtotal score in controls (n=266), mean 85.17, SD 9.77.	QoL data not deemed appropiate for the CEA (not possible to acurately convert to health utility values).
Nathan *et al.*, 2007[95]	Survivors of Wilms tumour and NB who were participants of the Childhood Cancer Survivor Study (CCSS) aged 18y. or older at the time of the CCSS follow-up questionnaire. They were diagnosed before the age of 21 y. between 1970 and 1986 and were alive at least 5y. from their original diagnosis.	HRQoL assessed with the 36-Item Short Form Health Survey (SF-36).	Adjusted mean scores on SF-36 subscales for NB survivors (Mean, SE): ・Physical function: 52.02, 1.16 ・Role physical: 52.09, 1.90 ・Bodily pain: 52.84, 1.56 ・General health: 48.99, 1.76 ・Vitality: 39.97, 2.03 ・Social function: 46.30, 1.62 ・Role emotional: 42.41 2.68 ・Mental health: 50.08, 1.69 NB survivors who scored poor HRQoL (lower than 40, greater than one standard deviation below the mean): ・Physical function: 30 (7.4%) ・Role physical: 53 (13.0%) ・Bodily pain: 45 (11.0%) ・General health: 68 (16.7%)	QoL data not deemed appropriate for the CEA (not possible to accurately convert to health utility values).

			・Vitality: 159 (39.1%) ・Social function: 87 (21.4%) ・Role emotional: 98 (24.1%) ・Mental health: 35 (8.6%)	
Portwine *et al.*, 2016[86]	Survivors of high-risk NBL, diagnosed between 1991 and 2010 and treated with HSCT.	HUI1, HUI2 and HUI3	On a scale of 0 (being dead) to 1.0 (perfect health), mean HRQoL utility scores were 0.89 (SD = 0.11) in HUI2 and 0.84 (SD = 0.18) in HUI3. Mean HRQoL in survivors of high-risk NBL was significantly less than that of the general population (HUI3 mean = 0.96; P < 0.001). Parents reported morbidity in sensation (52.5%), pain (30.3%), cognition (28.0%), and emotion (24.2%) in HUI2 and in hearing (38.4%), pain (30.3%), cognition (27.3%), and speech (23.2%) in HUI3. HRQoL was not significantly different compared to NBL survivors treated without HSCT, but was less than in non-transplanted survivors of acute lymphoblastic leukaemia and Wilms tumour, and children in the general population, yet higher than in survivors of brain tumours.	The study is considered appropriate for the CEA due to: ・The population is the most consistent with one of the DB target population (high-risk NB patients who underwent ASCT) ・Reports Health utility values ・Provides a comparison of HRQoL between NB population and the general population
Wengenroth *et al.*, 2015[91]	Survivors of childhood cancer. 8% of participants were survivors of NB	Self- and parent-reported HRQoL through the KIDSCREEN-27 instrument and standardized norms in the five dimensions of Physical well-being, Psychological well-being, Autonomy, Peers, and School environment	Self-reported physical well-being was comparable to norms. Other HRQoL dimensions were higher than norms, with the highest mean = 52.2 (p<0.001) for school environment. Parent-reported HRQoL in survivors was comparable to population norms; physical	QoL data not deemed appropiate for the CEA (not possible to acurately convert to health utility values).

			well-being was lower (mean = 47.1, p<0.001), and school environment was higher (mean = 51.1, p = 0.035).	
Abbreviations in table: AT, after therapy; BT, before therapy; CCSS, childhood cancer survivor study; CEA, cost-effectiveness analysis ; CI, confidence interval; HRQoL, health-related quality of life;HSCT, Hematopioetic Stem Cell Transplant; HUI2, Health Utilities Index Mark 2; HUI3, Health Utilities Index Mark 3; NB/NBL, neuroblastoma; NR, not reported; OR, odds ratio; PedsQL, Pediatric Quality of Life Inventory; SD, standard deviation; SE, standard error; SF-36, 36-Item Short Form Health Survey; WQOLQ, Wisconsin Quality of Life Questionnaire.				

5.4.8.2 Health-related quality of life data used in cost-effectiveness analysis

As mentioned throughout this report, the CS has not been appropriately described and lacks transparency around the methods used for analysis of the data. As such, the description of health state utility values (HSUVs) in the high-risk model is based on the ERG's interpretation of how utility data have been estimated and implemented in the model, rather than on the description provided in the CS.

The HSUVs used in the model were estimated by applying utility decrements to age-specific UK EQ-5D general population norms. Given that UK EQ-5D norms data are only available for ages between 18-75+, the company used a logistic regression (see equation 1) to estimate interpolated utility values for age 0 onwards.

$$U(age) = \frac{1}{1+e^{(\alpha * age+\beta)}} \text{ (equation 1)}$$

Where, α = coefficient for age; β = intercept

To estimate the utility value associated with the EFS and the failure states for each model cycle (and therefore age) in the economic model, the company applied a decrement to the UK EQ-5D general population values to reflect the fact that patients in the model have neuroblastoma. The percentage decrement associated with the EFS state for the high-risk model was calculated using data from a study by Portwine *et al*. 2016[86], identified in the systematic literature review of HRQoL. The study measured HRQoL using self-report versions of the Health Utility Index (HUI) 2 and the HUI3 with a 4-week recall period. The HUI belongs to a family of generic preference-based systems for measuring comprehensive health status and HRQoL. By considering vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition, this instrument is able to provide scores for each of these dimensions and an overall HRQoL utility value. The HUI2 describes 24,000 unique health states, while the HUI3 describes 972,000 unique health states. The utility functions for the HUI2 system are based on preference measurements obtained from a random sample of 194 parents of school-age children in the general population, while the HUI3 utility scoring functions have been developed using preference measurements from a random sample of 504 adults in the general population.[87]

The population in the Portwine *et al.* 2016[86] paper included children diagnosed with advanced neuroblastoma. The study estimated utility values for high-risk neuroblastoma survivors (0.84) and the general population (0.96) based on the HUI3. Using these values, the company estimated a percentage decrement of 12.5% associated with having the disease compared with the general population. Therefore, for each cycle in the economic model, the age-specific UK EQ-5D general population norms were adjusted using the 12.5% decrement, as shown in equation 2.

$$U\ EFS(age) = \frac{1}{1+e^{(\alpha*age+\beta)}} * (1 - 12.5\%)$$ (equation 2)

For the failure health state in the high-risk model, the percentage decrement was based on data obtained from a study by Barr *et al*. 1999[87]. In this study, a 15-item self-administered questionnaire was completed with respect to each child either by a parent, healthcare professional or the child itself. The information collected from the questionnaires was converted to health status classification system attribute levels of HUI2 and HUI3. The estimated the utility value associated with recurrent disease based on the HUI2 was 0.56. The company used this value and compared it with the general population HUI3 utility value (0.96), obtained previously from the Portwine *et al.* 2016 study[86], to calculate a percentage decrement of 41.7% associated with recurring disease. The percentage decrement is applied to the age-specific UK EQ-5D population norms (equation 3) for all cycles in the model.

$$U\ FS(age) = \frac{1}{1+e^{(\alpha*age+\beta)}} * (1 - 41.7\%)$$ (equation 3)

The company has assumed that utility values for each health state do not differ by treatment arm. In addition, the company did not identify any studies from the literature review which estimated the impact of AEs on patients' quality of life therefore, did not include utility values or decrements associated with AEs in the analysis.

5.4.8.3 ERG critique

The methodology for calculating age-specific UK EQ-5D utilities relies on a logistic regression using published UK EQ-5D general population norms. Given that the population norms are only available for ages 18 and above, the logistic regression is used to interpolate the values for ages 0 to 18. However, using a logistic regression to predict utility values is not appropriate, considering that logistic models predict the probability of a binary event happening, in this case the probability of the utility value being 1 (perfect health) or 0 (death). As such, the values estimated by the company are the probability of having a utility of 1 at different ages. For example, a value of 0.96 for someone who is 5 years of age indicates that there is a 96% chance of experiencing a utility of 1 at that specific age. The previous STA for dinutuximab alpha (GID-TAG507)[45] reported a published algorithm by Ara *et al.* 2010,[96] which was used to estimate mean EQ-5D HSUVs for individuals in the general population, using a multiple regression including gender, age and age^2 as covariates. The ERG considers this method to be more appropriate than using a logistic regression, as it produces utility values rather than probabilities and is based on a published, peer-reviewed methodology. Due to time constraints, the ERG did not have time to replace the logistic regression in the model with the published multiple regression to estimate age-specific UK EQ-5D. However, the ERG considers this an important recommendation for any future analysis, as discussed in Section 6.

5.4.8.3.1 Estimation of utility decrements

To estimate the decrement in neuroblastoma patients' quality of life in the EFS state compared with the UK general population, the company used the HUI3 utility values for stable patients and for the general population from the Portwine *et al.* 2016 study.[86] The study only provided HUI3 utility values for the general population (0.96) and so there were no HUI2 values available for this population.

To estimate the decrement in patients' utility in the failure state compared with the UK general population, the company used the general population HUI3 utility value in the Portwine *et al.* 2016 study[86] (0.96) and compared it to the HUI2 utility value derived in Barr *et al*. 1999[87] for the recurrent disease state (0.56), arriving at the 41.7% decrement.

Both studies used by the company do not provide health utilities based on the EQ-5D, as recommended by the NICE Reference Case. However, the Guide to the Methods of Technology Appraisal[88] and the NICE Decision Support Unit Technical Support Document 8[97] recommend the use of metrics and measures that are specifically developed for children, when examining a target population of children. The use of HUI2 is recommended by NICE as it has been developed specifically for use in children and a value set has been developed based on general population values in the UK.

Nonetheless, the company used the HUI3 values from the Portwine *et al.* 2016 study,[86] instead of the HUI2 values. The CS does not provide a justification for this decision, however, the ERG assumes that it is due to the fact that utility values for the general population were only available through the HUI3 and not HUI2 in the study. Therefore, the company might have used the HUI3 utility value for the stable state in order to compare two sets of HUI3 values (and not have to compare a HUI2 value with a HUI3 value).

Regardless, this rationale is inconsistent with the company's approach to estimating the utility decrement in the failure state of the model, where the HUI3 value from Portwine *et al.* 2016[86] is compared to the HUI2 value in Barr *et al*. 1999[87]. is the ERG notes that Barr *et al*. 1999[87] also estimated HUI3 utility values, with the utility attributed to the recurrent disease health state being 0.32 (instead of 0.56 with the HUI2). This would lead to an estimated decrement in patients' utility of 66.7% instead of the 41.7% calculated by the company, when using the HUI2 value from Barr *et al*. 1999[87] for the failure state (0.56). The different HUI2 and HUI3 utility estimates reported in both studies are presented in Table 42 below.

Table 42. Utility values used by the company in the economic analysis

Parameter	Portwine *et al.* 2016[86]		Barr *et al*. 1999[87]	
	HUI2	HUI3	HUI2	HUI3
EFS	0.89	**0.84**	0.81	0.56
Failure	-	-	**0.56**	0.32
General population	-	**0.96**	-	-
EFS % decrement (vs general population)	7.3%	**12.5%**	15.6%	41.7%
Failure % decrement (vs general population)	-	-	**41.7%**	66.7%

Abbreviations: HUI, health utility index; EFS, event free survival.

Note: Values that have been bolded have been used in the economic model.

Therefore, the ERG points to the inconsistency in the company's approach but acknowledges the flaws in each approach. On one hand the HUI2 is the metric recommended by NICE for measuring quality of life for children. On the other hand, using the HUI2 means comparing the HUI2 utility values to the HUI3 estimates in the analysis, therefore, assuming that the HUI2 and the HUI3 are interchangeable and that the utility values produced by one instrument and the other are comparable. However, the values may not be interchangeable as HUI2 and HUI3 values from Portwine *et al.* 2016[86] and Barr *et al*. 1999[87], as well as other published studies[98,99] reporting both HUI2 and HUI3 values, show that the values produced by each measure are substantially different.

Consequently, if the company had appreciated that the HUI2 and the HUI3 are not comparable and should not be used interchangeably, then the HUI3 value from Barr *et al*. 1999[87] should have been used in the comparison with the HUI3 value from Portwine *et al.* 2016[86], which would have led to a decrement of 66.7% in the utility experienced by patients in the failure state. Conversely, if the company followed the approach of using the NICE-recommended instrument, the HUI2, then this should have used whenever available, and the HUI2 value for the stable health state (0.89) should have been compared to the HUI3 value in the general population in Portwine *et al.* 2016[86], leading to a decrement of 7.3% in EFS state, compared to the UK general population.

The company's approach carries another underlying assumption, which was also not been mentioned or explored by the company. Using the Portwine *et al.* 2016[86] utility value for the general population and comparing it to the Barr *et al*. 1999[87] estimate, assumes that the study populations are comparable. The population in the Portwine *et al.* 2016[86] paper included children diagnosed with advanced neuroblastoma with a mean age at diagnosis of 4 years (mean time posttreatment in the study was approximately 4 years). Even though the company uses this study to estimate the utility in the EFS state, only 85% of patients in the study were disease free (with 10% of patients having residual/persistent disease and 5% with secondary malignancies/missing data). The population in the Barr *et al*. 1999[87] paper included children diagnosed with brain tumours (not including neuroblastoma) with a mean age

at diagnosis of 6 years. The mean time posttreatment in the study was approximately 3 years. Therefore, there is some discrepancy in study populations, the main difference being the fact that patients in Barr *et al*. 1999[87] did not have neuroblastoma. Furthermore, the sample sizes in Barr *et al*. 1999[87] are very small, with the relapse utility value based on a sample of three patients.

Clinical expert opinion sought by the ERG confirmed that neuroblastoma survivors tend to have health problems throughout their lifetime and thus would not have the same quality of life as the general population. Therefore, the ERG agrees with the company's approach to assuming a constant decrement to patients' utility for the entire analysis in the EFS health state. Furthermore, the ERG's clinical experts explained that patients' health will become considerably worse with every relapse but that in the case that a relapsed patient receives treatment and their disease stabilises, their quality of life should be about the same as that of a high risk (i.e. non-relapsed) stable patient. Nonetheless, the company's model does not capture patients who recover from a relapse.

In conclusion, even though the ERG agrees with having a constant utility decrement applied after the cure threshold, a few concerns remain surrounding the clinical plausibility of the values used by the company. The combination of HUI2 and HUI3 values was not substantiated by a clinical rationale, and thus from a methodological point of view, the company's approach seems flawed. From a population perspective, it is possible that the Portwine *et al.* 2016[86] study is overestimating the EFS-related utility as only 85% of patients in the study were disease free. Similarly, the Barr *et al*. 1999[87] study did not include neuroblastoma patients, and only three patients were relapsed in the study.

Table 43 provides a comparison between the company's approach to modelling HSUVs in the economic model and the approach followed by the company in GID-TAG507 (dinutuximab alpha STA). The main methodological difference in the approach taken by the company in GID-TAG507 is the fact that the utility value in the failure state did not change throughout the entire analysis. The ERG in the dinutuximab alpha STA (GID-TAG507) was concerned that the 12.5% decrement applied was not sufficient to capture the impact of disease and the intense treatments received by neuroblastoma patients and so used the Nathan *et al.* 2007[95] source to estimate a decrement in patients' quality of life compared with the general population. The ERG arrived at a 31.5% estimate for the decrement in patients' utility on the EFS state. However, the committee for GID-TAG507 considered the 12.5% a more clinically plausible decrement.

Table 43. Summary of utility assumptions for the high-risk population used in the STA for dinutuximab and dintuximab beta

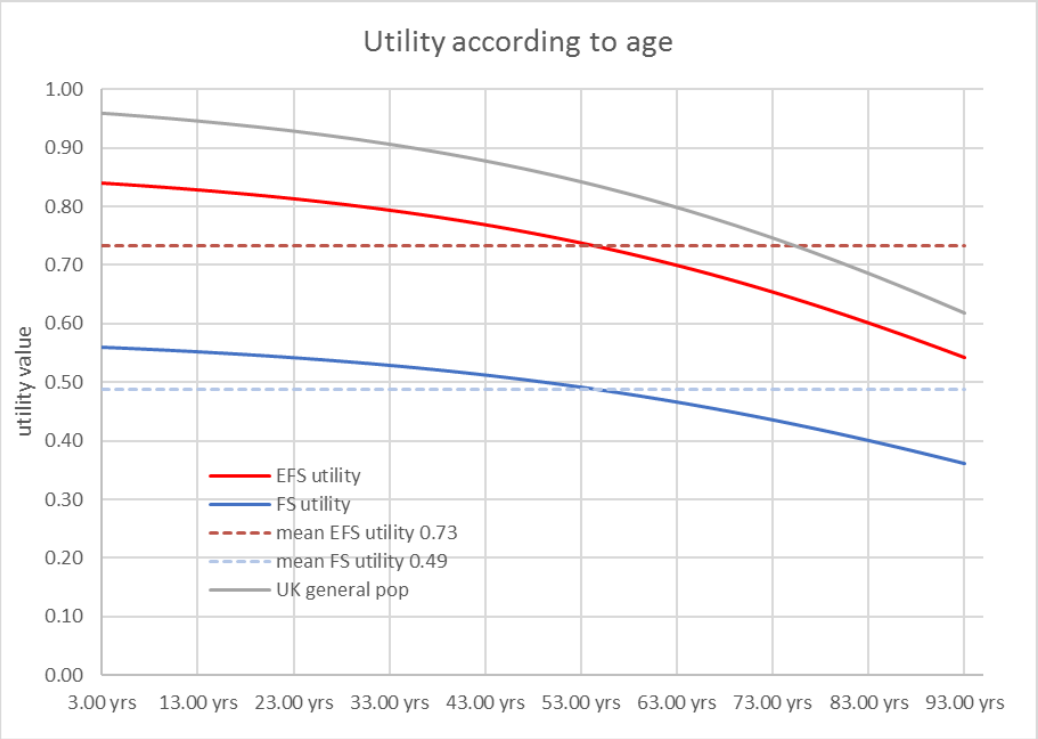
Health state	Methods and assumptions	
	Dinutuximab[45]	**Dinutuximab beta EUSA**
Stable (0-5 years)	**0.81** utility value based on patients with residual disease from the study by Barr *et al*. 1999[87]	**12.5% decrement** applied to age-specific UK EQ-5D general population norms. Decrement calculated using utility value for survivors of high risk neuroblastoma (**0.84**), compared with the utility value for the general population (**0.96**). Both values were obtained from the study by Portwine *et al*. 2016[86] and are based on the HUI3.
Stable (5+ years)	**12.5% decrement** applied to age-specific UK EQ-5D general population norms. Decrement calculated using utility value for survivors of high risk neuroblastoma (**0.84**), compared with the utility value for the general population (**0.96**). Both values were obtained from the study by Portwine *et al*. 2014[100] and are based on the **HUI**.	
Failure	**0.56** utility value based on patients with recurrent disease from the study by Barr *et al*.,2016[87]	**41.7% decrement** applied to age-specific UK EQ-5D general population norms. Decrement calculated using **HUI2** utility value for patients with recurrent disease (**0.56**) obtained from the study by Barr *et al*. 2016[87], compared with the **HUI3** utility value for the general population (**0.96**) obtained from the study by Portwine *et al*. 2016[86].
Age adjusted UK EQ-5D general population norms	EQ-5D = 0.9508566 + 0.0212126*male – 0.0002587*age – 0.0000332*age^2 based on paper by Ara *et al*. 2010[96]	U(age)= 1/(1+e^(α*age+β))
Abbreviations: HUI, health utility index; EQ-5D, euroqol-5 dimensions; UK, United Kingdom.		

Comparing the utility values used in the current STA (Figure 33) with the utility values used in the previous STA for dinutuximab alpha (Table 43) for the FS state, the ERG notes that for the FS-related utility, the STA for dinutuximab alpha used a constant utility value of 0.56 throughout the analysis. This compares to a mean 0.49 utility value for the FS state in the current STA (utility of 0.56 for median OS for isotretinoin and utility of 0.49 for median OS in the dinutuximab beta arm).

The ERG cannot draw any final conclusions on which values should be used to estimate quality of life in the economic model. Although from a methodological point of view it seems more appropriate to account for the impact of age for the entire model, for both the EFS and the FS health states, the decrements applied to the UK general population remain a source of uncertainty. Furthermore, the ERG disagrees with the methodology used to adjust for age and considers that the published algorithm by

Ara *et al.* 2010[96] should have been used instead. The ERG cannot anticipate the impact of using a different methodology for adjusting for age in the final ICER.

Figure 33. Utility trace with numbers at risk



Years	3	13	23	33	43	53	63	73	83	93
Isotretinoin	100%	44%	43%	42%	40%	36%	27%	14%	2%	0%
Dinutuximab beta	100%	62%	61%	60%	58%	52%	40%	21%	3%	0%

Finally, the company has assumed that utilities in the model do not differ by treatment arm. However, the company does not account for the impact of AEs on HRQoL, stating a lack of data available to inform the analysis from trials and in the published literature. As mentioned previously in Section 5.4.6, AEs are substantially worse for patients on dinutuximab beta than on isotretinoin. The ERG considers that this approach is potentially overestimating the QALY gain associated with dinutuximab, as the impact of its AEs are not being captured on patients' quality of life. In the previous STA for dinutuximab alpha (GID-TAG507), the company used expert opinion to estimate a utility decrement for AEs associated with treatment of dinutuximab alpha, which was mostly based on patients experiencing pain. The company assumed a utility value of 0 for the dinutuximab arm during the drug administration period (cycles 1-5) for a duration of 4, 8, 4, 8, and 4 days, which was consistent with the intravenous dosing schedule, however the assumption had minimal impact on the ICER. Given that AEs will be experienced during the treatment phase (6 months) at a declining rate based on the ERG's clinical expert opinion, and are mainly related with pain, the ERG considers that the impact of including these in the analysis is likely to be negligible.

Finally, as mentioned in Section 5.4.4.1. the ERG also found an error in the discounting applied in the model and in the inclusion of QALYs from the first model cycle in the final results. Therefore, the ERG corrected these in the model and presents results in Section 6.

5.4.9 Resources and costs

5.4.9.1 Systematic literature review for resource use and costs

The systematic literature review carried out by the company to identify studies reporting resource use and costs for neuroblastoma is described and critiqued in Section 5.3 of the ERG report. The review identified five studies, summarised in Table 44. Of the five studies, two[82,83] were set in the UK, two took place in Canada[81,85] and one[82] was set in the USA.

The first UK cost study (Rebholz *et al.*)[84] compared resource use in childhood cancer survivors with that of the general British population, using data collected in the British Childhood Cancer Survivor Study that followed up 17,981 individuals diagnosed with childhood cancer (1940-1991) who survived 5 years or more. Data on frequency of doctor appointments, hospital outpatient visits, and day-patient and inpatient hospitalisations were collected from 10,360 patients, including a total of 697 neuroblastoma patients.

The publication by George and Buckle[83] is an abstract of a study assessing the utilisation and costs of hospital services (hospital admissions, emergency department visits, and outpatient attendances) from a Clinical Commissioning Group perspective for 336 patients diagnosed with neuroblastoma and 33 patients with high-risk neuroblastoma. The company considered Rebholz *et al.*[84] to be the most appropriate source for resource use and costs among the studies identified for the reasons outlined in Table 44.

Table 44. Studies reporting resource use and costs identified in company's systematic literature search (CS, Appendix I, Table 1)

Category	Barr *et al.* 1996[81]	George and Buckle 2014[83] [abstract]	Soderstrom *et al.* 2005[85]	Rebholz *et al.* 2011[84]	Desai *et al.* 2016[82]
Country(ies) Time period	Canada 1986-1987	England April 2010 - September 2013	Canada 1989 - 2002	UK 1940-1991	USA January 1999 to June 2013
Aim of the study	To describe the monetary costs borne by families of patients with childhood cancer and to determine whether these costs represent an important component of the burden.	To report the utilisation and cost of hospital services related to patients who have a diagnosis of NB and high-risk NB reported in an England dataset from a Clinical Commissioning Group perspective.	Examine costs and benefits of a well-designed evaluation of health services, the Quebec Neuroblastoma Screening project.	To compare health care service utilization between childhood cancer survivors and the general British population and investigate potential risk factors.	Compare the resources required to support patients treated with ASCR conditioning regimens [carboplatin/etoposide/melphalan (CEM) and busulfan/melphalan (BuMel)]
Population	Families of children treated for high-risk acute lymphoblastic leukaemia (n=70), Wilms' tumour stages 2-5 (n=19), and neuroblastoma stages 3 inoperable and excluding 4S (n=16)	Patients under 18 years old who have a diagnosis of NB and high-risk NB (HRNB)	Patients from the Quebec Neuroblastoma Screening Project (QNSP)	Long-term (≥ 5y) survivors of childhood cancer	High-risk NB patients
Sample size	16 families	33 patients identified as HRNB. 336 newly diagnosed with NB but not identified as high risk was the control population.	N/A	n=10,360. Among these, n=697 (6.7%) are survivors of NB	n=1,289
Treatment exposure and regimen	Treatment according to protocols of the Children's Cancer Group, The National Wilms' Tumour Study and the Dana-Farber Cancer Institute	N/A	N/A	N/A	Two ASCR regimes were compared: ・ Carboplatin/etoposide/melphalan (CEM) ・Busulphan/melphalan (BuMel)

Information on recruitment	・Prospective diary survey completed by families about daily expenses incurred during each sample week of therapy. ・Retrospective, cross-sectional questionnaire survey about expenses, incurred during the entire duration of treatment, associated with major or one-time cost items	Not specified	Not specified	Not specified	Retrospective analysis of the Paediatric Health Information Systems database, which contains information regarding inpatient RU at free-standing children's hospitals across the United States. The database includes inpatient data from 43 not-for-profit tertiary care paediatric hospitals affiliated with the Children's Hospital Association (Overland Park, KS) and accounts for 85% of admissions to freestanding children's hospitals in the United States. Data include demographics, dates of service, discharge disposition, payor information, International Classification of Diseases, Ninth Revision (ICD-9) diagnosis and procedure codes, and billing data for medications, laboratory tests, imaging procedures, clinical services, and supplies.
Primary outcome measures	・Mean total expenses and weekly expenses (1986 Canadian dollars) incurred by families of NB patients during the three major phases of treatment: induction, consolidation and maintenance; inclusive and exclusive of costs attributed to loss of paid work time.	Cost and utilisation from: ・Hospital admissions ・Emergency department visits ・Outpatient attendances	・QNSP evaluation costs ・Health effects avoided by not implementing a NB wide screening ・Total costs avoided by not implementing a NB wide screening ・Net savings	OR of survivors compared to the general population for the following health care use outcomes: ・Use of non–hospital-based care (Talked to a doctor in the last 2 weeks) ・Hospital outpatient/casualty visits (Attended hospital outpatient department in the last 3 months) ・Outpatient hospitalisation for	・Toxicities: Sepsis, sinusoidal obstruction syndrome, and death. ・Resource utilization (for the first 30 and 60 days from the start of ASCR conditioning): Hospitalization and ICU level care, Cardiorespiratory support, Renal support, Antibiotics, Pain management and nutrition support.

	・Medians of total family expenses.			treatment (Hospitalized as a day patient in the last year) ・Inpatient hospitalization for treatment (Hospitalized as an inpatient in the last year)	
Response rates	・Weekly expenses: 6/9 families (66.7%) ・Major one-time expenses: 10/13 families (76.9%)	Not specified	92% of new-borns were screened	70.70%	N/A
Results	・Mean total expenses incurred by families of NB patients was $10,376 (median: $4726). They are 38.2% of the average family's after-tax income (median: 17.4%) ・On-going weekly costs, rather than major one-time purchases account for the largest share of expenses.	・Inpatient admits: 22 per patient for the HRNB population, 12 per patient for newly diagnosed population. ・Total costs: £4.3m for the HRNB pop., £24.3m for the newly diagnosed pop. ・Costs per patient: £130,303 per HRNB patient, £72,321 per newly diagnosed pt. ・Average length of stay: 6 days for both sets of pts.	・The QNSP evaluation cost was $8.77 million (2002 US dollars). ・Health effects avoided: 5003 false-positive cases and 9223 silent tumours were avoided. ・In total, the United States and Canada avoided $574.1 million in health costs by not using neuroblastoma screening between 1989 and 2002. ・Net saving was $565.4 million, which is 64.5 times the evaluation costs.	・There were no cost reported ・The following percentages were reported for "at least once vs never" and "more than once vs once": ・Talked to a doctor in the last 2 weeks: 14.2% (OR 1 95%CI 0.7-1,3) vs 24.1%(OR 0.9, 95% CI 0.5 to 1.8) ・Attended hospital outpatient department in the last 3 months: 24.1% (OR 2.4, 95% CI 1.9 to 3.1) vs 33.3% (OR 1.3, 95% CI 0.8 to 2.1) ・Hospitalized as a	CEM patients required more extended use of analgesics, antibiotics, and anti-hypertensive, while duration of hospitalization was longer, and SOS and the use of mechanical ventilation were more frequent following BuMel.

				day patient in the last year: 11.8% (OR 1.7, 95% CI 1.2 to 2.3) vs 38.8% (OR 1.3, 95% CI 0.7 to 2.4) ・Hospitalized as an inpatient in the last year: 9.6% (OR 1.9 95% CI 1.3 to 2.7) vs 35% (OR 2.1, 95% CI 1.0 to 4.3)	
Cost valuations/resource use reported in the study	・Mean total out-of-pocket weekly expenses were $344.54 +112 km +0.75 h of work lost (median values are $58.50 +22 km +0.0 h). ・Mean total out-of-pocket major one-time expenses, for the complete course of therapy was $472. Added to this is the extra burden of time lost from work. ・Mean total on-going costs for a treatment period: $9904.	・Inpatient admits: 22 per patient for the HRNB population, 12 per patient for newly diagnosed population. ・Total costs: £4.3m for the HRNB pop., £24.3m for the newly diagnosed pop. ・Costs per patient: £130,303 per HRNB patient, £72,321 per newly diagnosed pt. ・Average length of stay: 6 days for both sets of pts.	Resource units (added units per 100000 births) and costs (average cost per additional resource unit) avoided for particular types of healthcare services (diagnosis, treatment, and follow-up): ・Inpatient nursing and hotel costs, inpatient days: 411 units, $197/unit ・Outpatient services, outpatient contacts: 464 units, $74/unit ・Drugs, doses prescribed: 3214 units, $3/unit ・Radiology examinations: 493 units, $46/unit ・Laboratory tests: 2071 units, $9/unit ・Surgical procedures: 49 units, $426/unit ・Other procedures: 180 units, $33/unit ・Physician consultations: 254 units	・There was no cost reported ・The following percentages were reported for "at least once vs never" and "more than once vs once": ・Talked to a doctor in the last 2 weeks: 14.2% (OR 1 95%CI 0.7-1,3) vs 24.1%(OR 0.9, 95% CI 0.5 to 1.8) ・Attended hospital outpatient department in the last 3 months: 24.1% (OR 2.4, 95% CI 1.9 to 3.1) vs 33.3% (OR 1.3, 95% CI 0.8 to 2.1) ・Hospitalized as a day patient in the last year: 11.8% (OR 1.7, 95% CI 1.2 to 2.3) vs 38.8% (OR 1.3, 95% CI 0.7 to 2.4) ・Hospitalized as an inpatient in the last year: 9.6% (OR 1.9	RU days for 30-day study period (CEM mean [range] vs BuMel mean [range], p-value) ・Hospital days: 27.38 [8–30] vs 27.83, [21–30], 0.37 ・Intensive care days: 1.32 [0–24] vs 0.42 [0–24], 0.72 ・Opiates: 13.77 [0–30] vs 9.90 [3–20], <0.0001 ・Nonnarcotic analgesics: 8.57 [0–22] vs 6.32 [0–16], 0.0052 RU days for 60-day study period (CEM mean [range] vs BuMel mean [range], p-value) ・Hospital days: 32 [8–60] vs 38 [21–60], 0.01 ・Intensive care days: 1.96 [0–47] vs 3.02 [0–39], 0.13 ・Opiates: 15.57 [0–54] vs 15.10 [3–45], 0.08 ・Nonnarcotic analgesics: 9.35 [0–32] vs 7.92 [0–28], 0.07

			・Diagnostic and therapeutic procedures: 2713 units, $15/unit	95% CI 1.3 to 2.7) vs 35% (OR 2.1, 95% CI 1.0 to 4.3)	
Costs/resource use data for use in economic analysis	Cost and/or resource use data deemed not useful for the economic analysis (costs incurred by parent are not considered in the economic analysis and only expenses incurred by families were reported)	Cost and/or resource use data deemed not useful for the economic analysis, as only total costs per patient starting from diagnosis were reported (i.e. not specific to the maintenance phase).	Cost and/or resource use data are not appropriate for the economic analysis, as detailed resource information and health state-specific data were not reported to support model inputs	Resource utilization data from this study combined with UK-specific unit costs can be used in the economic analysis for patients in the stable state	Cost and/or resource use data deemed not useful for the economic analysis, as only total costs per patient starting from induction therapy until 60-days reported (i.e. not specific to the maintenance phase).
Technology costs	Costs or resource use specific to the technology was not reported	Costs or resource use specific to the technology was not reported	Costs or resource use specific to the technology was not reported	Costs or resource use specific to the technology was not reported	Costs or resource use specific to the technology was not reported
Applicability to clinical practice in England	No	No	No	Yes	No
Abbreviations: ASCR= Autologous Stem Cell Rescue; BuMel= Busulfan/Melphalan; CEM= Carboplatin/Etoposide/Melphalan; CI, confidence interval; HRNB= high-risk neuroblastoma; N/A, not applicable; NB= Neuroblastoma; OR= odds ratio; QNSP= Quebec Neuroblastoma Screening Project; RU=Resource Utilization.					

5.4.9.2 Resource use and costs included in the model

The costs considered in the model are drug acquisition costs, administration and hospitalisation costs, monitoring costs, concomitant medication costs, disease management costs and costs of managing adverse events, which are described in turn below.

5.4.9.2.1 Drug acquisition costs

Total drug acquisition costs per cycle for patients in each treatment arm are based on the unit price of each therapy and number of units consumed based on body surface area (BSA). The cycle costs for each treatment are applied to all patients in the stable health state for the first five model cycles (i.e. for five months). The doses and costs of each treatment per cycle in the high-risk model are summarised in Table 45. For the high-risk model, drug dosage is based on median BSA of 0.63m^2 obtained from the APN311-302 study. is the ERG notes that the median age of the trial population was of three years.

The total cost of immunotherapy for all five cycles in the high-risk model is £152,486 versus a total cost for isotretinoin of £286 for all five cycles. The company included the cost of treatment with IL-2 in the isotretinoin arm of the economic model. This was not reported in the CS, and the ERG does not see a clinical justification for IL-2 to be given with isotretinoin. Therefore, the ERG corrected this in the economic model and removed the IL-2 costs from the comparator arm. Results are presented in Section 6.

The cost of immunotherapy included the cost of dinutuximab, isotretinoin and IL-2. It should be noted that 100% of patients in the model were assumed to receive IL-2. However, in APN311-302 only 51% of the population was randomised to receive IL-2. List prices for isotretinoin and IL-2 have been obtained from the British National Formulary (BNF)[101] in order to calculate the unit costs of tablets and vials.

Table 45. Drug acquisition costs in the high-risk model (adapted from Table 62 in the CS)

Treatment	Dose regimen	Units	Cost per unit	Number of units per	Cost per cycle
Immunotherapy					
Dinutuximab beta	10mg/m^2 per day continuous i.v. infusion for 5 days, twice per cycle (10 days in total).	20mg vial	£7,610	4	£30,440
Isotretinoin	160mg/m^2 per day, to be taken orally over 14 days per cycle.	20mg tablet	£0.68	84	£57.12

IL-2*	6.106 IU/m^2 per day, s.c. injection over 10 days per cycle.	18x10^6 vial	£112	4	£1,120
Total cost per cycle					£30,497.12
Standard therapy					
Isotretinoin	160mg/m^2 per day, to be taken orally over 14 days per cycle.	20mg tablet	£0.68	84	£57.12
Abbreviations: mg, milligram; m^2, metre squared; i.v., intravenous, s.c., subcutaneous injection. *Not included in the table in the original CS, but included in the revised model sent to the ERG with the company's clarification response.					

5.4.9.2.2 Administration, hospitalisation, monitoring and concomitant medication costs

Administration and hospitalisation costs associated with dinutuximab beta for the high-risk population are summarised in Table 46. Based on clinical expert opinion, the company has assumed that during the first treatment cycle and the first half of the second cycle, dinutuximab beta is administered in a hospital setting. As mentioned previously, dinutuximab beta is given continuously (i.e. for 24 hours) for 5 days twice per cycle. The CS reports that treatment with dinutuximab beta requires hospitalisation for 10 days for the first treatment cycle and 5 hospital days for the second cycle. However, in the model the company has assumed 7.5 hospital days for the first cycle and 2.5 days for the second cycle, with no justification provided for the deviation. Therefore, the ERG has corrected this in the model, to reflect the hospitalisation schedule reported in the CS (also supported by the ERG's clinical experts) in the model (please refer to Section 6 for results). For the remainder of treatment, dinutuximab beta is delivered in an outpatient setting, however patients receiving IL-2 concomitantly with dinutuximab beta still require hospitalisation as treatment with IL-2 is given in the hospital. Patients are assumed to require 10 days in the hospital to receive treatment with IL-2. The company has assumed no administration costs associated with isotretinoin as it is an oral medication.

Table 46. Administration and hospitalisation costs – high-risk model (adapted from Table 64 in the CS)

Cycle	Resource	No. Units	Unit cost	Total	Source
1	1st administration (Dinutuximab beta) - Inpatient	1	£407	£407	NHS Reference Costs 2015-2016. Service code DCDRN; Currency code SB14Z
	2nd administration (Dinutuximab beta) - Inpatient	1	£273	£273	NHS Reference Costs 2015-2016. Service code DCDRN; Currency code SB14Z
	Pump/ syringe device for infusion	2	£80	£160	Average cost of providing a syringe or a pump (based on expert opinion)

	Hospital days	10	£934	£9,340	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Currency code PM43C
	Total for Cycle			**£10,180**	
2	1st administration (Dinutuximab beta) - Inpatient	1	£273	£273	NHS Reference Costs 2015-2016. Service code DCDRN; Currency code SB14Z
	2nd administration (Dinutuximab beta) - Outpatient	1	£212	£212	NHS Reference Costs 2015-2016. Service Code: OP; Currency code: SB15Z
	Pump/ syringe device for infusion	2	£80	£160	Average cost of providing a syringe or a pump (based on expert opinion)
	Hospital days	5	£934	£4,670	NHS Reference Costs 2015-2016; Chemotherapy; Service Code: IP; Currency code PM43C
	Total for Cycle			**£5,449**	
3	Outpatient administration (Dinutuximab beta)	2	£212	£424	NHS Reference Costs 2015-2016. Service Code: OP; Currency code: SB15Z
	Pump/ syringe device for infusion	2	£80	£160	Average cost of providing a syringe or a pump (based on expert opinion)
	Total for Cycle			**£584**	
4	**Same as cycle 3**			**£584**	
5	**Same as cycle 3**			**£584**	

To manage pain and allergic reactions associated with being on treatment with dinutuximab beta, the company has applied the costs of concomitant medications for the first 5 cycles of the model. Table 47 presents the concomitant medications (other than IL-2 and isotretinoin) and the costs that have been used in the model. To calculate the average drug dose based on weight, the company calculated the average weight based on the mean weight from APN311-302 (high-risk) and APN311-202 (relapsed or refractory) by taking the high-risk population mean weight, adding the relapsed or refractory population mean weight), and dividing the sum by two.

Table 47. Concomitant medication costs (Table 66 from the CS, costs corrected to reflect used values in economic model)

Concomitant Medication	Unit price	Number of units per treatment cycle	Cost per continuous infusion	Description taken from economic model	Source
Opioids (morphine)	£5.78	10	£57.80	• Before initiation of a continuous intravenous morphine infusion, a bolus infusion of 0.02 to 0.05 mg/kg/hour morphine should be started 2 hours before dinutuximab beta infusion. • Subsequently, a dosing rate of 0.03 mg/kg/hour is recommended concomitantly with dinutuximab beta infusion. • With continuous infusion, in response to the patient's pain perception, it may be possible to wean off morphine over 5 days by progressively decreasing its dosing rate (e.g. to 0.02 mg/kg/hour, 0.01 mg/kg/hour, 0.005 mg/kg/hour). • If continuous morphine infusion is required for more than 5 days, treatment should be gradually reduced by 20% per day after the last day of dinutuximab beta infusion.	BNF (1mg/ml injection, 1x50ml vial = £5.78)
Nonopioid analgesics	£3.16	1	£3.16	Nonopioid analgesics should be used permanently during the treatment, e.g. paracetamol or ibuprofen.	BNF/MIMS Paracetamol Oral solution Child 2–4 years 180 mg every 4–6 hours (max. 4 doses in 24 hours) (120mg/5ml solution, 500 ml = £3.16)
Gabapentin	£66.13	0.9	£59.34	The patient should be primed with 10 mg/kg/day, starting 3 days prior to dinutuximab beta infusion. The daily dose of gabapentin is increased to 2×10 mg/kg/day orally, the next day and to 3×10 mg/kg/day orally, the day before the onset of dinutuximab beta infusion and thereafter. The maximum single dose of gabapentin is 300 mg. This dosing schedule should be maintained for as long as required by the patient. Oral gabapentin should be tapered off after weaning off intravenous morphine infusion, at the latest after dinutuximab beta infusion therapy has stopped.	BNF (Oral solution, gabapentin 50 mg/mL, net price 150-mL pack = £66.13)
Antihistamine premedication	£1.87	1	£1.87	Antihistamine premedication (e.g. diphenhydramine) should be administered by intravenous	BNF (cetirizine hydrochloride 5 mg/5 mL, net

				injection approximately 20 minutes before starting each dinutuximab beta infusion. It is recommended that antihistamine administration be repeated every 4 to 6 hours as required during dinutuximab infusion. Patients should be closely monitored for anaphylaxis and allergic reactions, particularly during the first and second treatment course. Cetirizine: 2—6 years, 2.5mg twice daily	price 200 mL = £1.87)
Sodium chloride/human albumin for dilution	£3.10 £27.00	2	£60.20	Dinutuximab beta should be diluted aseptically to the patient specific concentration/dose with sodium chloride 9 mg/mL (0.9%) solution for infusion containing 1% human albumin (e.g. 5 mL of human albumin 20% per 100 mL sodium chloride solution).	IHS database (Wholesaler price Fresenius Kabi for 1L solution for infusion in polyethylene bottle) IHS database (Wholesaler price Zenalb Human Albumin solution for infusion 20% 200mg/ml)
Abbreviations: mg, milligram; ml, millilitre; L, litre.					

The monitoring costs associated with treatment with dinutuximab beta are pulse oximetry and a full blood count, liver and renal function test per cycle (see Table 48). Patients receiving isotretinoin do not incur treatment monitoring costs.

Table 48. Monitoring costs per cycle (Table 67 in the CS)

Monitoring costs	Unit cost per cycle	Source
Pulse oximetry	£55.03	NHS Reference Costs 2015-2016; Directly Accessed Diagnostic Services; Currency code: DZ57Z; Currency description: Oximetry or Blood Gas Studies
Full blood count, Liver, and Renal function test	£3.10	NHS Reference Costs 2015-2016; Directly Accessed Pathology Services; Currency code: DAPS05; Currency description: Haematology

5.4.9.2.3 Disease management costs

Resource use for the stable health state (EFS in the model) was obtained from the previous STA of dinutuximab alpha (GID-TAG507)[45], which was based on a paper by Rebholz *et al.* 2011.[84] This study aimed to compare the extent of healthcare use of individuals who were diagnosed with cancer (including neuroblastoma) before the age of 15, who had survived at least 5 years from date of diagnosis with the general population. Questionnaires were designed to investigate quality of life, medical conditions, health behaviour, social outcomes and use of healthcare services and were sent to 10,037 individuals identified from the British Childhood Cancer Survivor Study (BCCSS). Data on the general population

healthcare utilisation were taken from the General Household Survey (GHS). Healthcare utilisation was measured using four categories; talked to a doctor in the last two weeks, attended a hospital outpatient department in the last three months, hospitalised as a day patient in the last year, hospitalised as an inpatient in the last year. Response to each category was either never, at least once or more than once.

The study looked at the frequency (in terms of percentage) of healthcare resource used by survivors of childhood cancers, which included estimates for survivors of neuroblastoma. Frequencies were translated into dichotomous outcomes to represent when a resource was used once vs never, and more than once vs never. As units of resources consumed were not available from the study, the company for the STA of dinutuximab alpha calculated the distribution of level of use (never, once, and more than once) for each resource item using reported percentages of "at least once vs never" and "more than once vs once". The company then assumed that the "more than once" category consumed 2 units, and thus calculated the weighted average number of units for each resource item and converted these units into monthly amounts.

The company for the current STA used these data and applied unit costs obtained from NHS references costs to the monthly resource use to calculate monthly costs in the model. The company then applied the monthly cost to each cycle of the model up until the cure threshold, after which an annual cost was applied to each cycle (given that after the cure threshold the model cycles are one year in length) for the lifetime of the model. Table 49 presents the resource use and costs for the stable health state used in the model.

Table 49. Stable state resource use and costs (Table 68 in the CS)

Resource	Average monthly units of resource used	Unit cost	Monthly cost	Source
Talked to a doctor in the last 2 weeks	0.35	£128.63	£45.02	Source: NHS Reference Costs 2015-2016 Consultant-led outpatient attendances, currency code: WF01C, currency description: non-admitted non-face-to-face attendance follow-up, service code: 300, service description: general medicine
Attended hospital outpatient department in the last 3 months	0.11	£156	£17.99	Source: NHS Reference Costs 2015-2016 Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 300, service description: general medicine
Hospitalized as a day patient (no overnight stay) in the last year	0.01	£733.31	£7.33	National day-case hospital visit average

Hospitalized as an inpatient (overnight stay) in the last year	0.01	£615.83	£6.16	National non-elective inpatient short stay average
Total			**£76.50**	

Costs and resource use for the failure health state were assumed to be the same as the treatment regimen given during the phase II randomised trial of topotecan/cyclophosphamide.[64] After the clarification stage, the company confirmed that the assumptions of costs in the failure health state were informed not only by clinical expert opinion but also by the previous STA of dinutuximab alpha (GID-TAG507).[45] The treatment regimen given in the phase II randomised trial included intravenous topotecan 0.75mg/m^2/d and cyclophosphamide 250mg/m^2/d for 5 days and subcutaneous filgrastim 5µg/kg/d on day 6, with a treatment cycle length of 21 days. The trial protocol permitted continued treatment until disease progression or up to 1 year without progression.

Table 50 presents the costs and resource use for the failure health state. The company calculated a total cost per model cycle, that is one month in length, up until the cure threshold and yearly thereafter for the lifetime of the model. The cost per cycle is calculated based on the dosage required adjusted for changes in BSA and weight over time.

Table 50. Failure state costs and resource use (Table 69 in the CS)

Treatment	Unit cost	Cost per cycle calculation	Source
Topotecan	£261.55	Dosage per cycle = 0.75mg x BSA x 5days Cost per mg per day =(unit cost / 4mg) / 21 days Cost per cycle = dosage per cycle x cost per mg per day x days per month or year	Topotecan 4mg/4ml concentrate for solution for infusion vials, BNF price £261.55 (Hospital only). Monthly costs calculated based on one 4 mL vial at 1 mg/mL per 21-day cycles
Cyclophosphamide	£17.06	Dosage per cycle = 0.25g x BSA x 5days Cost per g per day =unit cost / 21 days Cost per cycle = dosage per cycle x cost per mg per day x days per month or year	Cyclophosphamide 1g powder for solution for injection vials), BNF price £17.06 (Hospital only). Monthly costs calculated based on one 1g powder for solution for injection vial per 21-day cycles
Filgrastim	£30.60	Dosage per cycle = 5ug x kg x 16days Cost per million units per day =(unit cost/ 120) / 21 days	Nivestim 12million units/0.2ml solution for injection pre-filled syringes, BNF price £153 for 5 pre-filled syringes (Hospital only). Monthly costs calculated based on one prefilled syringe per day during 16 days per 21-day cycles

		Cost per cycle = dosage per cycle x cost per million units per day x days per month or year	
Administration costs	£1,808.01	Cost per cycle = (unit cost/ 21 days) x days per month or year	NHS Reference Costs 2015-2016, Chemotherapy; Service Code: IP; Service Description: Inpatient Currency code: SB10Z; Currency description: procure chemotherapy drugs for regimen in Band 10. Monthly costs calculated based on one overall administration cost per 21-day cycles
Abbreviations:			

5.4.9.2.4 Adverse event costs

Resource use and costs associated with managing AEs are presented in Table 51. The company provided no justification for how resource use for AEs in the economic analysis was determined. The company calculated a total weighted cost of AEs for each treatment arm of the model by multiplying the proportion of dinutuximab beta-related AEs or the isotretinoin-related AEs (Section 5.4.6) by the cost per event, arriving at a final total cost per treatment, which was then applied as a one-off cost in the model, to the entire population in the receptive treatment arm. The total weighted cost of adverse events for dinutuximab beta is £1,319 and for isotretinoin the total weighted cost is £337.

Table 51. Resource use and costs for managing adverse events (Table 70 in the CS)

Items	Per event Cost (£)	Explanation
Pain (including abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia)	£288.13	Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 241, service description: paediatric pain management
Hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release syndrome, serious anaphylactic reactions)	£220.38	Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 260, service description: Paediatric Clinical Immunology and Allergy Service
Capillary Leak Syndrome	£2,834.88	Non-Elective Long Stay: Currency Code: PX57A; Currency Description: Paediatric, Examination, Follow-Up, Special Screening or Other Admissions, with CC Score 4+
Eye problems	£118.59	Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance first attendance, service code: 216, service description: paediatric ophthalmology
Peripheral neuropathy	£343.79	Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 421, service description: paediatric neurology
Pyrexia, Infection	£358.97	Day cases, currency code: PW20B, currency description: paediatric fever of unknown origin with CC score 2+
Vomiting, Diarrhoea	£547.96	Day cases, currency code: PF26B, currency description: paediatric other gastrointestinal disorders with CC score 1–3

5.4.9.3 ERG critique

One of the main drivers of the cost-effectiveness results is BSA. This parameter is the basis for calculating the dosage of the majority of the drugs included in the economic analysis and as such has a substantial influence on total costs. Median BSA from APN311-302 ($0.63m^2$) has been used for most of the cost calculations in the model. The ERG's clinical experts reviewed the BSA data used in the analysis and confirmed that the data seem reasonably reflective of what would be seen in UK clinical practice. Nonetheless the ERG notes that the estimates used are based on median values instead of mean BSA values. The ERG calculated the mean BSA for the entire trial population in APN311-302 and arrived at an estimate of $0.67m^2$ (mean age in the trial was four years). Not only are the median and mean estimates similar, but the ERG also replaced the median BSA by the mean BSA in the model, and concluded that the change had no impact on the final ICER.

However, while in patients with an average BSA of $0.63m^2$, 4 vials of dinutuximab beta are required, in patients with a BSA greater than $0.83m^2$, 6 vials may be required to achieve the recommended dose for dinutuximab beta. The company does not provide the BSA categories for APN311-302, but from the maximum height and weight provided in the CSR, the ERG estimated a maximum BSA of $1.66m^2$ in the trial. It remains uncertain what percentage of patients would have a BSA greater than $0.83m^2$ and thus require 6 vials of treatments. The company assessed the impact of changing the BSA estimate used in the economic model on the final ICER by using the upper and lower bounds of BSA values in the APN311-302 population. The results are presented in Table 52, and it can be seen that when the maximum BSA is considered, the impact on the final ICER is considerable. The ERG's preferred assumption would be to use a weighted average dose of vials per cycle according to the BSA categories in APN311-302.

Table 52. Body surface area deterministic sensitivity analysis

Model	Lower BSA ICER	Upper BSA ICER
High-risk (0.37 – $1.66m^2$)	£9.083	£61,576
Abbreviations: BSA, body surface area; ICER, incremental cost-effectiveness ratio; m^2, metre square.		

The ERG has concerns regarding the estimation of IL-2 costs in the high-risk model. The marketing authorisation states that, "*in patients with a history of relapsed/ refractory disease and in patients who have not achieved a complete response after first line therapy, dinutuximab beta should be combined with interleukin 2 (IL-2)*". During the clarification stage the ERG asked the company to include the costs of IL-2 (including administration and hospitalisation costs) in the high-risk model to accurately reflect the proportion of patients who received IL-2 in APN311-302 (51% randomised to IL-2). In their clarification response, the company explained that concomitant administration of IL-2 does not have an impact on EFS or OS and thus patients will not receive it in clinical practice. However, as mentioned in Section 5.4.9.2.1, and even though the company seems to imply that IL-2 costs were not included in

the model, all patients in the high-risk model were considered to receive IL-2 (and therefore costed as such). Given that the company's reply to the ERG's clarification's request seems to imply that the company's intention was to not include IL-2 costs in the high-risk model, but the model costs IL-2 treatment for 100% of patients, the ERG considered this to be a mistake in the model. The correction applied by the ERG changed the 100% assumption to 51% of patients receiving IL-2 in the model (given that 51% in APN311-302 received IL-2). This estimate is not very dissimilar to the proportion of patients with evidence of disease at baseline in APN311-302 (41%), which according to the marketing authorisation would be the group of patients receiving IL-2 concomitantly with dinutuximab beta in clinical practice. Furthermore, the company has not included the administration costs associated with treatment with IL-2 in the model. Therefore, the ERG has included these costs for patients receiving treatment with IL-2. Results of the ERG's analysis are reported in Section 6.

Concomitant medication costs have included wastage, except for gabapentin The ERG lists this a relevant scenario analysis (i.e. adjusting the calculation of gabapentin to include wastage) and reports this in Section 6.

Patients received five cycles of treatment with isotretinoin. It is unclear to the ERG why the company modelled five cycles of treatment with isotretinoin instead of six, which is the recommended clinical practice. The ERG ran a scenario analysis including six cycles of isotretinoin in the intervention and comparator arms of the economic model. Not surprisingly, the increase in costs in both treatment arms cancelled out and the final ICER did not change.

5.4.9.4 Stable health state resource use

The ERG considers that the approach to estimating resource use in the stable state is reasonable. The company assumed that stable health state costs apply for the lifetime of the model, including the period after patients achieve the cure threshold. This assumption was not justified in the CS. The ERG's clinical experts explained that if patients reach the cure threshold, their health would not be equal to that of the general population as they are more likely to experience other health issues during the rest of their lives. As such the ERG considers that it is reasonable to assume that neuroblastoma survivors will have greater health resource utilisation than the general population (as also reported in the study by Rebholz *et al*. 2011[84]) for the remainder of their lifetime.

5.4.9.5 Failure health state resource use

Resource use for the failure state was based on the treatment regimen of a phase II RCT of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma (defined as first recurrence or progression after treatment with aggressive multidrug therapy or second recurrence after a single regimen of aggressive chemotherapy after first recurrence).[64] The ERG recognises that prior treatment with immunotherapy is not part of the inclusion criteria for the RCT,

and considers that this could be due to the timing of the published study (2010) coinciding with the publication of the results for immunotherapy use in neuroblastoma (Yu *et al*. 2010[29]). The ERG's clinical experts confirmed that this treatment regimen for relapsed patients is reasonable, but it is one of a variety of options available. The ERG's clinical experts added that currently there is not a defined NHS pathway for treating patients with relapsed neuroblastoma and all patients would be treated through a clinical trial. Thus, the ERG considers that the treatment regimen assumed for patients in the failure state is reasonable.

As requested by the ERG during clarification stage, the company adjusted the cost per cycle to reflect changes in population weight by multiplying the dose required each cycle by the cost per unit of weight of each drug. However, when the company implemented this, it did not take into account wastage. Therefore, the ERG lists this a relevant scenario analysis (adjusting the failure state costs to account for wastage) and reports this in Section 6.

Furthermore, the ERG assessing the STA for dinutuximab alpha (GID-TAG507) pointed out that the administration cost used for the failure state is not appropriately estimated, as it is based on a procurement cost for chemotherapy drugs rather that the delivery of the therapy. Instead, given the failure state treatment regimen will be delivered as inpatient care over 5 days (topotecan/cyclophosphamide is given intravenously for 5 days), an inpatient hospital cost would have been more appropriate.[64] The ERG agrees and considers that the company should have used the cost of a hospital day (£934 per day as presented in Table 46) to calculate the administration costs per cycle, which amounts to a total of £4,670 for 10 days in the hospital (which compares to the chemotherapy procurement cost of £2,620.54 used in the model originally). Therefore, the ERG lists this a relevant scenario analysis (adjusting the failure state costs to account for wastage) and reports this in Section 6.

In the model, once patients enter the failure health state, they accrue the costs associated with the failure state until dead. However, based on the study by London 2010[64] and as mentioned in the CS, the treatment regimen associated with the failure state should only be given until further disease progression or up to one year without progression. Therefore, it would have been more appropriate to calculate the proportion of newly relapsed patients entering the failure state in each cycle and tracking disease progression for these patients. The approach taken by the company, although not justified, can be seen as a proxy for subsequent treatments in the model. This however, implies that all patients will have subsequent relapses in the model. If one assumes that everyone in the FS will experience disease progression, and therefore switch to a different subsequent treatment, then it could be hypothesised that having patients in the FS accruing treatment costs until death is a proxy for the costs of subsequent treatments. This assumption is caveated by the fact that some patients would not experience further disease progression and would stop treatment after a year, and also by the uncertainty in the cost of

subsequent treatments. Therefore, it is likely that the FS treatment costs are being overestimated in the analysis.

Finally, upon investigation of both stable and failure state health costs, the ERG found that the undiscounted (instead of the discounted) total costs for the short-term model were being included in the final ICER. As mentioned in Section 5.4.4.1, the ERG also found an error in the discounting applied in the model and in the inclusion of costs from the first model cycle in the final results. Therefore, the ERG corrected these in the model and results are presented in Section 6.

5.5 Results included in company's submission

5.5.1 Base case results

According to the company's updated base case analysis, the ICER for dinutuximab beta compared with isotretinoin is £22,338 per QALY gained, for the high-risk population. The company's revised base case ICERs for the high-risk model is reported in Table 53.

Table 53. Company's revised base case results – high-risk population

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£190,521	13.97	-	-	£22,338
Dinutuximab beta + isotretinoin	£311,569	19.39	£121,048	5.42	
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.					

5.5.2 Sensitivity analysis

5.5.2.1 Scenario analysis

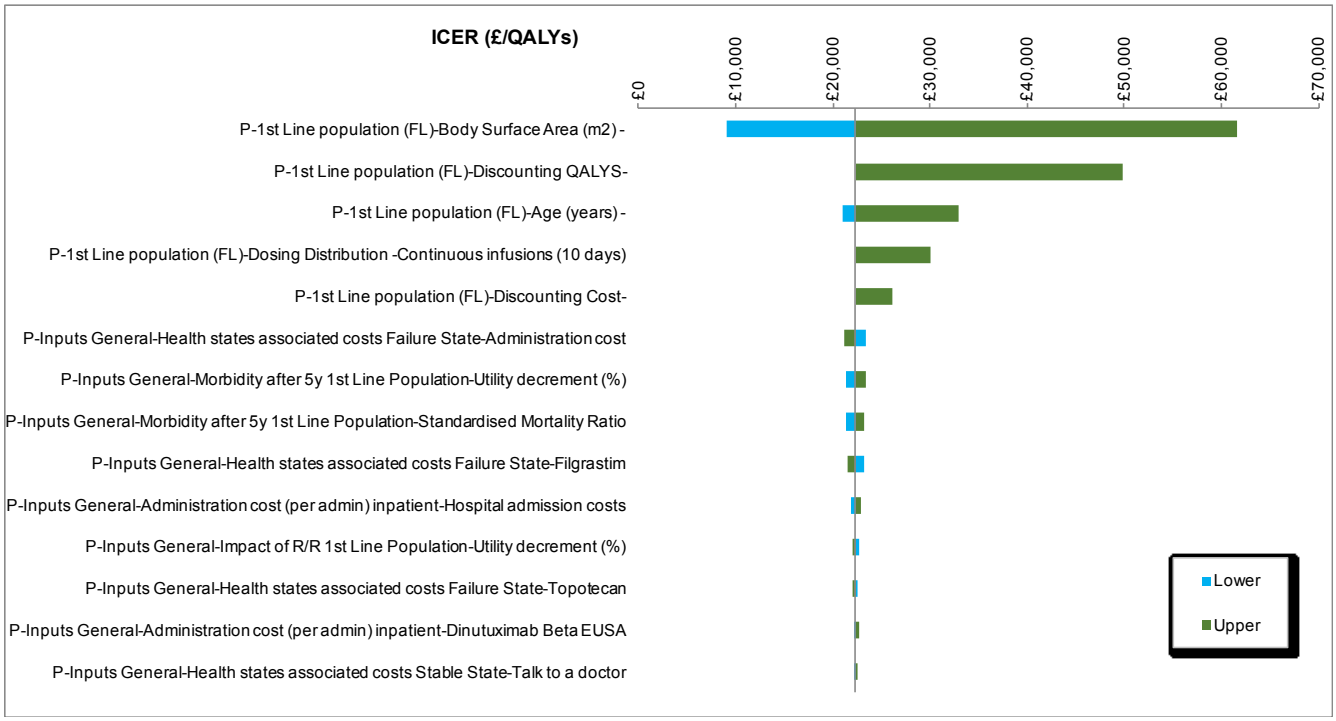
The company carried out a range of scenario analyses exploring the impact of changing assumptions surrounding various parameters. Some analysis were provided in the updated model, however, the ERG found a few mistakes in these analysis. For example, the company reports that a scenario analysis was undertaken to assess the impact of using a 31.5% utility decrement for the stable health state (instead of 12.5%) and provides the results, but the latter correspond to changing the discount rate in the model from 1.5% to 3.5% in the analysis. Given the uncertainty in the company's reported results, and the limited time available to review and correct the company's scenario analysis, the ERG lists all the relevant scenario analysis that should be undertaken, once the base case ICER is considered robust. These are reported in Section 6.

5.5.2.2 One way sensitivity analysis

The results of the company's one-way sensitivity analysis (OWSA) on the updated model are presented in Figure 34. According to the analysis the main drivers of the high-risk model are the BSA used in the

cost calculations and discount rate applied to QALYs. Using the upper and lower limits of BSA causes the ICER to range from £9.083 to £61,576 per QALY gained.

Figure 34. Tornado diagram for deterministic sensitivity analysis results for the high risk model (Figure 1, company clarification response part 2)



5.5.2.3 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the updated base case results. The results across 1,000 iterations are presented in Table 55. The PSA results produced a mean ICER of £22,171 per QALY gained for dinutuximab beta + isotretinoin compared to isotretinoin for the high-risk population. The scatterplots, and cost-effectiveness acceptability curves are presented in Figure 35 and Figure 36. The ERG is concerned with the face validity of Figure 35 and Figure 36. When analysing Figure 35, it is noticeable that the company's PSA only impacted the incremental costs. Therefore, the observations concentrate vertically, indicating that varying all parameters in the model simultaneously, only seemed to have led to a variation in incremental costs from zero to £150,000, and a variation in incremental QALYs between 4.5 and 5.5 QALYs gained (however, for the higher incremental costs, the incremental QALYs seem to draw a vertical line at 5.5 QALYs gained). The main reason for this is that treatment effectiveness was not explored in the company's PSA, as there were no parameters related with relative treatment effectiveness in terms of OS or EFS included in the PSA. The only parameters included in the PSA that would vary QALY estimation in the analysis are related with the assumed mortality rates in the long-term model and the utility values used for the EFS and the FS states in the model.

The other contributing factor is that the parameters varied (shown in Table 54) were not allowed to vary a great amount in the analysis. The utility decrements were varied by using a beta distribution. The ERG disagrees with the use of a beta distribution in this case, as the parameter is a decrement estimate, and not a probability. Therefore, using a beta distribution assuming that (in the case of the utility decrement applied to the EFS state, as an example) 12.5% is the proportion of events of interest observed and 87.5% (100% - 12.5%) is the proportion of "non-events", is not appropriate in this case, as these are not binomial data.

In conclusion, the ERG does not consider that the PSA undertaken by the company is informative in this case, as it does not account for the uncertainty in the effectiveness and QALY-estimation aspect (therefore on the x axis of Figure 35) of the sensitivity analysis.

Table 54. Parameters included in PSA influencing QALY estimation

Parameter (base case value)	Distribution used	Mean	Minimum	Maximum
Utility decrement applied to the EFS state, compared with general population (12.5%)	Beta (12.5, 87.5)	12.6%	4.8%	26.4%
Utility decrement applied to the FS state, compared with general population (41.7%)	Beta (41.7, 58.3)	42%	29%	58%
Standardised mortality factor for patients in the EFS state in the long-term model, compared with the general population (5.6)	Normal (5.6, 0.6)	5.6	3.9	7.6
Increase in mortality for patients in the FS state in the long-term model, compared with the patients in the EFS state (90%)	Beta (90, 10)	90%	77%	97%

Table 55. PSA results for the high-risk model (Table 30, company clarification response part 2)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£190,005	14.04	-	-	£22,171
Dinutuximab beta	£311,576	19.49	£121,571	5.45	
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.					

Figure 35. Cost-effectiveness plane for dinutuximab beta for the high-risk model with a £30,000/QALY threshold - revised model (Figure 2, company clarification response part 2)

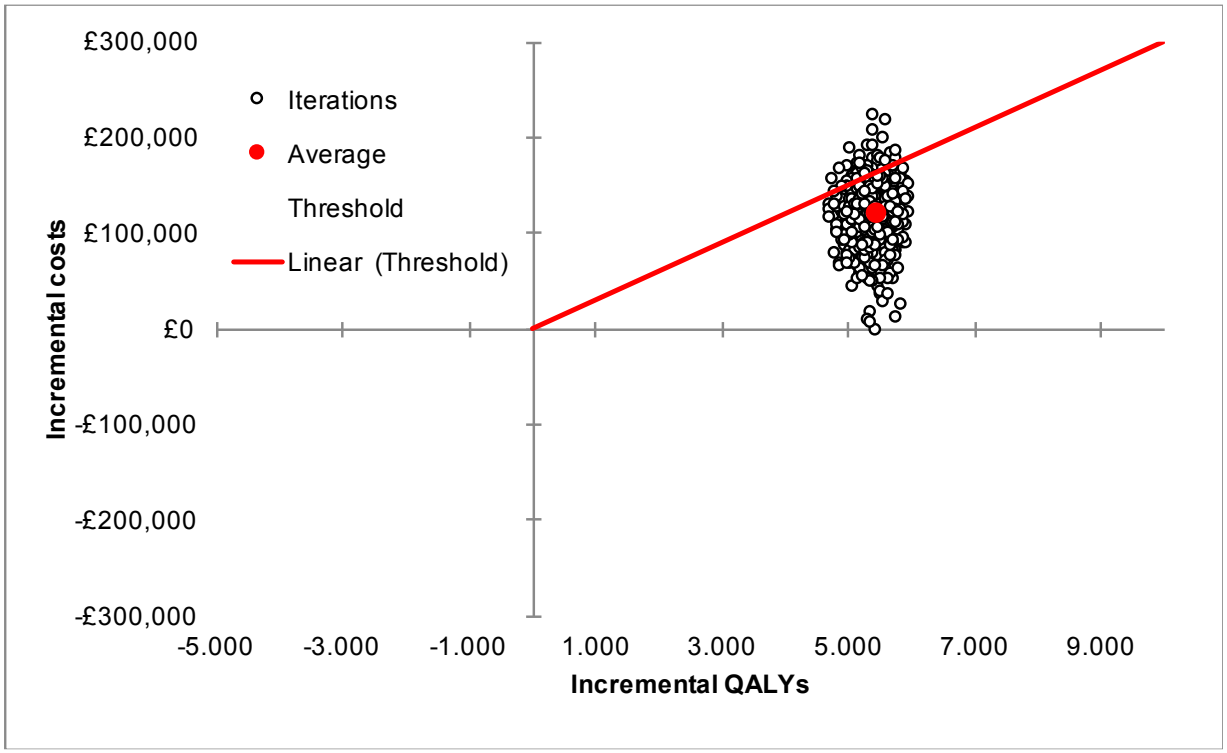
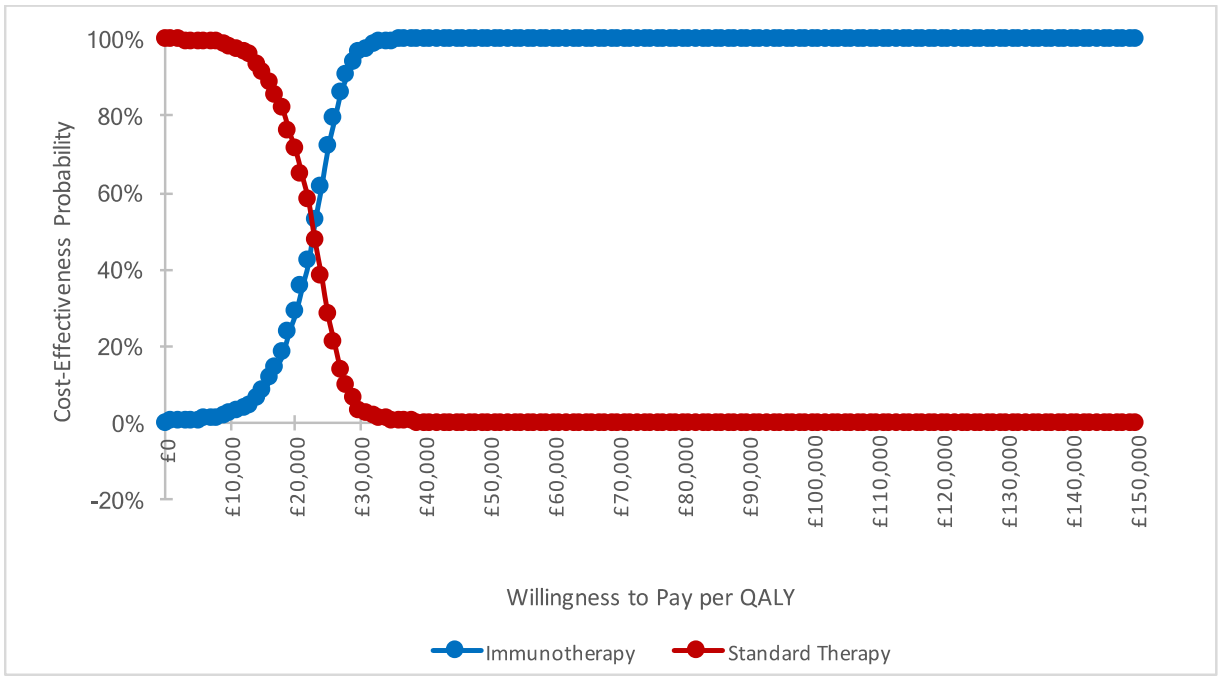


Figure 36. Cost effectiveness acceptibility curve for dinutuximab beta for the high-risk model - revised model (Figure 3, company clarification response part 2)



5.5.3 Model validation

The CS reports that clinical experts validated the model clinical inputs. The company does not report having undertaken any quality assessment of the model or any validation processes (including formula checking) or model functionality.

As reported throughout the report, the ERG is extremely concerned with the internal validity of the economic model, as a considerable number of mistakes in data implementation was found, and there is no reference in the CS, or any other company's correspondence of the model having undergone internal validity checks.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG described the errors found in the company's analysis throughout Section 5 of the report. These are summarised here, together with the combined impact of the corrections on the final ICER. The ERG made the following corrections:

1. The long-term model has annual cycles which have not been adjusted. Therefore, the ERG applied a half-cycle correction in the long-term model;

2. The ERG identified an error in the formulae used by the company, where the 5.6 increase in mortality factor was being applied to female mortality instead of the weighted male and female mortality in the UK general population;

3. The company included the cost of treatment with IL-2 in the isotretinoin arm of the economic model. This was not reported in the CS, and the ERG does not see a clinical justification for IL-2 to be given with isotretinoin. Therefore, the ERG removed the costs of IL-2 from the isotretinoin arm of the model;

4. The CS reports that treatment with dinutuximab beta requires hospitalisation for 10 days for the first treatment cycle and 5 hospital days for the second cycle. However, in the model the company has assumed 7.5 hospital days for the first cycle and 2.5 days for the second cycle, with no justification provided for the deviation. Therefore, the ERG has corrected this in the model, to reflect the hospitalisation schedule reported in the CS (also supported by the ERG's clinical experts);

5. The ERG changed the 100% assumption to 51% of patients receiving IL-2 in the dinutuximab beta arm of the model (given that 51% of patients in APN311-302 received IL-2);

6. The company has not included the administration costs associated with treatment with IL-2 in the model. Therefore, the ERG has included these costs for patients receiving treatment with IL-2;

7. The ERG found that undiscounted total costs for the stable and failure states of the short-term model were being included in the final ICER. Therefore, the ERG replaced these with discounted costs;

8. The company did not include the first row of costs and QALYs in the Excel model results. Therefore, the sum of all model outcomes, included in the final ICER, excluded the costs and benefits related with the first model cycle. The ERG corrected this in the model.;

9. The discounting factor being applied in the model was estimated on a monthly basis instead of an annual basis. For example, at 1.5 years in the model, instead of using an annual discount factor of 1, the company used a discount factor of 1.5. The ERG corrected this to reflect annual discounting in the analysis.

The company's base case results with the implemented ERG's corrections are presented in Table 56 below. The company's base case ICER rose from £22,338 to £31,366 per QALY gained, when the corrections were applied.

Table 56. Company's corrected base case results – high-risk population

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£172,236	13.61	—	—	£31,366
Dinutuximab beta + isotretinoin	£36,172	18.83	£163,808	5.22	
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.					

As discussed in Section 5.4.5, the ERG does not consider that a naïve comparison of APN311-302 and R1 data is a reliable method for estimating treatment effectiveness. Therefore, the ERG used the only available evidence providing an alternative to the company's analysis. This consisted on the following:

3. Restructuring the high-risk economic model to incorporate the use of the OS HR ([redacted]) to estimate OS for isotretinoin.

4. Using the relative difference between the OS HR and the EFS HR (for dinutuximab alpha compared with isotretinoin) in the dinutuximab alpha submission and applying it to the adjusted OS HR estimated for dinutuximab beta of [redacted]. The ERG notes that the EFS HR for dinutuximab alpha vs isotretinoin was found to be not statistically significant in the dinutuximab alpha STA (GID-TAG507). The ERG's estimated EFS HR for dinutuximab beta compared with isotretinoin is 1.656/1.319*[redacted]=[redacted];

As discussed in Section 5.4.5, the ERG replaced the dinutuximab beta KM curves for OS and EFS by the fitted and extrapolated Gompertz curves in the short-term model, in order to estimate OS after the 7-year KM OS curve, and also to try and minimise the structural issues found in the KM data from APN311-302. In doing so, the ERG had to subsequently cap the EFS curve by the OS curve in the isotretinoin arm of the model as the curves cross in the model at approximately 70 months.

The company's base case results with the implemented ERG's corrections and the applied HRs to estimate isotretinoin curves are presented in Table 57 below. Using HRs to estimate relative treatment effectiveness in the model leads to an ICER of £111,858 per QALY gained (with all the ERG's corrections incorporated in the analysis).

Table 57. Company's corrected base case ICER with HRs incorporated

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£29,898	16.12	—	—	£111,858
Dinutuximab beta + isotretinoin	£331,939	18.82	£302,041	2.70	
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.					

As explained in Section 5.4.5.2.3, the ERG considers that while some of the amendments made to the model provide step changes in the right direction, when combined in the final analysis these produce inconsistent outcomes and introduce a paramount level of uncertainty in the analysis. Therefore, the ERG does not consider that the changes made to the company's model produce an ICER sufficiently robust to inform decision making and emphasises that the results shown in Table 57 are provided for illustrative purposes only.

6.2 ERG's recommended scenario analysis

The scenario analyses which the ERG considers relevant are explained throughout Section 5 of the report. However, due to the problems encountered when estimating a relative treatment effectiveness measure and the underlying uncertainty in the KM OS and EFS data for APN311-302, the ERG's assessment is that the departing ICER of £111,858 is fundamentally flawed. Therefore, the ERG did not proceed to implement the different scenario analyses as all the resulting ICERs would be departing from a fundamentally flawed base case estimate and thus meaningless.

The ERG lists below the analyses that would be required to explore further uncertainty in the economic model, once the base case ICER is robust enough to be used to carry sensitivity analysis:

1. Changing the assumption that patients entering the failure state of the economic model receive chemotherapy for the rest of their lives. In the base case model, some patients receive chemotherapy for more than 20 years, which is not clinically plausible. Therefore, the partitioned survival model should be changed to estimate newly progressed patients in both the dinutuximab beta and isotretinoin arms of the model. Once newly progressed patients are estimated, an assumption needs to be made for treatment duration. For example, it could be assumed that relapsed patients would stay on treatment for a maximum of one year. An assumption should also be made for the resource use required to manage relapsed patients who have gone off chemotherapy treatment, but are still alive and in the failure state;

2. The cost estimations regarding the chemotherapy regimens used in the failure state should include wastage;

3. The cost of treatment administration in the failure state should use the cost of an inpatient stay (£4,670 for five days), instead of procurement cost for chemotherapy drugs, which is used in the base case model (£2,620.54);

4. Concomitant medication costs in the stable state should include wastage for gabapentin;

5. The proportion of patients receiving IL-2 in the dinutuximab beta arm of the model should be explored. Instead of assuming that 51% of patients received IL-2 (as per APN311-302), the assumption that 41% of patients would receive IL-2 should also be explored. This is to reflect the fact that 41% of children in APN311-302 had residual disease at baseline and therefore would require IL-2 as a concomitant medication, as per dinutuximab beta's licence;

6. The previous STA for dinutuximab alpha (GID-TAG507) reported a published algorithm by Ara *et al.* 2010,[96] which was used to estimate mean EQ-5D HSUVs for individuals in the general population, using a multiple regression including gender, age and age^2 as covariates. The ERG considers this method to be more appropriate than using a logistic regression, as it produces utility values rather than probabilities and is based on a published, peer-reviewed methodology. Therefore, the ERG recommends that the logistic regression in replaced with the published multiple regression to estimate age-specific UK EQ-5D in the model;

7. Given that BSA is one of the key drivers of costs in the economic model, a weighted analysis of costs taking into consideration the proportion of patients falling into different BSA categories would be advisable (for example, while in patients with an average BSA of 0.63m^2, 4 vials of dinutuximab beta are required, in patients with a BSA greater than 0.83m^2, 6 vials may be required to achieve the recommended dose for dinutuximab beta);

8. A discount rate of 3.5% (instead of 1.5%) for costs and benefits should be used to explore structural uncertainty in the analysis;

9. Probabilistic sensitivity analysis should be undertaken to incorporate the impact of varying relative treatment effectiveness estimates on the final ICER.

7 END OF LIFE

The company does not explicitly state that they are requesting that dinutuximab beta be considered in the end of life setting, but they provide a rationale for end of life considerations outlined by the National Institute for Health and Care Excellence (NICE; Table 58). The ERG disputes the company's assertions, as outlined in Table 58. In brief, data reported in the CS contradict data cited by the company in support of a life expectancy of less than 24 months in high-risk neuroblastoma, and the evidence submitted in support of the application does not quantify the additional survival time, if any, afforded by dinutuximab beta-based maintenance therapy over isotretinoin alone (Table 58).

Table 58. End of life considerations

NICE criterion	Company assessment	ERG assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Children diagnosed with high-risk neuroblastoma have a poor prognosis. Based on the historical controls included in this submission (the Italian Neuroblastoma Registry from 1979 to 2006 (Garaventa *et al*. 2009) and the SIOPEN HRNBL1 in an earlier phase (R1, 2002-2010)), survival in both relapsing and high-risk patients is expected to be shorter than 2 years. Indeed, the median survival for relapsing patients who did not receive immunotherapy (Garaventa control) was 318 days. Similarly, for high-risk patients included in the SIOPEN HRNBL1 study and who did not receive immunotherapy (R1 control), the median survival was 629 days.	The ERG agrees with the company that prognosis of people with high-risk neuroblastoma is poor, but questions the company's estimate of median survival of 629 days for those not receiving immunotherapy in historical control R1. It is unclear whether the data cited are post-relapse. In the CS, the company reports a median OS of 1,869 days (95% CI 1,304 to 3,302 days) and a mean OS of 2,447.1 days (SE 90.3 days) for those receiving isotretinoin alone (historical control R1). Based on the data reported in the CS, the ERG considers that the end of life criterion of life expectancy of less than 24 months has not been met for high-risk neuroblastoma.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Immunotherapy with dinutuximab beta and 13-cis RA with or without IL-2 has shown to provide statistically significantly better OS for patients with high-risk neuroblastoma as compared to patients receiving standard of care treatment without immunotherapy. Study APN311-303 and -202: 54.2% of the patients died in the APN311-202 + APN311-303 group compared to 86.2% patients in the historical control group (Garaventa study). Median OS time was longer in APN311-202+ APN311-303 patients compared with the historical control patients (1254 days vs. 318 days, respectively). Most of the relapsed patients of the APN311-202+APN311-303 group survived the first year and 50% of the patients survived until the third year (1-year, 2-year, and 3-year OS rates of 83%, 60% and 50%, respectively). Of the relapsed patients from the Garaventa study included in this analysis, less than 50% survived the first year and only 24% survived the third year (1-year, 2-year, and 3-year OS rates of 45%, 31% and 24%, respectively). The difference in OS was statistically highly significant (p = 0.0031), in favour of dinutuximab beta. The same trend was observed by comparing these two studies vs the historical control R1. The median OS was substantially longer in patients in the combined APN311-202+APN311-303 group (1254	Although the log rank test indicated that there is a statistically significant difference between dinutuximab beta-based maintenance therapy and isotretinoin alone in OS in high-risk neuroblastoma (p <0.0001), an estimate of the additional survival time afforded, if any, is not yet available. Moreover, as highlighted in its critique, the ERG considers that OS data for APN311-302 are immature. For relapsed neuroblastoma, as discussed in its critique, the ERG considers that the populations enrolled in APN311-202 and APN311-303 are not representative of those experiencing relapse in the UK.

	days) than in the historical control R1 (630 days). In addition, yearly OS rates were clearly higher than in the historical control R1 group. OS in the APN311-202 + APN311-303 combined group was 83% at 1 year, 60% at 2 years and 50% at 3 years, compared to 56%, 46% and 28%, respectively, in historical control R1. Study APN311-302: A lower percentage of patients died in the MAT+immunotherapy group compared with the historical control who did not receive immunotherapy (31.3% vs 52.9%, respectively). The vast majority of the patients in the MAT+immunotherapy group survived the first year and more than 70% of the patients survived the third year (1-year, 2-year, and 3-year OS rates of 89%, 78% and 71%, respectively). Of the MAT patients, the majority survived the first year, but only 59% survived the third year (1-year, 2-year, and 3-year OS rates of 83%, 69% and 59%, respectively). These differences were statistically significant ($p<0.0001$) in favour of dinutuximab beta.	
The treatment is licensed or otherwise indicated, for small patient populations	Not discussed	Dinutuximab beta was designated an orphan medicinal product on 8 November 2012.[39] An orphan medicine is a treatment for a debilitating condition that affects no more than 5 in 10,000 people in the European Union, or where the medicine is unlikely to generate sufficient profit to justify research and development costs.[39]

8 OVERALL CONCLUSIONS

The clinical evidence presented in the company's submission (CS) for dinutuximab beta-containing maintenance treatment is derived from one open-label randomised study, APN311-302, in high-risk neuroblastoma and two single-arm observational studies, APN311-202 and APN311-303, in relapsed and refractory neuroblastoma. None of the identified studies presents direct evidence on the comparative clinical effectiveness of dinutuximab beta versus comparators of interest to the decision problem.

The main objective of APN311-302 was to evaluate the clinical benefit of adding interleukin-2 (IL-2) to dinutuximab beta and differentiation therapy with isotretinoin in people with high-risk neuroblastoma who had achieved at least a partial response to induction therapy and had gone on to complete consolidation therapy with myeloablative chemotherapy and autologous stem cell transplant (ASCT): the population included in APN311-302 aligns with the European marketing authorisation for dinutuximab beta. The primary outcome of APN311-302 was EFS at 3 years. APN311-302 is a single phase of the High-Risk Neuroblastoma (HR-NBL-1) clinical trial, which had several randomisation phases and was set up to test various hypotheses in treating high-risk neuroblastoma.

The population enrolled in APN311-302 was comparable with people in the UK who would likely be eligible for treatment with dinutuximab beta in the UK: moreover, a large proportion of people were recruited from the UK ([redacted]). The ERG has several concerns around the design and conduct of APN311-302, which impact on confidence in the results generated from indirect comparison, including:

- potential lack of concealment of allocation;
- potential lack of masked independent review of disease progression;
- lack of intention-to-treat (ITT) analysis;
- loss of electronic case report forms (eCRFs) for some people;
- use of rapid infusion schedule of dinutuximab beta, where continuous infusion would be preferred in UK clinical practice;
- short duration of follow-up, potentially insufficient to evaluate fully the clinical effectiveness of dinutuximab beta;
- lack of pre-specified regular follow-up assessment;

- disparity between groups [redacted].

To inform a naïve indirect comparison versus isotretinoin, the company created a historical cohort (450 people) derived from people enrolled in an earlier phase of the HR-NBL-1 study than those enrolled in APN311-302. People forming the historical control R1 were randomised in the R1 phase of HR-NBL-1, which was designed to compare the effectiveness of BuMel (busulfan and melphalan hydrochloride) versus CEM (carboplatin, etoposide and melphalan) as consolidation myeloablative therapy in high-risk neuroblastoma. After induction therapy and myeloablative therapy followed by ASCT, people received only isotretinoin during the maintenance phase. Baseline characteristics for the full population of APN311-302 and the historical control R1 indicate that the groups are similar in terms of key prognostic factors. However, one difference between APN311-302 and the historical control R1 is the proportion of people receiving BuMel as their consolidation myeloablative therapy: the R1 phase of HR-NBL-1 established that BuMel was the more effective consolidation therapy and the regimen became the standard of care. In APN311-302, 383 people from the 406 (94.3%) initially randomised received BuMel. By contrast, because the R1 randomisation phase of HR-NBL-1 was designed to compare the effectiveness of BuMel versus CEM, half of the people in the R1 phase received CEM as their consolidation therapy (302/598; 50.5%). The exact proportion of the 450 people in the historical control R1 who received CEM as consolidation therapy is unclear from the CS, but it is likely to be substantially lower than that in APN311-302: the ERG considers that the maximum number of people who could have received CEM in the historical control is 71.1% (302/450).

A comparative estimate of clinical effectiveness of dinutuximab beta-containing regimen versus isotretinoin is available for only OS. In the naïve indirect comparison, the log rank test identified a statistically significant difference in OS between dinutuximab beta, with or without IL-2, in combination with isotretinoin compared with isotretinoin alone that favoured immunotherapy-based treatment ($p<0.0001$). A multivariate Cox regression analysis found that dinutuximab beta, with or without IL-2, plus isotretinoin [redacted] compared with isotretinoin alone [redacted]): the HR was adjusted for the key prognostic factors of age, International Neuroblastoma Staging System (INSS) stage at initial diagnosis, MYCN status, and prior myeloablative therapy.

Evidence for clinical effectiveness of dinutuximab beta-based treatment in relapsed and refractory neuroblastoma is derived from two small observational studies – APN311-202 and APN311-303 – that included only those with relapsed or refractory neuroblastoma. The primary aim of both studies was to identify a tolerable treatment schedule of dinutuximab beta that reduced the pain and toxicity profile yet maintained the immunomodulatory effect of the immunotherapy. APN311-202 (N=44) is an ongoing study and so results are based on an interim analysis. APN311-202 is an open-label, single-

arm prospective study whereas APN311-303 (N=54) is a retrospective analysis of a compassionate use programme. APN311-202 and APN311-303 are single-arm observational studies and are, by nature, inherently at a high risk of bias. In addition, both studies have a small sample size in each subgroup of relapsed and refractory neuroblastoma, which leads to considerable uncertainty in any estimates of effect. A substantial amount of data, particularly for prognostic factors, were not captured in APN311-303 and, despite a review of the data, could not be retrieved. The retrospective nature of APN311-303 and absence of data could lead to selection bias, and a lack of standardisation in data recording and outcome assessment.

Based on the company's response to clarification, [redacted] in APN311-202 or APN311-303 has previously received treatment with dinutuximab beta. In the UK, people with high-risk neuroblastoma are likely have received dinutuximab beta as part of their front-line multimodal treatment because they participated APN311-302. As part of the clarification process, the company indicated that they do not support re-treatment with dinutuximab beta. Taking comments from clinical experts and the company together, the ERG considers that dinutuximab beta would not be considered as a treatment option in UK clinical practice for those experiencing relapse of high-risk neuroblastoma, which forms the largest proportion of those who relapse.

To generate estimates of comparative clinical effectiveness, the company utilised two historical cohorts derived from people with relapsed or progressed neuroblastoma. One historical cohort was generated from people enrolled in the R1 phase of the HR-NBL-1 study who experienced relapse during follow-up, historical control R1 (relapsed) comprising 52 people. The second historical control was based on data from a retrospective study of children with relapse or progression of neuroblastoma and captured in the Italian Neuroblastoma Registry from 1979 to 2006, the Garaventa historical control. People forming the Garaventa cohort had received tumour resection, chemotherapy, radiotherapy, and myeloablation followed by ASCT, but no immunotherapy, and are therefore representative of treatments used before dinutuximab beta-containing regimens in APN311-202 and APN311-303. Due to changes in neuroblastoma management, for the purposes of comparison with APN311-202 and APN311-303, Garaventa comprised only those with a date of initial diagnosis of 1999 or later, which led to a historical cohort of 29 people.

Various naïve indirect comparisons were reported for relapsed neuroblastoma: no comparisons for refractory neuroblastoma were presented, with the company stating that the data precluded comparative analyses.

[redacted]. The ERG concerns around the small sample size of the studies

informing the analyses, and the observational nature of the studies. Considering the quality of the studies informing the analysis, together with the naive indirect nature of the comparison, the ERG considers the results of the naïve indirect comparisons in OS to be unreliable and advises that the results are interpreted with extreme caution.

The ERG has serious concerns with the robustness of the economic analysis undertaken by the company. The second (updated) version of the company's model provided to the ERG incorporated paramount changes, which were only accompanied by a brief document as a reply to the ERG's clarification questions. Thus, most of the ERG's critique is based on the inspection of the economic model and not on written evidence submitted by the company. The ERG notes that several calculations and assumptions were changed in the updated model, without being reported or justified by the company (or requested by the ERG during the clarification stage). The consequences of this are twofold: the ERG cannot guarantee that some aspects of the economic analysis and/or economic model were not missed; and there were several instances where the ERG had to make assumptions with regards to what was the company's approach. The ERG identified implementation and formulae errors in the updated economic model (described throughout the report). The ERG is concerned that this reflects a poor level of internal quality assessment of the model by the company.

Overall, the company's modelling approach and model structure is unnecessarily burdensome and removes transparency from the formulae and calculations within the model. It is the ERG's view that the use of a decision-tree to estimate short-term outcomes was unnecessary, especially when the cohort data populating the decision-tree structure is taken from the cohort-based partitioned survival model. The decision-tree model is extremely difficult to navigate and has several circular references in its data implementation. All this makes the ERG's review unnecessarily complex. This also leads to a higher probability of errors in formulae, and a lower probability of all errors being identified during the ERG's review process. In total, the company's model was structured in three different model engines, the decision-tree model, the short-term partitioned survival model and the long-term partitioned survival model. The company could have simplified the model structure, and have a single cohort-based partitioned survival model, which would have been more efficient and transparent, and potentially avoided formulae, and calculation errors.

The ERG has severe concerns with the estimation of treatment effectiveness in the economic analysis. These, stem mainly from three overarching issues. The first one is related to the lack of face validity of the OS and EFS KM data from APN311-302. The second relates to the lack of maturity of OS data and the non-existence of EFS data in historical control R1. Finally, the third issue relates to the naïve (unadjusted) analysis of the relative effectiveness of dinutuximab beta, when compared with isotretinoin.

The ERG's proposed alternatives to overcome the methodological shortcomings of the company's analysis are, to some degree, flawed, when considered in isolation. However, when combined and incorporated in the final analysis, the synergies resulting from the individual changes made by the ERG, contribute to an increase in the level of uncertainty if the analysis.

The ERG identified issues relating with the estimation of costs and utility values in the economic analysis. These, however, only become relevant once the fundamental issues aforementioned are addressed.

8.1 Implications for research

The ERG considers there is a need for further research into:

- the relative effectiveness of dinutuximab beta-based maintenance therapy compared with isotretinoin and with dinutuximab alpha-based maintenance therapy in high-risk neuroblastoma, particularly in the long-term (10 years);
- the efficacy of dinutuximab beta-based therapy in those who have relapsed and who have and who have not received prior dinutuximab beta;
- the efficacy of dinutuximab beta-based therapy in those who are refractory to treatment and who have and who have not received prior dinutuximab beta;
- the effects of IL-2 in those with high-risk neuroblastoma and not achieving a complete response (i.e., those with a partial or very good partial response) to induction therapy;
- health-related quality of life for those with neuroblastoma and those surviving in the longer term.

9 REFERENCES

1. National Institute for Health and Care Excellence (NICE). APN311 for treating high-risk neuroblastoma. 2017. Available from: https://www.nice.org.uk/guidance/gid-ta10069/documents/final-scope. Last accessed 23 August 2017.
2. Shohet J, Foster J. Neuroblastoma. *BMJ*. 2017;357:j1863.
3. Cancer Research UK. Neuroblastoma. 2014. Available from: http://www.cancerresearchuk.org/about-cancer/childrens-cancer/neuroblastoma. Last accessed 23 August 2017.
4. Children's Cander and Leukemia Group. Neuroblastoma. 2017. Available from: http://www.cclg.org.uk/Neuroblastoma. Last accessed 29 September 2017.
5. Matthay KK, Maris JM, Schleiermacher G, Nakagawara A, Mackall CL, Diller L, *et al*. Neuroblastoma. *Nat Rev Dis Primers* 2016;2:16078.
6. Cohn SL, Pearson AD, London WB, Monclair T, Ambros PF, Brodeur GM, *et al*. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *J Clin Oncol* 2009;27(2):289–97.
7. Breslow N, McCann B. Statistical estimation of prognosis for children with neuroblastoma. *Cancer Res* 1971;31(12):2098–103.
8. Zhou MJ, Doral MY, DuBois SG, Villablanca JG, Yanik GA, Matthay KK. Different outcomes for relapsed versus refractory neuroblastoma after therapy with (131)I-metaiodobenzylguanidine ((131)I-MIBG). *Eur J Cancer* 2015;51(16):2465–72.
9. Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, *et al*. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. *New Eng J Med* 1999;341(16):1165–73.
10. London WB, Castel V, Monclair T, Ambros PF, Pearson AD, Cohn SL, *et al*. Clinical and biologic features predictive of survival after relapse of neuroblastoma: a report from the International Neuroblastoma Risk Group project. *J Clin Oncol* 2011;29(24):3286–92.
11. Moreno L, Rubie H, Varo A, Le Deley MC, Amoroso L, Chevance A, *et al*. Outcome of children with relapsed or refractory neuroblastoma: a meta-analysis of ITCC/SIOPEN European phase II clinical trials. *Pediatr Blood Cancer* 2017;64(1):25–31.
12. Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, *et al*. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol* 1993;11(8):1466–77.

13. Ness KK, Mertens AC, Hudson MM, Wall MM, Leisenring WM, Oeffinger KC, *et al*. Limitations on physical performance and daily activities among long-term survivors of childhood cancer. *Ann Intern Med* 2005;143(9):639–47.
14. Gurney JG, Tersak JM, Ness KK, Landier W, Matthay KK, Schmidt ML, *et al*. Hearing loss, quality of life, and academic problems in long-term neuroblastoma survivors: a report from the Children's Oncology Group. *Pediatrics* 2007;120(5):e1229–36.
15. Barrera M, Shaw AK, Speechley KN, Maunsell E, Pogany L. Educational and social late effects of childhood cancer and related clinical, personal, and familial characteristics. *Cancer* 2005;104(8):1751–60.
16. Jones BL. The challenge of quality care for family caregivers in pediatric cancer care. *Semin Oncol Nurs*. 2012;28(4):213–20.
17. Kazak AE, Alderfer M, Rourke MT, Simms S, Streisand R, Grossman JR. Posttraumatic stress disorder (PTSD) and posttraumatic stress symptoms (PTSS) in families of adolescent childhood cancer survivors. *J Pediatr Psychol* 2004;29(3):211–9.
18. Buchbinder D, Casillas J, Krull KR, Goodman P, Leisenring W, Recklitis C, *et al*. Psychological outcomes of siblings of cancer survivors: a report from the childhood cancer survivor study. *Psychooncology* 2011;20(12):1259–68.
19. Laverdiere C, Cheung NK, Kushner BH, Kramer K, Modak S, LaQuaglia MP, *et al*. Long-term complications in survivors of advanced stage neuroblastoma. *Pediatr Blood Cancer* 2005;45(3):324–32.
20. Laverdiere C, Liu Q, Yasui Y, Nathan PC, Gurney JG, Stovall M, *et al*. Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2009;101(16):1131–40.
21. National Cancer Institute. Neuroblastoma Treatment (PDQ®)–Health Professional Version. 2016. Available from: https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq#section/_230. Last accessed 27 September 2017.
22. NICE. Improving outcomes in children and young people with cancer, NICE guideline [CSG7]. 2005. Available from: https://www.nice.org.uk/guidance/csg7. Last accessed 23 August 2017.
23. NICE. Cancer services for children and young people, Quality Standard [QS55]. 2014. Available from: https://www.nice.org.uk/guidance/qs55. Last accessed 23rd August 2017.
24. NICE. Suspected cancer: recognition and referral, NICE guideline [NG12]. 2017. Available from: https://www.nice.org.uk/guidance/ng12. Last accessed 23 August 2017.
25. Children's Cancer and Leukemia Group. Treatment guidelines. 2017. Available from: http://www.cclg.org.uk/corecode/search/searchresults.aspx?q=guideline. Last accessed 26 September 2017.

26. Peinemann F, Tushabe DA, van Dalen EC, Berthold F. Rapid COJEC versus standard induction therapies for high-risk neuroblastoma. Cochrane Database of Systematic Reviews. 2015(5):CD010774.
27. Ladenstein R, Potschger U, Pearson ADJ, Brock P, Luksch R, Castel V, *et al*. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. *Lancet Oncol* 2017;18(4):500–14.
28. Children's Oncology Group. Neuroblastoma: In treatment. 2011. Available from: https://www.childrensoncologygroup.org/index.php/in-treatment-for-neuroblastoma. Last accessed 27 July 2017.
29. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, *et al*. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *New Eng J Med* 2010;363(14):1324–34.
30. Moreno L, *et al*. A randomised phase IIb trial of bevacizumab added to temozolomide +/- irinotecan for children with refractory/relapsed neuroblastoma [Protocol]. 2015. Available from: https://www.birmingham.ac.uk/Documents/college-mds/trials/crctu/beacon/BEACON-Protocol-v5.0a-23Sep2015-signed.pdf. Last accessed 10 October 2017.
31. National Institute of Health Reasearch. A phase IIa trial of 177 lutetium dotatate in children with primary refractory or relapsed high-risk neuroblastoma. 2012. Available from: http://www.hra.nhs.uk/news/research-summaries/ludo. Last accessed 10 October 2017.
32. EUSA Pharma Limited. APN311: Company Submission to NICE: Appendix L, Clinical Study Reports (CSRs) of main studies (APN311-202, APN311-302, APN311-303). 2017.
33. Spix C, Pastore G, Sankila R, Stiller CA, Steliarova-Foucher E. Neuroblastoma incidence and survival in European children (1978–1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;42(13):2081–91.
34. UK Office for National Statistics. Population statistics. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates. Last accessed 10 October 2017.
35. Cohn SL, Pearson AD, London WB, Monclair T, Ambros PF, Brodeur GM, *et al*. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *J Clin Oncol* 2009;27(2):289–97.
36. Kushner BH, Modak S, Kramer K, LaQuaglia MP, Yataghene K, Basu EM, *et al*. Striking dichotomy in outcome of MYCN-amplified neuroblastoma in the contemporary era. *Cancer* 2014;120(13):2050–9.
37. Bagatell R, Beck-Popovic M, London WB, Zhang Y, Pearson AD, Matthay KK, *et al*. Significance of MYCN amplification in international neuroblastoma staging system stage 1

and 2 neuroblastoma: a report from the International Neuroblastoma Risk Group database. *J Clin Oncol* 2009;27(3):365–70.

38. Baker DL, Schmidt ML, Cohn SL, Maris JM, London WB, Buxton A, *et al*. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. *New Eng J Med* 2010;363(14):1313–23.
39. European Medicines Agency (EMA). Dinutuximab beta Apeiron. European Public Assessment Report (EPAR). 2017. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003918/WC500227726.pdf. Last accessed 10 October 2017.
40. SIOPEN. High-risk neuroblastoma Study 1 of SIOP-Europe (SIOPEN). 2002. Available from: https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=0ahUKEwi-6_TMvr3VAhWEXhoKHfuUANIQFggsMAE&url=http%3A%2F%2Fwww.oncauvergne.fr%2Findex.php%3Foption%3Dcom_docman%26task%3Ddoc_download%26gid%3D928%26Itemid&usg=AFQjCNGXAPlUjPx8WC8S4wKgUBOm3Z83uw. Last accessed 4 August 2017.
41. EUSA Pharma Limited. APN311: Company Submission to NICE: Appendix L, Clinical Study Reports (CSRs) of main studies (APN311-202, APN311-302, APN311-303). 2017.
42. Yang RK, Sondel PM. Anti-GD2 strategy in the treatment of neuroblastoma. *Drugs Future* 2010;35(8):665.
43. EUSA Pharma (UK) Limited. APN311: Company Submission to NICE: Appendix C, Summary of Product Characteristics for dinutuximab beta EUSA. 2017.
44. US Food and Drug Administration (FDA). Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2007 Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf. Last accessed 16 August 2017.
45. NICE. Dinutuximab for treating high-risk neuroblastoma. 2015. Available from: https://www.nice.org.uk/guidance/gid-tag507/documents/committee-papers. Last accessed 14 July 2017.
46. National Institute for Health and Care Excellence (NICE). APN311 for treating high-risk neuroblastoma. 2017. Available from: https://www.nice.org.uk/guidance/gid-ta10069/documents/final-scope. Last accessed 23 August 2017.
47. Yalcin B, Kremer LC, van Dalen EC. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Cochrane Database Systematic Reviews. 2015(10):CD006301.

48. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. 2011.
49. European Medicines Agency. Unituxin (dinutuximab). 2017. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002800/human_med_001891.jsp&mid=WC0b01ac058001d124. Last accessed 28 July 2017.
50. Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, *et al*. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. *J Clin Oncol* 2009;27(7):1007–13.
51. Park JR, Villablanca JG, London WB, Gerbing RB, Haas-Kogan D, Adkins ES, *et al*. Outcome of high-risk stage 3 neuroblastoma with myeloablative therapy and 13-cis-retinoic acid: a report from the Children's Oncology Group. *Pediatr Blood Cancer* 2009;52(1):44–50.
52. Ashraf K, Shaikh F, Gibson P, Baruchel S, Irwin MS. Treatment with topotecan plus cyclophosphamide in children with first relapse of neuroblastoma. *Pediatr Blood Cancer* 2013;60(10):1636–41.
53. Donfrancesco A, Jenkner A, Castellano A, Ilari I, Milano GM, De Sio L, *et al*. Ifosfamide/carboplatin/etoposide (ICE) as front-line, topotecan/cyclophosphamide as second-line and oral temozolomide as third-line treatment for advanced neuroblastoma over one year of age. Acta Paediatr Suppl. 2004;93(445):6–11.
54. El-Sabban K, Al Sakhri H, Alsulaimani A, Al Malky T. Management of neuroblastoma. Comparative study between first-and second-line radioionated meta-iodobenzylguanidine therapy and chemotherapy alone. *Clin Cancer Invest J* 2013;2:41–7.
55. Garaventa A, Luksch R, Biasotti S, Severi G, Pizzitola MR, Viscardi E, *et al*. A phase II study of topotecan with vincristine and doxorubicin in children with recurrent/refractory neuroblastoma. *Cancer* 2003;98(11):2488–94.
56. George SL, Falzone N, Chittenden S, Kirk SJ, Lancaster D, Vaidya SJ, *et al*. Individualized 131I-mIBG therapy in the management of refractory and relapsed neuroblastoma. *Nucl Med Commun* 2016;37(5):466–72.
57. Hartmann O, Lumbroso J, Lemerle J, Schlumberger M, Ricard M, Aubert B, *et al*. Therapeutic use of 131I-metaiodobenzylguanidine (MIBG) in neuroblastoma: a phase II study in nine patients. *Med Pediatr Oncol* 1987;15(4):205–11.
58. Howard JP, Maris JM, Kersun LS, Huberty JP, Cheng SC, Hawkins RA, *et al*. Tumor response and toxicity with multiple infusions of high dose 131I-MIBG for refractory neuroblastoma. *Pediatr Blood Cancer* 2005;44(3):232–9.
59. Hutchinson RJ, Sisson JC, Shapiro B, Miser JS, Normole D, Shulkin BL, *et al*. 131-I-metaiodobenzylguanidine treatment in patients with refractory advanced neuroblastoma. *Am J Clin Oncol* 1992;15(3):226–32.

60. Johnson K, McGlynn B, Saggio J, Baniewicz D, Zhuang H, Maris JM, *et al*. Safety and efficacy of tandem 131I-metaiodobenzylguanidine infusions in relapsed/refractory neuroblastoma. *Pediatr Blood Cancer* 2011;57(7):1124–9.
61. Klingebiel T, Treuner J, Ehninger G, Keller KD, Dopfer R, Feine U, *et al*. [131I]-metaiodobenzylguanidine in the treatment of metastatic neuroblastoma. Clinical, pharmacological and dosimetric aspects. *Cancer Chemother Pharmacol* 1989;25(2):143–8.
62. Kushner BH, Kramer K, Modak S, Cheung NK. Irinotecan plus temozolomide for relapsed or refractory neuroblastoma. *J Clin Oncol* 2006;24(33):5271–6.
63. Ladenstein R, Potschger U, Hartman O, Pearson AD, Klingebiel T, Castel V, et al. 28 years of high-dose therapy and SCT for neuroblastoma in Europe: lessons from more than 4000 procedures. *Bone Marrow transplantation* 2008;41 Suppl 2:S118–27.
64. London WB, Frantz CN, Campbell LA, Seeger RC, Brumback BA, Cohn SL, *et al*. Phase II randomized comparison of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a Children's Oncology Group study. *J Clin Oncol* 2010;28(24):3808–15.
65. Matthay KK, Yanik G, Messina J, Quach A, Huberty J, Cheng SC, *et al*. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. *J Clin Oncol* 2007;25(9):1054–60.
66. Pession A, Prete A, Locatelli F, Pierinelli S, Pession AL, Maccario R, *et al*. Immunotherapy with low-dose recombinant interleukin 2 after high-dose chemotherapy and autologous stem cell transplantation in neuroblastoma. *British J Cancer* 1998;78(4):528–33.
67. Polishchuk AL, Dubois SG, Haas-Kogan D, Hawkins R, Matthay KK. Response, survival, and toxicity after iodine-131-metaiodobenzylguanidine therapy for neuroblastoma in preadolescents, adolescents, and adults. *Cancer* 2011;117(18):4286–93.
68. Saylors RL, 3rd, Stine KC, Sullivan J, Kepner JL, Wall DA, Bernstein ML, *et al*. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. *J Clin Oncol* 2001;19(15):3463–9.
69. Simon T, Berthold F, Borkhardt A, Kremens B, De Carolis B, Hero B. Treatment and outcomes of patients with relapsed, high-risk neuroblastoma: results of German trials. *Pediatr Blood Cancer* 2011;56(4):578–83.
70. Garaventa A, Parodi S, De Bernardi B, Dau D, Manzitti C, Conte M, *et al*. Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. *Eur J Cancer* 2009;45(16):2835–42.
71. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

72. Parikh NS, Howard SC, Chantada G, Israels T, Khattab M, Alcasabas P, *et al*. SIOP-PODC adapted risk stratification and treatment guidelines: Recommendations for neuroblastoma in low- and middle-income settings. *Pediatr Blood Cancer* 2015;62(8):1305–16.
73. Rubie H, Chisholm J, Defachelles AS, Morland B, Munzer C, Valteau-Couanet D, *et al*. Phase II study of temozolomide in relapsed or refractory high-risk neuroblastoma: a joint Societe Francaise des Cancers de l'Enfant and United Kingdom Children Cancer Study Group-New Agents Group Study. *J Clin Oncol* 2006;24(33):5259–64.
74. Basta NO, Halliday GC, Makin G, Birch J, Feltbower R, Bown N, *et al*. Factors associated with recurrence and survival length following relapse in patients with neuroblastoma. *British J Cancer* 2016;115(9):1048–57.
75. Simon T, Langler A, Harnischmacher U, Fruhwald MC, Jorch N, Claviez A, *et al*. Topotecan, cyclophosphamide, and etoposide (TCE) in the treatment of high-risk neuroblastoma. Results of a phase-II trial. *J Cancer Res Clin Oncol* 2007;133(9):653–61.
76. Bland JM, Altman DG. The logrank test. *BMJ*. 2004;328(7447):1073.
77. electronic Medicines Compendium. Proleukin: Summary of Product Characteristics. 2017. Available from: https://www.medicines.org.uk/emc/medicine/19322. Last accessed 9 October 2017
78. Siebert N, Jensen C, Troschke-Meurer S, Zumpe M, Juttner M, Ehlert K, *et al*. Neuroblastoma patients with high-affinity FCGR2A, -3A and stimulatory KIR 2DS2 treated by long-term infusion of anti-GD2 antibody ch14.18/CHO show higher ADCC levels and improved event-free survival. *Oncoimmunology* 2016;5(11):e1235108.
79. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, NJ W. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
80. Eficacy and tolerability of nitric-zinc complex in the treatment of external genital warts and "dificult-To-Treat" warts: A "proof of concept", prospective, multicentre, open study. Giornale Italiano di Dermatologia e Venereologia 150 (6) (pp 643-648), 2015. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/435/CN-01196435/frame.html.
81. Barr R, Furlong W, Horsman J, Feeny D, Torrance G, Weitzman S. The monetary costs of childhood cancer to the families of patients. *Int J Oncol* 1996;8(5):933–40.
82. Desai AV, Seif AE, Li Y, Getz K, Fisher BT, Huang V, *et al*. Resource utilization and toxicities after carboplatin/etoposide/melphalan and busulfan/melphalan for autologous stem cell rescue in high-risk neuroblastoma using a national administrative database. *Pediatr Blood Cancer* 2016;63(5):901–7.
83. George S, Buckle J. Health care utilisation and selected expenditures associated with neuroblastoma in england. *Value Health* 2014;17(7):A541.

84. Rebholz CE, Reulen RC, Toogood AA, Frobisher C, Lancashire ER, Winter DL, et al. Health care use of long-term survivors of childhood cancer: the British Childhood Cancer Survivor Study. *J Clin Oncol* 2011;29(31):4181–8.
85. Soderstrom L, Woods WG, Bernstein M, Robison LL, Tuchman M, Lemieux B. Health and economic benefits of well-designed evaluations: some lessons from evaluating neuroblastoma screening. *JNCI* 2005;97(15):1118–24.
86. Portwine C, Rae C, Davis J, Teira P, Schechter T, Lewis V, *et al*. Health-related quality of life in survivors of high-risk neuroblastoma after stem cell transplant: a national population-based perspective. *Pediatr Blood Cancer* 2016;63(9):1615–21.
87. Barr RD, Simpson T, Whitton A, Rush B, Furlong W, Feeny DH. Health-related quality of life in survivors of tumours of the central nervous system in childhood--a preference-based approach to measurement in a cross-sectional study. *Eur J Cancer* 1999;35(2):248–55.
88. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. 2013.
89. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data2013 01/03/2017. Available from: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf. Last accessed 10 October 2017.
90. Cai W, Wu R, Zhao H, Wang W, Wen D, Zhang J, *et al*. Institutional experience of five-day courses of irinotecan as palliative chemotherapy in chinese patients with refractory neuroblastoma HK. *J Paediatr* 2012;17: 223–9.
91. Wengenroth L, Gianinazzi ME, Rueegg CS, Luer S, Bergstraesser E, Kuehni CE, *et al*. Health-related quality of life in young survivors of childhood cancer. *Qual Life Res* 2015;24(9):2151–61.
92. Hudson MM, Mertens AC, Yasui Y, Hobbie W, Chen H, Gurney JG, *et al*. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA* 2003;290(12):1583–92.
93. Jubab A, Alnamshan M, AlTurki A, Marzogi M, Faris a. Quality of life in children treated for neuroblastoma: a multicentre study. *Int J Advanced Res* 2016;4(12):2725–31.
94. Mort S, Salantera S, Matomaki J, Salmi TT, Lahteenmaki PM. Cancer related factors do not explain the quality of life scores for childhood cancer survivors analysed with two different generic HRQL instruments. *Cancer Epidemiol* 2011;35(2):202–10.
95. Nathan PC, Ness KK, Greenberg ML, Hudson M, Wolden S, Davidoff A, *et al*. Health-related quality of life in adult survivors of childhood Wilms tumor or neuroblastoma: A report from the childhood cancer survivor study. *Pediatr Blood Cancer* 2007;49(5):704–15.

96. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. 2010;13(5):509–18.
97. Brazier JE, Longworth L. NICE DSU Technical Support Document 8: An introduction to the measurement and valuation of health for NICE submissions. 2011.
98. Grutters JP, Joore MA, van der Horst F, Verschuure H, Dreschler WA, Anteunis LJ. Choosing between measures: comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. *Qual Life Res* 2007;16(8):1439–49.
99. Neumann PJ, Sandberg EA, Araki SS, Kuntz KM, Feeny D, Weinstein MC. A comparison of HUI2 and HUI3 utility scores in Alzheimer's disease. *Medical Decision Making* 2000;20(4):413–22.
100. Portwine C, Rae C, Schecter T. Health-related quality of life in a population-based sample of survivors of advanced neuroblastoma in Canada. *Pediatric Blood Cancer* 2014;61(Suppl 2):S208.
101. British National Formulary (BNF). BNF Online 2017. Available from: https://www.bnf.org/. Last accessed 10 October 2017.

10 APPENDICES

10.1 Modified International Neuroblastoma Response Group criteria to determine level of risk of relapse

Table 59. Modified INRG criteria (adapted from CS, Table 6 [pg. 15])

Risk group for treatment	INRG stage	IDRFs in primary tumour	Distant metastases	Patient age (months)	Histological category	Grade of differentiation	MYCN status	Genomic profile	Ploidy
Very-low	L1	Absent	Absent	Any	GNB nodular, NB	Any	NA	Any	Any
Very-low	L1 or L2	Any	Absent	Any	GN, GNB intermixed	Any	NA	Any	Any
Low	L2	Present	Absent	<18	GNB nodular, NB	Any	NA	Favourable	Any
Low	MS	Present	Absent	≥18	GNB nodular, NB	Differentiating	NA	Favourable	Any
Low	L2	Any	Present	<12	Any	Any	NA	Favourable	Any
Intermediate	L2	Present	Absent	<18	GNB nodular, NB	Any	NA	Unfavourable	Any
Intermediate	L2	Present	Absent	≥18	GNB nodular, NB	Differentiating	NA	Unfavourable	Any
Intermediate	L2	Present	Absent	≥18	GNB nodular, NB	Poorly differentiated, undifferentiated	NA	Any	Any
Intermediate	M	Any	Present	<18	Any	Any	NA	Any	>1 (Hyperploidy)
Intermediate	M	Any	Present	<12	Any	Any	NA	Unfavourable and/or diploid	
Intermediate	MS	Any	Present	12-18	Any	Any	NA	Favourable	Any
Intermediate	MS	Any	Present	<12	Any	Any	NA	Unfavourable	Any
High	L1	Absent	Absent	Any	GNB nodular, NB	Any	Amp	Any	Any
High	L2	Present	Absent	≥18	GNB nodular, NB	Poorly differentiated, undifferentiated	Amp	Any	Any
High	M	Any	Present	12-18	Any	Any	NA	Unfavourable and/or diploid	
High	M	Any	Present	<18	Any	Any	Amp	Any	Any
High	M	Any	Present	≥18	Any	Any	Any	Any	Any
High	MS	Any	Present	12-18	Any	Any	NA	Unfavourable	Any
High	MS	Any	Present	<18	Any	Any	Amp	Any	Any

Risk stratifying groups have been updated from the original INRG report (Cohn 2009) to account for emergent genomic data and current treatment approaches. Favourable and unfavourable corresponds to the absence or presence, respectively, of segmental chromosome alterations.

Abbreviations: Amp, amplified; CS, company submission; GN, ganglioneuroma; GNB, ganglioneuroblastoma; IDRF, image-defined risk factor; INRG, International Neuroblastoma Risk Group; NA, non-amplified; NB, neuroblastoma; pg, page.

10.2 PRISMA flow schematics

Figure 37. Schematic for the search of the literature on high-risk neuroblastoma (reproduced from CS, pg. 24, Figure 2)

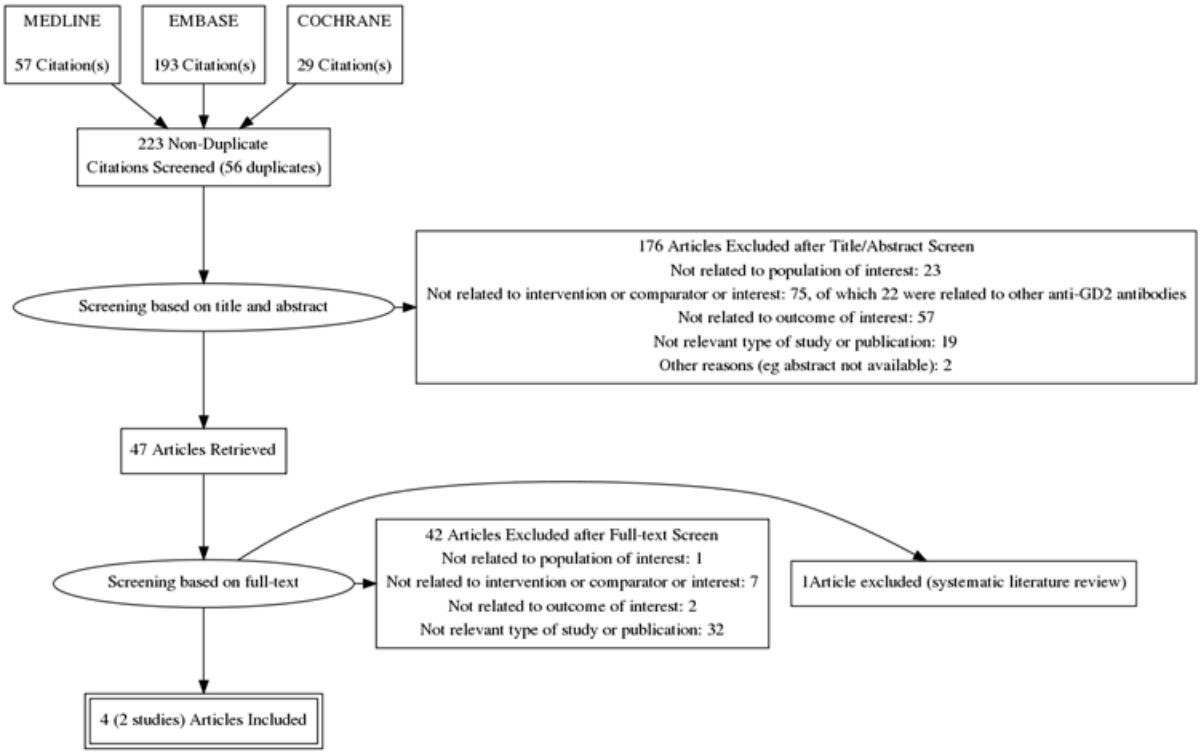
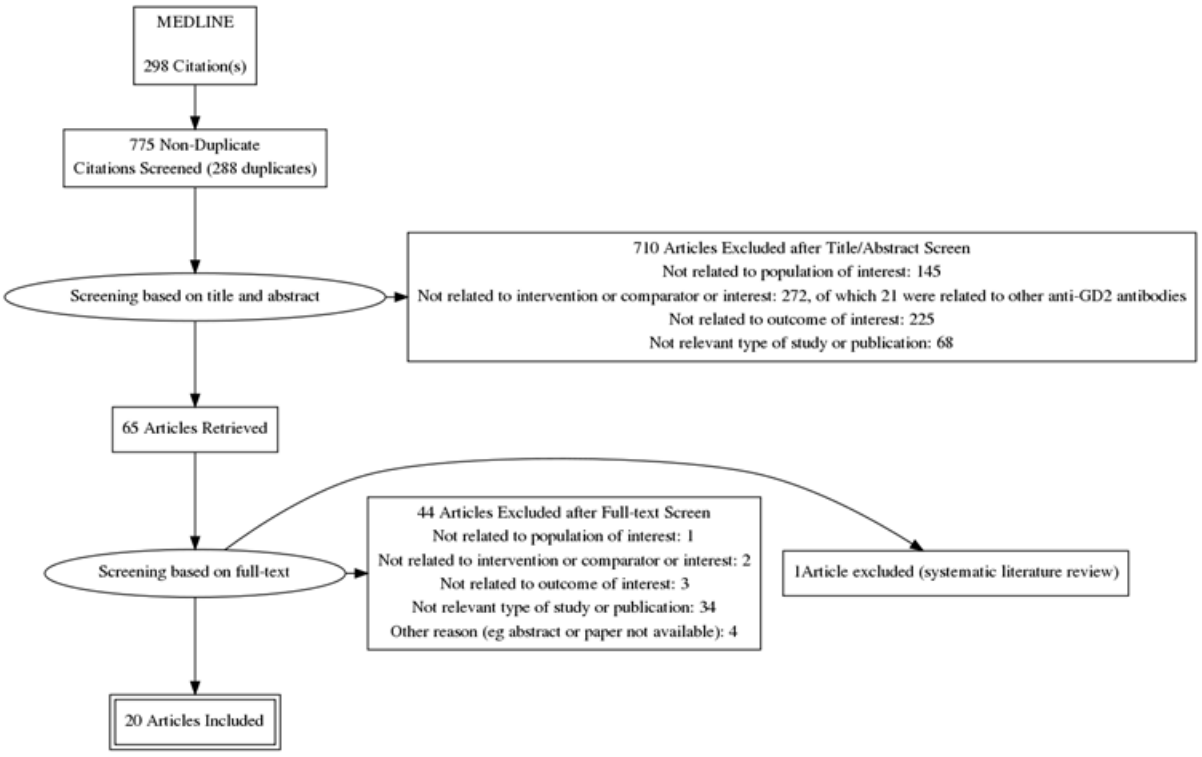


Figure 38. Schematic for the search of the literature on relapsed or refractory neuroblastoma (reproduced from CS, pg. 26, Figure 3)



10.3 Quality assessment

Table 60. Quality assessment for APN311-302 (adapated from CS, Table 22, pg. 53)

Trial characteristic	**APN311-302**	
	Company assessment	**ERG assessment**
Was the method used to generate random allocations adequate?	Yes	Yes Patients were randomised using a web-based centralised system (no further details available). Randomisation was stratified by national group and by previous treatment
Was the allocation adequately concealed?	N/A	Unclear Details not available on methods used to conceal allocation from recruiters or those allocating patients to treatment groups.
Were the groups similar at the outset of the study in	Yes	Yes

terms of prognostic factors, e.g. severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the	No	No Study was open label in design. Development of second neoplasm and disease relapse or progression, which are components of EFS, were evaluated by an assessor who was not masked to treatment. Therefore, EFS might be at risk of performance bias. Death from any cause (also a component of EFS) and OS are objective measures and unlikely to be at risk of bias from knowledge of treatment

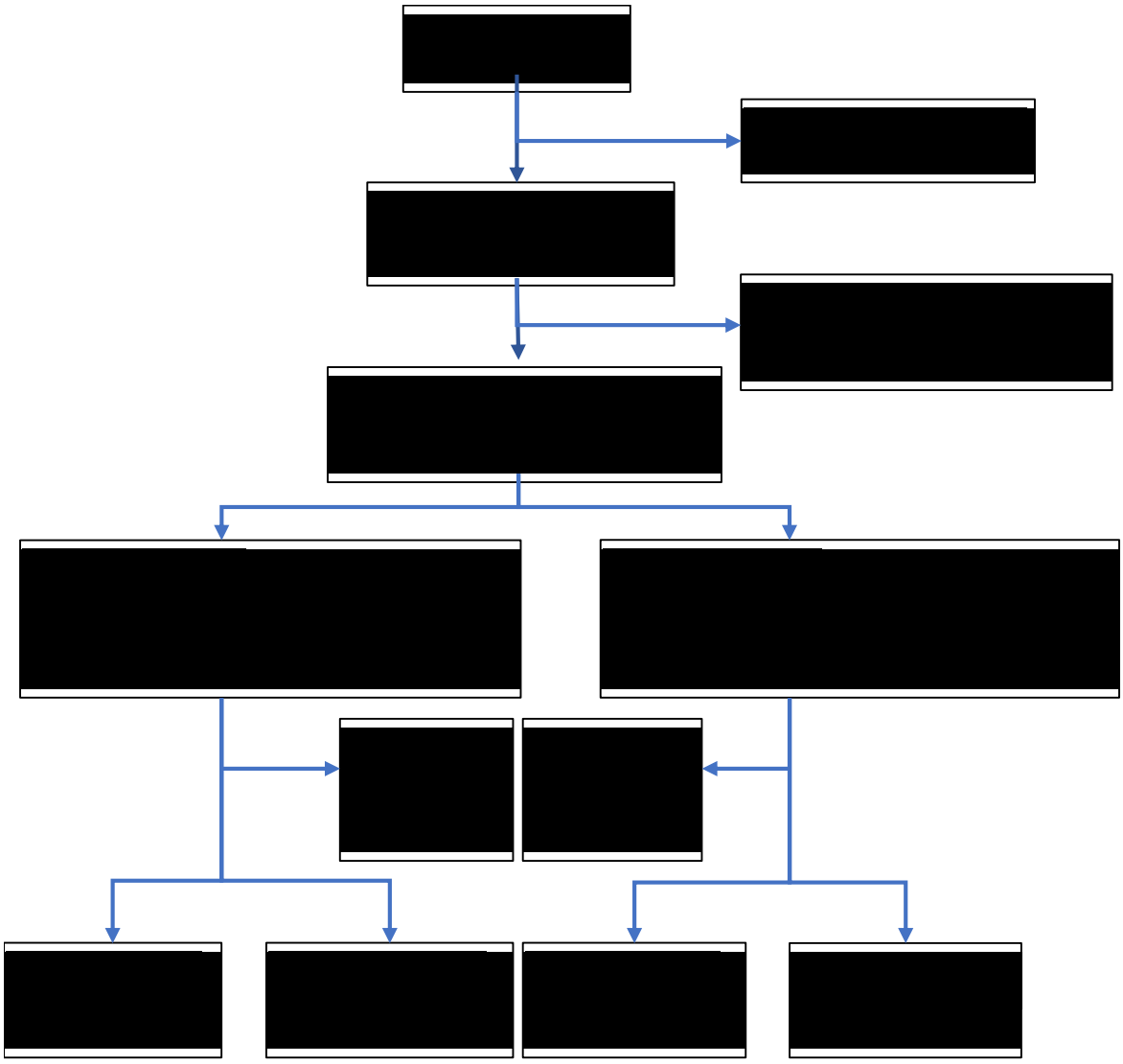
risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No Although a larger proportion of people receiving IL-2 discontinued treatment compared with those not receiving IL-2, the difference in withdrawal could be anticipated because it is recognised that IL-2 administration is associated with adverse effects (e.g., capillary leak syndrome): 17.5% of patients receiving IL-2 experienced a SAE leading to withdrawal compared with 6% of patients not receiving IL-2
Is there any evidence to suggest that the authors measured more outcomes than they rep	No	No The CSR for APN311-302 indicates that "[redacted]".[41] However, all clinical effectiveness outcomes of interest to the STA are reported: EFS; OS; tumour response; and adverse effects.

orted?		
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	No It is stated that analyses were based on the intention-to-treat principle, but not all people randomised were included in the analyses. Analyses are based on those for whom an electronic case report form was available and who received their allocated treatment. The ERG considers that the company has carried out the equivalent of a complete case analysis.

Abbreviations: CS, company submission; EFS, event-free survival; ERG, Evidence Review Group; IL-2, interleukin-2; N/A, not applicable; OS, overall survival; pg, page; SAE, serious adverse effect.

10.4 Participant flow for APN311-302 (reproduced from company's response to initial ERG questions dated 11/07/2017)

Figure 39. Participant flow in APN311-302



[a] 175 subjects in APN311-302 CSR. Baseline disease evaluation was missing for patient BE-0098, but is available for CSR Addendum analysis. Patient FR-0600 with missing response evaluation at BL was included in the group with EoD at BL.

[b] 181 subjects in APN311-302 CSR. Baseline disease evaluation was missing for patients BE-0096 and IT-0428, but is available for CSR Addendum analysis.

[c] 105 subjects in APN311-302 CSR.

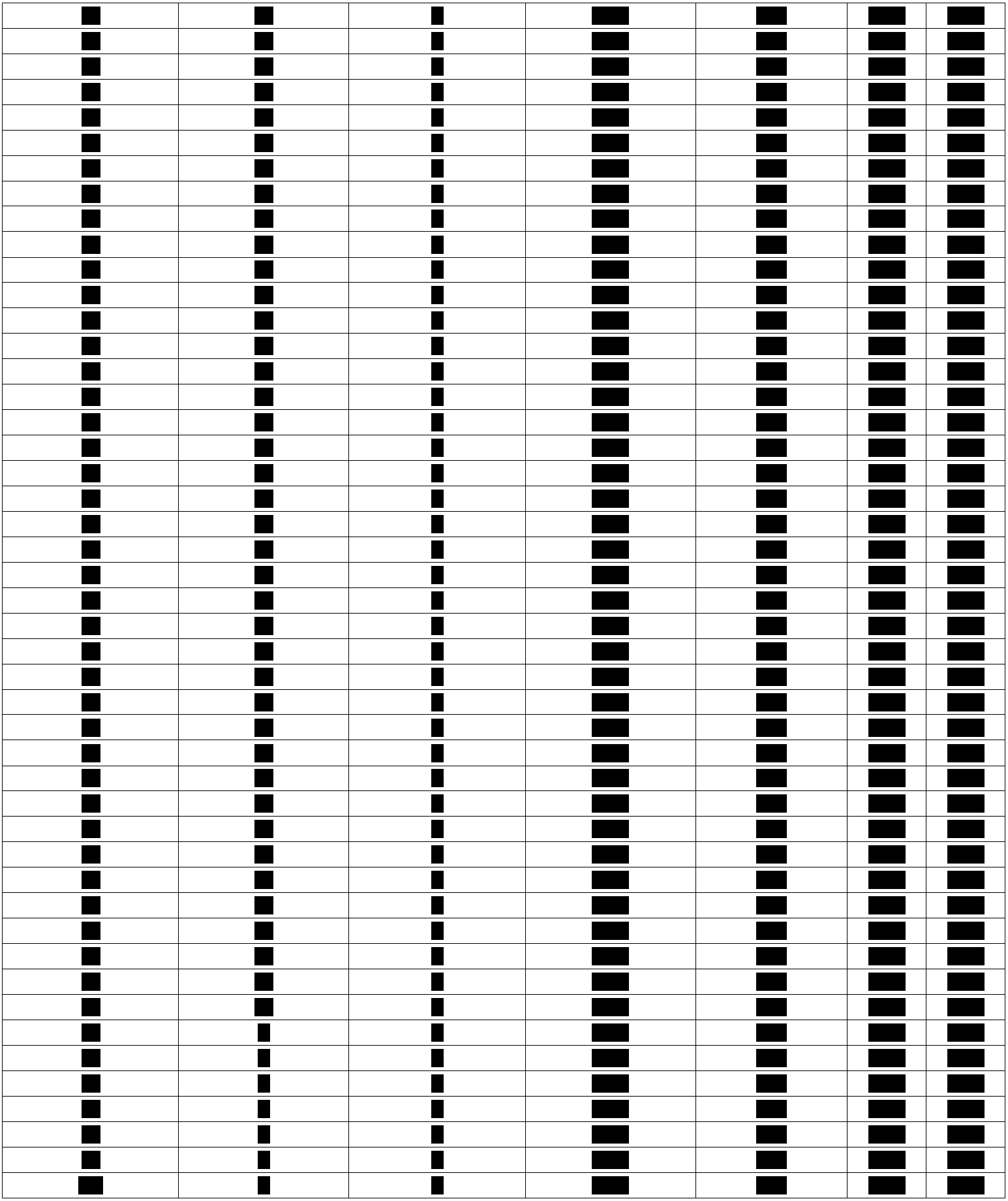
10.5 Data on analysis of event-free survival for APN311-302

Figure 40. Adjusted KM curves for event-free survival by treatment group in APN311-302 (reproduced from company's clarification response dated 16 August 2017, Figures 22 [pg. 32] and 25 [pg. 37])

Abbreviations:

KM, Kaplan–Meier; pg, page.

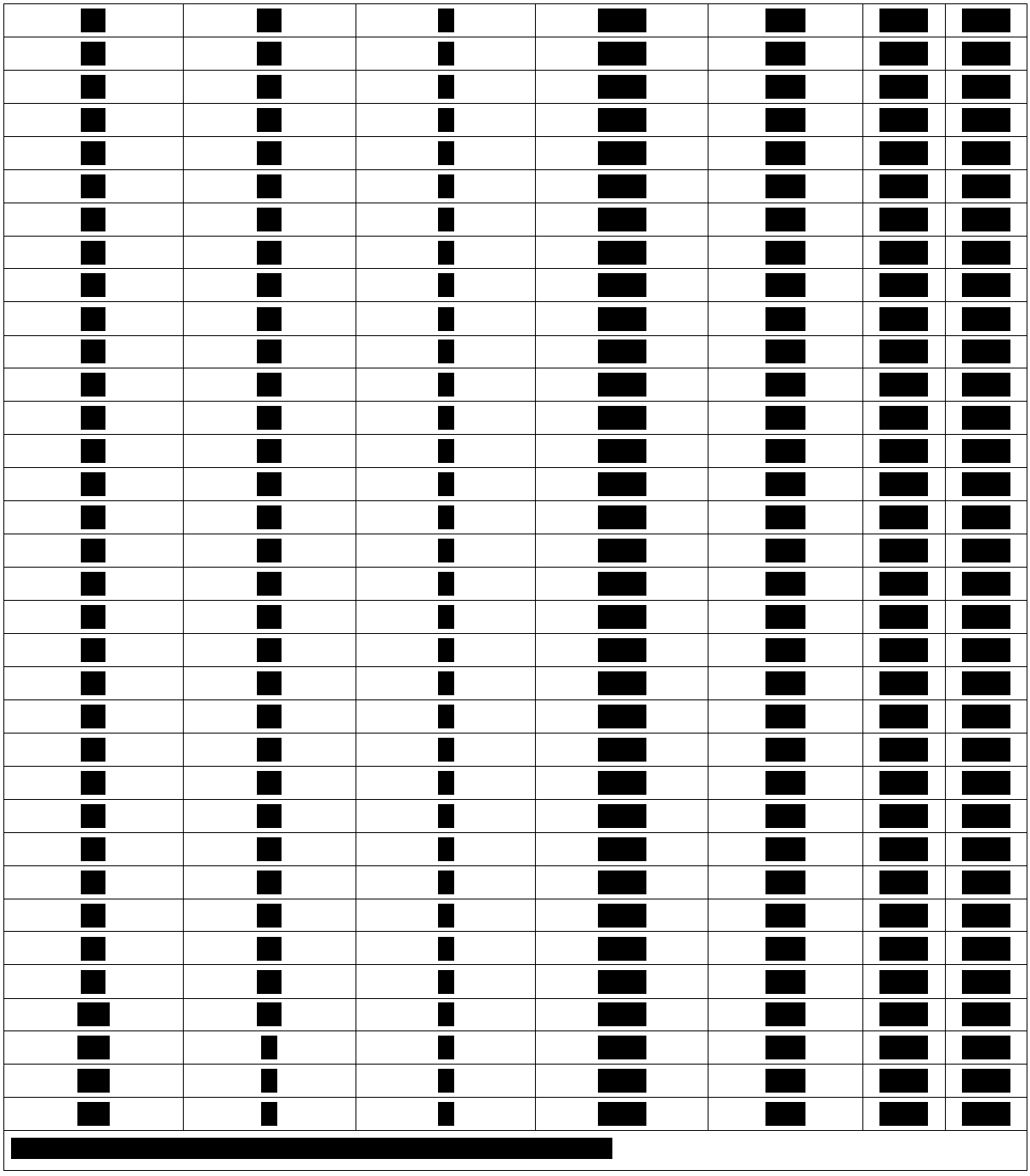
Table 61. Survival analysis on event-free survival for dinutuximab beta plus isotretinoin, (reproduced from company's response to clarification dated 16 August 2017, Table 23 [pgs 33–34]



[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

Table 62. Survival analysis on event-free survival for dinutuximab beta plus isotretinoin plus IL-2, [redacted] (reproduced from company's response to clarification dated 16 August 2017, Table 26 [pgs 38–39]

					[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



10.6 Data on analysis of overall survival for APN311-302

Figure 41. Adjusted KM curves for overall survival by treatment group in APN311-302 (reproduced from company's clarification response dated 16 August 2017, Figures 9 [pg. 17] and 13 [pg. 22])

[redacted]

Abbreviations:

[redacted] KM, Kaplan–Meier; pg, page.

Table 63. Survival analysis on overall survival for dinutuximab beta plus isotretinoin, [redacted] (reproduced from company's response to clarification dated 16 August 2017, Table 11 [pgs 19–20]

					[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

Table 64. Survival analysis on overall survival for dinutuximab beta plus isotretinoin plus IL-2, [redacted] (reproduced from company's response to clarification dated 16 August 2017, Table 14 [pgs 23–24]

					[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

10.7 Additional details on adverse effects

Table 65. Summary of treatment-emergent adverse events possibly related to dinutuxumab beta experienced by ≥20% people (adapted from company's response to clarification dated 25 August 2017, Table 18, [pgs 24–25])

System organ class **Preferred term**	**APN311-202** **n (%), (N=44)**	**APN311-303** **n (%), (N=54)**
Overall	44 (100.0%)	54 (100.0%)
General disorders and administration site conditions	43 (97.7%)	54 (100.0%)
Pyrexia	42 (95.5%)	53 (98.1%)
Pain	28 (63.6%)	35 (64.8%)
Fatigue	11 (25.0%)	22 (40.7%)
Face oedema	5 (11.4%)	19 (35.2%)
Chills	17 (38.6%)	9 (16.7%)
Oedema	4 (9.1%)	12 (22.2%)
Asthenia	5 (11.4%)	11 (20.4%)
Malaise	11 (25.0%)	3 (5.6%)
Skin and subcutaneous tissue disorders	26 (59.1%)	50 (92.6%)
Pruritus	16 (36.4%)	46 (85.2%)
Rash	7 (15.9%)	16 (29.6%)
Urticaria	12 (27.3%)	12 (22.2%)
Gastrointestinal disorders	33 (75.0%)	49 (90.7%)
Abdominal pain upper	1 (2.3%)	30 (55.6%)
Vomiting	23 (52.3%)	24 (44.4%)
Diarrhoea	19 (43.2%)	14 (25.9%)
Nausea	16 (36.4%)	15 (27.8%)
Abdominal pain	18 (40.9%)	9 (16.7%)
Constipation	8 (18.2%)	3 (5.6%)
Vascular disorders	27 (61.4%)	49 (90.7%)
Capillary leak syndrome	15 (34.1%)	45 (83.3%)
Hypotension	20 (45.5%)	32 (59.3%)
Musculoskeletal and connective tissue disorders	8 (18.2%)	46 (85.2%)
Pain in extremity	7 (15.9%)	42 (77.8%)
Back pain	–	16 (29.6%)
Respiratory, thoracic and mediastinal disorders	33 (75.0%)	45 (83.3%)
Cough	27 (61.4%)	39 (72.2%)
Hypoxia	17 (38.6%)	18 (33.3%)
Pleural effusion	–	11 (20.4%)
Cardiac disorders	9 (20.5%)	39 (72.2%)
Tachycardia	3 (6.8%)	39 (72.2%)
Investigations	39 (88.6%)	32 (59.3%)
Weight increased	25 (56.8%)	24 (44.4%)
Alanine aminotransferase increased	25 (56.8%)	4 (7.4%)
Transaminases increased	–	–
Aspartate aminotransferase increased	13 (29.5%)	–
Gamma glutamyl transferase increased	23 (52.3%)	1 (1.9%)
Platelet count decreased	19 (43.2%)	–
Neutrophil count decreased	14 (31.8%)	–

Blood bilirubin increased	10 (22.7%)	–
Blood alkaline phosphatase increased	9 (20.5%)	–
Nervous system disorders	16 (36.4%)	15 (27.8%)
Headache	3 (6.8%)	11 (20.4%)
Blood and lymphatic system disorders	27 (61.4%)	11 (20.4%)
Anaemia	24 (54.5%)	5 (9.3%)
Eye disorders	10 (22.7%)	13 (24.1%)
Metabolism and nutrition disorders	19 (43.2%)	9 (16.7%)
Immune system disorders	11 (25.0%)	2 (3.7%)
Renal and urinary disorders	12 (27.3%)	4 (7.4%)
Infections and infestations	13 (29.5%)	3 (5.6%)

Table 66. Adverse effects from APN311-302 (adapted from CS, Table 46 [pgs 94–95])

System organ class **Toxicities**	**Dinutuximab beta plus isotretinoin** **n (%), (N=183)**	**Dinutuximab beta plus isotretinoin plus IL-2** **n (%), (N=183)**	**All** **n (%), (N=366)**
Any	181 (98.9)	181 (98.9)	362 (98.9)
General condition	140 (76.5)	164 (89.6)	304 (83.1)
Gut toxicity	135 (73.8)	145 (79.2)	280 (76.5)
Stomatitis	29 (15.8)	40 (21.9)	69 (18.9)
Nausea or vomiting	99 (54.1)	121 (66.1)	220 (60.1)
Diarrhoea	92 (50.3)	114 (62.3)	206 (56.3)
Constipation	76 (41.5)	47 (25.7)	123 (33.6)
Skin toxicity	147 (80.3)	159 (86.9)	306 (83.6)
Skin	124 (67.8)	138 (75.4)	262 (71.6)
Allergy	101 (55.2)	119 (65.0)	220 (60.1)
Liver toxicity	118 (64.5)	126 (68.9)	244 (66.7)
Bilirubin	15 (8.2)	35 (19.1)	50 (13.7)
SGOT and SGPT	118 (64.5)	121 (66.1)	239 (65.3)
Cardiac toxicity	61 (33.3)	88 (48.1)	149 (40.7)
Cardiac function	6 (3.3)	10 (5.5)	16 (4.4)
ECHO:LV-SF	1 (0.5)	8 (4.4)	9 (2.5)
Hypotension	48 (26.2)	78 (42.6)	126 (34.4)
Hypertension	24 (13.1)	11 (6.0)	35 (9.6)
Infections	147 (80.3)	170 (92.9)	317 (86.6)
Infections	106 (57.9)	132 (72.1)	238 (65.0)
Fever	145 (79.2)	168 (91.8)	313 (85.5)
Haematological toxicity	164 (89.6)	174 (95.1)	338 (92.3)
Haemoglobin	162 (88.5)	174 (95.1)	336 (91.8)
WBC	148 (80.9)	153 (83.6)	301 (82.2)
Granulocytes	140 (76.5)	154 (84.2)	294 (80.3)
Platelets	124 (67.8)	156 (85.2)	280 (76.5)
Renal toxicity	46 (25.1)	56 (30.6)	102 (27.9)
Creatinine	25 (13.7)	35 (19.1)	60 (16.4)
Proteinuria	16 (8.7)	11 (6.0)	27 (7.4)
Haematuria	18 (9.8)	24 (13.1)	42 (11.5)
GFR	14 (7.7)	10 (5.5)	24 (6.6)
Tubular phosphate reabsorption	1 (0.5)	3 (1.6)	4 (1.1)

Neurological toxicity	28 (15.3)	44 (24.0)	72 (19.7)
Central neurotoxicity	19 (10.4)	28 (15.3)	47 (12.8)
Peripheral neurotoxicity	13 (7.1)	25 (13.7)	38 (10.4)
Vascular toxicity	70 (38.3)	116 (63.4)	186 (50.8)
Capillary leak syndrome	45 (24.6)	91 (49.7)	136 (37.2)
Cytokine release syndrome	49 (26.8)	64 (35.0)	113 (30.9)
Pain	115 (62.8)	138 (75.4)	253 (69.1)
Pain related to dinutuximab beta	115 (62.8)	138 (75.4)	253 (69.1)
Ocular toxicity	33 (18.0)	45 (24.6)	78 (21.3)
Dilated pupils	23 (12.6)	40 (21.9)	63 (17.2)
Accommodation defects	15 (8.2)	23 (12.6)	38 (10.4)
Papilloedema	5 (2.7)	3 (1.6)	8 (2.2)

Abbreviations: CS, company submission; ECHO: LV-SF, echocardiogram: left ventricle–systolic function; GFR, glomerular filtration rate; IL-2, interleukin-2; pgs, pages; SGOT, serum glutamic-oxaloacetic transaminase (= AST); SGPT, serum glutamic pyruvic transaminase (= ALT); WBC, white blood cells.

10.8 Company's response to the ERG's request to provide clinical and cost effectiveness analysis for those with refractory neuroblastoma

We agree that from a diagnosis standpoint the refractory and relapsed patients are not the same, however we could not disentangle any difference in background risk in the refractory subgroup in terms of clinical outcomes with the data we have due to the following reasons:

- The treatment algorithm is the same for both refractory (i.e. refractory patients receiving induction therapy, high-dose chemotherapy and reinjection of hematopoietic stem cells) and relapsed neuroblastoma patients (expert opinion, SIOPEN clinical guidelines to be published soon).

- Most of the literature already reported in the SLR are combining the relapsed and refractory patients when they report their clinical outcomes. In the 17 articles reported in the SLR having OS outcomes (attached a revised Appendix D, 1.3.1), only 2 were reporting the OS data separated for relapsed and refractory patients (Zhou et al, 2015 (3) and Moreno et al, 2017 (4)) and the other articles were always pooling the R/R patient data together. Zhou et al (3) reported significantly higher 24-month OS for refractory patients was significantly higher at 65.3% (95% CI 51.8%–75.9%), compared to 38.7% (95% CI 30.4%–46.8%) for relapsed patients ($p < 0.001$). However, this difference could be due to the different background risk of relapsed or refractory patients or if it is due to the differential treatment effects due to mIBG treatment in these patients. Neither study had an adequate control arm that would be needed to unconfound the two potential hypotheses. That is, the data limitation due to non-controlled studies does not allow us to answer that the ERG posed.

- In the clinical data of Dinutuximab beta EUSA, all patients received dinutuximab beta, since a control arm without immunotherapy was excluded due to ethical reasons. Thus, the requested analysis of the hypothesis test for testing whether there are differences in the two patient subgroups is confounded. I.e. We don't know if it is a differential effect on dinutuximab beta in the two patient sets or a difference in background risk of dying. As requested, by using APN311-202 and APN311-303 clinical data, we have run a Cox proportional hazards regression model adjusting for baseline disease status, prior treatment, age at diagnosis, MYCN status and INSS stage. We have analysed the effect of baseline disease status on overall survival and event-free survival in the patients treated with Dinutuximab beta EUSA. [redacted]

  However, we do not know if the difference in OS observed for relapsed and refractory patients (Table 9A) is due to the different background risk of R/R patients or due to dinutuximab beta working differently in these populations. We do not have a control arm in maintenance treatment to clarify whether the difference is due to dinutuximab beta (since a control arm without immunotherapy is currently considered unethical).

Table 9. Effect of baseline disease status on overall survival (OS) (A) or event-free survival (EFS) (B) in patients receiving dinutuximab beta in Study APN311-202. Results derived from proportional hazards regression analysis (Cox model)

(A)

[redacted]

(B)

[redacted]

Table 10. Effect of baseline disease status on overall survival (OS) (A) or event-free survival (EFS) (B) in patients receiving dinutuximab beta in Study APN311-303. Results derived from proportional hazards regression analysis (Cox model)

(A)

[redacted]

(B)

[redacted]

For those reasons, the base case for the cost-effectiveness analysis is considering both populations together.

10.9 Previous treatments in people experiencing relapse

Table 67. Treatment at first-line and prior to diagnosis of relapse or refractory neuroblastoma in APN311-202, APN311-303, and Garaventa (adapted from CSR for relevant study and company clarification response dated 25 August 2017)

Treatment	APN311-202 n (%), (N=44)	APN311-303 n (%), (N=30)	Garaventa N (%), (N=29)
[redacted]			
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

APN311 for treating high-risk neuroblastoma [ID910]

You are asked to check the ERG report from BMJ- TAG to ensure there are no factual inaccuracies contained within it.

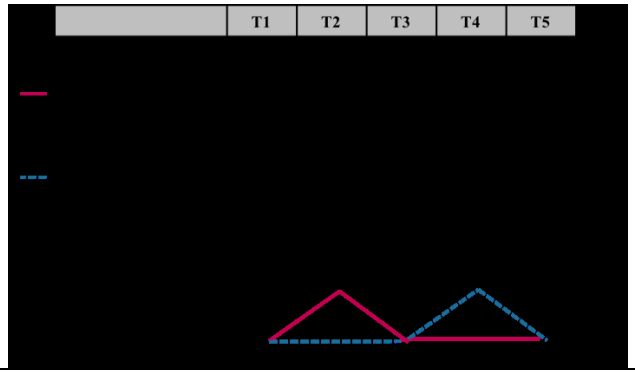
If you do identify any factual inaccuracies you must inform NICE by **5pm on 20 October 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Relevance of R/R Population in UK

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 16, section 1.1 The ERG questioned the relevance of the Relapsing and Refractory (R/R) population. Reservations were made with regard to the comparability of patients with R/R neuroblastoma in clinical trials APN311-202 and APN311-303 with people of the same disease status in England, particularly in terms of prior dinutuximab beta treatment through HR-NBL-1 study and with the company not supporting re-treatment with dinutuximab beta	Please consider focusing the appraisal to high-risk neuroblastoma patients who did not previously receive Dinutuximab beta EUSA	Because relapsed and refractory patients create confusions for NICE (since most early line patients have been treated with Dinutuximab beta in clinical trials), EUSA suggests simplifying the technology evaluation and focus committee's attention on high-risk neuroblastoma patients who have not previously received Dinutuximab beta EUSA.	Not a factual error.

Issue 2 CEA: Inconsistency in OS and EFS KM curves in APN311-302

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 33-34, section 1.4.2.2 and page 153 section 5.4.5.2.1 The ERG noted in the STA Report an inexplicable inconsistency in the proportion of patients moving out of the OS and EFS KM curves in the APN311-302 clinical trial. The ERG does not see any possible logical explanation for why the proportion of deaths in the OS curve are higher than the proportion of deaths, added to the proportion of disease, relapse and neoplasm events (captured in the EFS curve).	EUSA would urge the ERG to reconsider its reasoning and approach to the clinical data.	EUSA disagrees with this inconsistency statement. EUSA did not misreport the outcomes from APN311-302 and has been transparent. EFS was assessed in APN311-302 as the primary outcome and was defined as the time to an event from randomisation until the first occurrence of relapse, disease progression, secondary neoplasm or death from any cause. The OS curve only takes into account death events. The term censoring was used to remove a patient from the survival curve at the end of their follow-up time. The proportion of patients who leave the OS curve could be higher than the proportion of patients who leave the EFS curve if patients have a non-fatal event before they experience a fatal event. In an illustrative example below, with a set of 2 patients only: if a patient X has his first event at time T2 (e.g. relapse), this patient will have an EFS event and won't be able to have another EFS event, representing a peak of change at time T2. However, this patient will be still recorded by the OS curve, until his death at a later time point, T4, is recorded in OS. At time T4, the curve of change in OS will be above the curve of change in EFS. 	The ERG thanks the company for identifying this error. The statements mentioned by the company have been removed from the ERG report.

Issue 3 CEA: lack of maturity of OS data and non-existence of EFS data

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 40 and Page 167, section 5.4.5.2.3 The HR estimation method to Unituxin used by the ERG is flawed and it is unlikely to be an appropriate method of analysis, as mentioned by the ERG.	Please consider results from the MAIC analysis to produce a meaningful ICER	EUSA believes that the ERG approach using HRs from Unituxin is not a robust methodology, and unsafe to calculate ICERs, as it has cumulative layers of embedded uncertainty, and thus their resulting economic analysis needs reconsideration. The impact of this flawed analysis moves the ICER from less than £30,000 to £111'858, way above the highest value produced by sensitivity analyses provided by all previous model assumptions and scenarios. Although EUSA acknowledges some of the limitations inherent in the assumptions around the MAIC analysis (eg. potential bias particularly without anchored MAIC, availability of prognostic factors, assumption of similar study designs and treatment), the MAIC may provide a more acceptable alternate supportive analysis, if the ERG has concerns using unadjusted KM analysis. Please find below the MAIC results, as requested by the ERG during clarification, following the methods described in NICE Decision Support Unit Technical Support Document 18, comparing EFS and OS for dinutuximab beta+isotretinoin+/-IL2 (APN311-302) versus isotretinoin alone (Yu et al, 2010). The prognostic factors (i.e. age, INSS stage, MYCN status and response to treatment before ASCT) were incorporated in the analysis to reduce bias in the indirect comparison. With the MAIC data as input and after correcting the mathematical errors spotted by the ERG in the company model, the base case ICER has only risen to £33'976. Using the ERG model with MAIC data, the ICER is at £38'044 (assuming that 51% of patients received IL-2) or at £33'802 without IL-2 usage (see Issue 4). This clearly reinforces our believe in the inherent flaw of the ERG model assumptions leading to an exceptionally high ICER of £111,858	Not a factual error. The company has not provided the MAIC analysis or results to the ERG at any point during the ERG's assessment of dinutuximab beta. The company has introduced these new results without supporting documentation at the FAC.

Issue 4 CEA: Use of IL-2 in UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 43, section 1.5.1 The ERG model considers that 51% of children had residual disease at baseline and therefore would require IL-2 as a concomitant medication, as per dinutuximab beta's licence.	Please consider a CEA model which follows clinical practice and therefore does not require use of IL-2 for treatment of high-risk neuroblastoma in UK	Clinical expert opinion provided to EUSA clarified that in high-risk neuroblastoma patients treated in a first-line setting (complete response and partial response), use of IL-2 is not considered by the paediatric oncologist clinical community in the NHS given the results of HR-NBL1 trial (i.e. no added benefit of the addition of IL-2 to Dinutuximab beta EUSA) and the significant toxicity profile of IL-2. In patients with relapse settings as well as patients who are refractory to the initial phases of treatment (induction chemotherapy), use of IL-2 is now considered standard of care given the potential clinical benefit of IL-2 and the lack of evidence. This is still assessed within two SIOPEN clinical trials (APN311-304 and APN311-202 V3 randomisation phase).	Not a factual error. The ERG has adhered to the marketing authorisation for dinutuximab beta.

APN311 for treating high-risk neuroblastoma

ERRATA

This report was commissioned by the NIHR HTA Programme as project number 15/194/02

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
30	First complete paragraph on page deleted. Deleted text outlined ERG's reservations around the KM data provided by the company.
33	The sentence "The ERG has severe concerns with the estimation of treatment effectiveness in the economic analysis. These, stem mainly from three overarching issues. The first one is related to the lack of face validity of the OS and EFS KM data from APN311-302. The second relates to the lack of maturity of OS data and the non-existence of EFS data in historical control R1. Finally, the third issue relates to the naïve (unadjusted) analysis of the relative treatment effectiveness of dinutuximab beta, when compared with isotretinoin." has been amended to "The ERG has severe concerns with the estimation of treatment effectiveness in the economic analysis. These, stem mainly from two overarching issues. The first one is related to the lack of maturity of OS data and the non-existence of EFS data in historical control R1. The second issue relates to the naïve (unadjusted) analysis of the relative treatment effectiveness of dinutuximab beta, when compared with isotretinoin." The following paragraph was deleted: "1) The ERG investigated the KM data provided by the company in the model and noted an inexplicable inconsistency in the proportion of patients moving out of the OS and EFS KM curves in the APN311-302 trial. The ERG produced Figure B to show the proportion of patients in cycle t minus the proportion of patients in cycle t+1 in the OS and EFS KM curves in APN311-302. As the proportion of patients in the EFS and OS curves decreases over time (because patients progress or die), the difference in the proportion of patients each cycle is always positive (Figure B). The red curve in Figure B shows the proportion of patients who leave the EFS curve over time (representing the additional number of patients who progress, relapse or die in that cycle) and the blue curve shows the proportion of patients who leave the OS curve over time (representing the additional number of patients who die that cycle). What would be expected is that the change in the EFS curve is always higher (or the same) as the change in the OS curve. This is because the OS curve only takes into account death events, while the EFS curve takes into account disease progression or relapse, second neoplasm and death events (according to the CS). Therefore, the ERG does not see any possible logical…"
34	The following paragraph was deleted: "explanation for why the proportion of deaths in in the OS curve are higher than the proportion of deaths, added to the proportion of disease, relapse and neoplasm events (captured in the EFS curve). In Figure B, this is illustrated where the blue curve is above the red curve. This might be related with the company potentially misreporting the outcomes included in the KM curves (for example, if the EFS curve censored death events), or with the time intervals not being consistent across the OS and EFS curves. Either case is worrying, and removes the validity of the KM curves in APN311-302 provided by the company. Finally, the ERG is also concerned that the company did not provide numbers at risk to accompany the unadjusted KM data for APN311-302 and R1, despite the ERG's requests for these data at the clarification stage. In conclusion, the ERG considers that the uncertainty and the lack of face validity of the KM data from APN311-302 renders the use of these data inappropriate in the analysis. Using the fitted Gompertz curves to the KM data helps adding some face validity to the OS and EFS curves for dinutuximab beta, however, the fitted and extrapolated curves are still based on the underlying KM data from APN311-302, and are therefore, flawed." Figure B was also deleted. The text "2) Equally concerning, is the fact that the company's model relies on the naïve …" was replaced with "1) The company's model relies on the naïve …"
36, 37, 38,39,40,41,42	Throughout the text, Figure C has been replaced with Figure B; Figure D has been replaced with Figure C; Figure E has been replaced with Figure D; Figure F has been replaced with

	Figure E; Figure G has been replaced with Figure F; Figure H has been replaced with Figure G and Figure I was replaced with Figure I. The title “Figure C” has been replaced with “Figure B”; The title “Figure D” has been replaced with “Figure C”; The title “Figure E” has been replaced with “Figure D”; the title “Figure F” has been replaced with “Figure E” and the title “Figure G” has been replaced with “Figure F”; the title “Figure H” has been replaced with “Figure G” and the title “Figure I” has been replaced with “Figure H”.
39	The first row of Table D was removed from the table.
43	The sentence “and also to try and minimise the structural issues found in the KM data from APN311-302” has been removed from the text.
127	Third complete paragraph on page deleted. Deleted text outlined ERG’s reservations around the KM data provided by the company.
128	Figure 9 deleted.
138	Final bullet point deleted. Deleted text outlined ERG’s reservations around the KM data provided by the company.
153,154	The following text “The ERG is extremely concerned with the lack of face validity of the KM data provided by the company. While visual inspection of the OS and EFS curves for APN311-302 might appear valid (Figure 17), the difference between the curves (which gives the proportion of patients in the failure state) and the between-curve relationship lacks face validity, as seen in Figure 18. The ERG investigated the KM data provided by the company in the model and noted an inexplicable inconsistency in the proportion of patients moving out of the OS and EFS KM curves in the APN311-302 trial. To illustrate this issue, the ERG produced Figure 19 to show the proportion of patients in cycle t minus the proportion of patients in cycle t+1 in the OS and EFS KM curves in APN311-302. As the proportion of patients in the EFS and OS curves decrease over time (because patients progress or die), the difference in the proportion of patients each cycle are always positive (Figure 19). The red curve in Figure 19 shows the proportion of patients who leave the EFS curve over time (representing the additional number of patients who progressed, relapsed or died that cycle) and the blue curve shows the proportion of patients who leave the OS curve over time (representing the additional number of patients who die that cycle). What would be expected to observe, would be that the change in the EFS curve is always higher (or the same) as the change in the OS curve. This is because the OS curve only takes into account death events, while the EFS curve takes into account disease progression or relapse, second neoplasm and death events (according to the CS). Therefore, the ERG does not see any possible logical explanation for why the proportion of deaths in in the OS curve are higher than the proportion of deaths, added to the proportion of disease, relapse and neoplasm events (captured in the EFS curve). In Figure 19, this is illustrated where the blue curve is above the red curve. This might be related with the company potentially misreporting the outcomes included in the KM curves (for example, if the EFS curve censored death events), or with the time intervals not being consistent across the OS and EFS curves. Either case is worrying, and removes the validity of the KM curves in APN311-302 provided by the company. The same issue was identified for the OS curve in R1 and the estimated EFS curve for isotretinoin (also shown in Figure 18). Finally, the ERG is also concerned with the fact that the company did not provide numbers at risk to accompany the unadjusted KM data for APN311-302 and R1, despite the ERG’s requests for these data at the clarification stage.” has been replaced with “Figure 17 presents the OS and EFS curves for APN311-302, while Figure 18 shows the FS curve, derived by estimating OS-EFS. The ERG is concerned with the fact that the company did not provide numbers at risk to accompany the unadjusted KM data for APN311-302 and R1, despite the ERG’s requests for these data at the clarification stage.” Figure 19 has been deleted.
155	The text “In conclusion, the ERG considers that the uncertainty and the lack of face validity of the KM data from APN311-302 renders the use of these data inappropriate in the analysis. Using the fitted Gompertz curves to the KM data helps adding some face validity to the OS and EFS curves for dinutuximab beta, however, the fitted and extrapolated curves are still based on the underlying KM data from APN311-302, and are therefore, flawed.” has been replaced with

	"The ERG considers that using fitted curves for the 10-year analysis is a more robust approach". The text "the ERG notes that using fitted curves instead of the KM data reflects smoother changes in the OS and EFS curves, (Figure 22 compared to Figure 19), however, the red curve crosses the blue curve at approximately month 22, and remains that way for the rest of the short-term model. As explained previously, this reflects an impossible scenario, where the number of deaths in a specific cycle are higher than the number of deaths, summed with the number of progression and relapse events in that same cycle." has been deleted from the paragraph.
157	Figure 22 has been deleted. The sentence "Equally concerning, is the fact that the company's model relies on the naïve (unadjusted) analysis of dinutuximab beta's effectiveness, compared with isotretinoin" has been replaced with "The ERG is concerned with the fact that the company's model relies on the naïve (unadjusted) analysis of dinutuximab beta's effectiveness, compared with isotretinoin."
167	The first row of Table 38 was removed from the table. The following text has been deleted: "When the ERG replaced the OS and EFS KM dinutuximab beta curves by the Gompertz curves in the model, it became apparent that the intrinsic problematic relationship between the OS and the EFS KM curves for dinutuximab beta (Figure 29) were carried to the isotretinoin OS and EFS curves (Figure 30), as HRs were applied to the OS and EFS dinutuximab beta curves to estimate isotretinoin curves. Using the extrapolated Gompertz curves in the short-term model for OS and EFS, is an attempt to minimise the structural issues found in the KM data from APN311-302. However, given that the underlying KM data is flawed (and the Gompertz curves seems to be a considerable good fit to the shape of the KM curves), the shape of the Gompertz curves carries the same problems as the KM curves. Even though the ERG cannot anticipate the direction or the extent of the error in the shape of the curves, it is known that the OS and EFS curves should have a wider gap, as there is either an underestimation of events being captured in the EFS curve, or an overestimation of deaths captured in the OS curve."
168	The sentence "Therefore, the ERG cannot anticipate if the "real" OS curve should sit lower than the one shown in Figure 29, or if the EFS curve should sit higher (or if both curves would move)." has been deleted.
212	The sentence "and also to try and minimise the structural issues found in the KM data from APN311-302" has been deleted.
220	The sentence "The ERG has severe concerns with the estimation of treatment effectiveness in the economic analysis. These, stem mainly from three overarching issues. The first one is related to the lack of face validity of the OS and EFS KM data from APN311-302. The second relates to the lack of maturity of OS data and the non-existence of EFS data in historical control R1. Finally, the third issue relates to the naïve (unadjusted) analysis of the relative treatment effectiveness of dinutuximab beta, when compared with isotretinoin." has been amended to "The ERG has severe concerns with the estimation of treatment effectiveness in the economic analysis. These, stem mainly from two overarching issues. The first one is related to the lack of maturity of OS data and the non-existence of EFS data in historical control R1. The second issue relates to the naïve (unadjusted) analysis of the relative treatment effectiveness of dinutuximab beta, when compared with isotretinoin."

continuously over 10 days. Evidence assessing whether rate of infusion affects clinical outcomes is not available.

The ERG considers the data from APN311-302 to be immature and the length of follow-up to be insufficient to determine fully the clinical effectiveness of dinutuximab beta, particularly whether any clinical benefit is maintained in the longer term. Additionally, there is a [redacted] between treatment groups in APN311-302 in [redacted]: based on data supplied by the company during clarification, the most recently captured event occurred at [redacted]' follow-up in the group given IL-2 compared with [redacted] for the group not receiving IL-2.

As no direct evidence on dinutuximab beta-based treatment versus comparators of interest is available, all estimates of comparative clinical effectiveness are based on naïve indirect comparisons. Furthermore, comparative effect estimates are available for only OS. EFS was not captured during the R1 phase of APN311-302 or in Garaventa, and so evaluation of EFS is not feasible. In a suspended STA (GID-TAG507) evaluating dinutuximab alpha, it was noted that immunotherapy might delay rather than prevent events (EFS in Figure C, Section 1.4.2.2). Taking the previous ERG's opinion together with the relatively short length of follow-up available for APN311-302, the ERG considers that the lack of availability of EFS estimates results in an incomplete representation of the short- and long-term clinical effectiveness of dinutuximab beta-containing regimens versus isotretinoin.

In support of the ERG's reservations about the maturity of the data presented for dinutuximab beta, the ERG proposes that results on clinical effectiveness of dinutuximab alpha could aid in understanding the clinical effectiveness, particularly in the long term, of dinutuximab beta. Considering OS, as raised by the ERG assessing dinutuximab alpha, there seems to be an abrupt change in the OS curve for the immunotherapy after approximately year 7, as depicted in Figure D (Section 1.4.2.2). Importantly, longer-term follow-up available for dinutuximab alpha (12 years) indicate a marked increase in mortality in the dinutuximab alpha group between 6.5 and 9 years (Figure D) and that the observed data for the immunotherapy-containing regimen and isotretinoin seem to converge between 6.5 and 11 years. OS at 10 years is only marginally higher for those receiving dinutuximab alpha compared with those allocated to isotretinoin alone (approximately 59% with immunotherapy vs 52% with no immunotherapy), but this observation is based on sparse data and it is unclear whether the difference is clinically meaningful (as reported by the ERG assessing dinutuximab alpha). The ERG acknowledges

2) The analysis provided by the company after the clarification stage, reporting the fully adjusted HRs, produced a HR below 1 for the relapsed population (when using the APN311-202 study), suggesting that dinutuximab is less effective that isotretinoin for this population. Therefore, the results, and thus the model results lack clinical meaningfulness;

3) Clinical expert opinion sought by the ERG reported that in the UK, dinutuximab beta is always given as a first line treatment to patients and added that they would not retreat patients with dinutuximab beta unless there was evidence substantiating the effectiveness of dinutuximab as a retreatment option (given that the company decided to not carry on with studies in the relapsed or refractory population, such studies are not foreseeable);

4) The company, in their reply to the ERG's clarification questions states that, "*given the lack of data for the use of dinutuximab beta EUSA in patients that may have already failed (relapsed) or those that are refractory to dinutuximab beta EUSA, EUSA Pharma does not support re-treatment with the drug*". The company adds that there are no on-going studies that evaluate the effectiveness of dinutuximab beta in relapsed or refractory patients;

The ERG has severe concerns with the estimation of treatment effectiveness in the economic analysis. These, stem mainly from two overarching issues. The first one is related to the lack of maturity of OS data and the non-existence of EFS data in historical control R1. The second issue relates to the naïve (unadjusted) analysis of the relative treatment effectiveness of dinutuximab beta, when compared with isotretinoin. The ERG summarises the key issues surrounding these aspects of the economic evaluation below:

1) The company's model relies on the naïve (unadjusted) analysis of dinutuximab beta's relative effectiveness, compared with isotretinoin. As reported in the NICE Decision Support Unit's Technical Support Document 18, in the case of a disconnected network of evidence, a naïve indirect comparison will include sampling error plus systematic error due to the imbalance in both prognostic factors and effect modifiers. In this case, children forming the historical control R1 were randomised in the R1 phase of HR-NBL-1 (see Section 4 for more details), which was designed to compare the effectiveness of BuMel

immunotherapy works in a different way from conventional chemotherapy, by potentially altering the disease pathway, it might be inappropriate to assume a constant HR between dinutuximab beta and isotretinoin. It is uncertain if the plateau that might be observed for immunotherapy agents is likely to be present for dinutuximab beta, and how this affects the comparison to isotretinoin.

As the ERG did not have any other available source of comparator data for EFS, it turned to the previous STA for dinutuximab alpha vs isotretinoin (GID-TAG507). Figure B and Figure C show the difference in OS and EFS KM curves when the latest data cut-off point became available for dinutuximab alpha and isotretinoin. The results show that the observed data for immunotherapy and standard therapy appear to converge between 4.5 and 11 years in the longer follow-up analysis. This could suggest that, had a longer follow-up period been allowed in APN311-302, the EFS and OS curves for dinutuximab beta would eventually drop to be closer to the EFS curve for isotretinoin. However, the unadjusted analysis of dinutuximab beta (Figure D and Figure E) shows a substantial separation of EFS and OS curves at around year 7. With regards to EFS, the ERG considers this separation to be unsubstantiated as it is not evidence-based (as R1 did not provide EFS data) and is very likely to represent an overestimation of the effect of dinutuximab beta in terms of preventing disease progression. Based on visual inspection of Figure B, long term EFS is only slightly better by 7% among immunotherapy patients (approximately 52% vs 45%) at 10 years. Despite the apparent difference between the two curves, this was not found to be statistically significant (p-value for log rank test: 0.153 as stated in the dinutuximab alpha ERG report).

Figure B. Observed EFS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis (Figure 19 in ERG report for dinutuximab alpha STA [GID-TAG507], page 86)

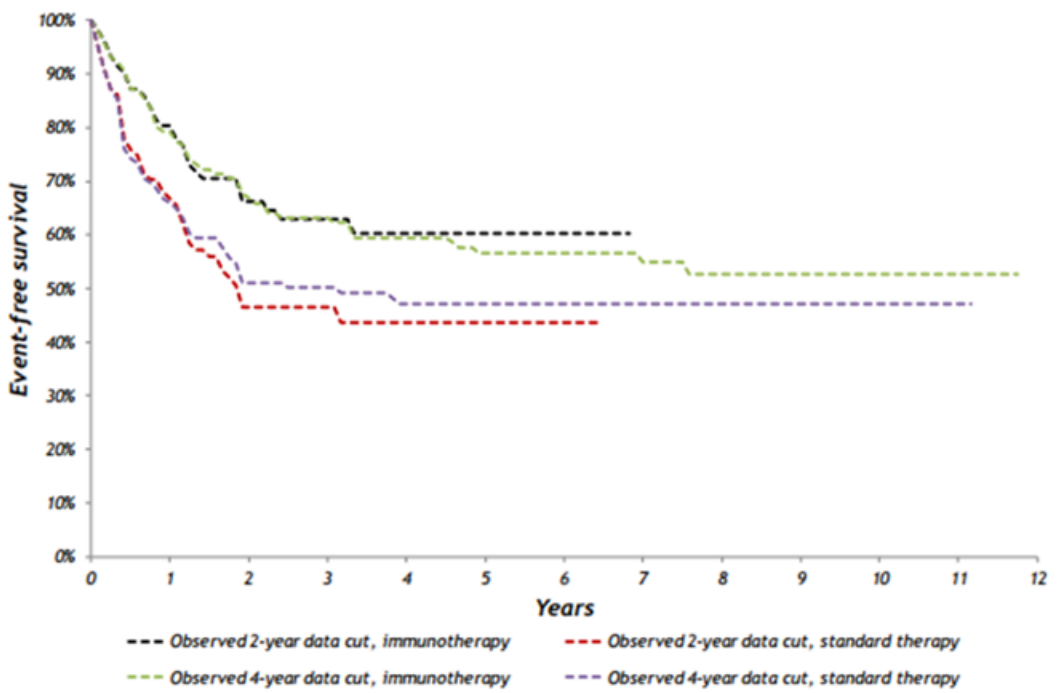


Figure C. Observed OS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis (Figure 20 in ERG report for dinutuximab alpha STA [GID-TAG507], page 87)

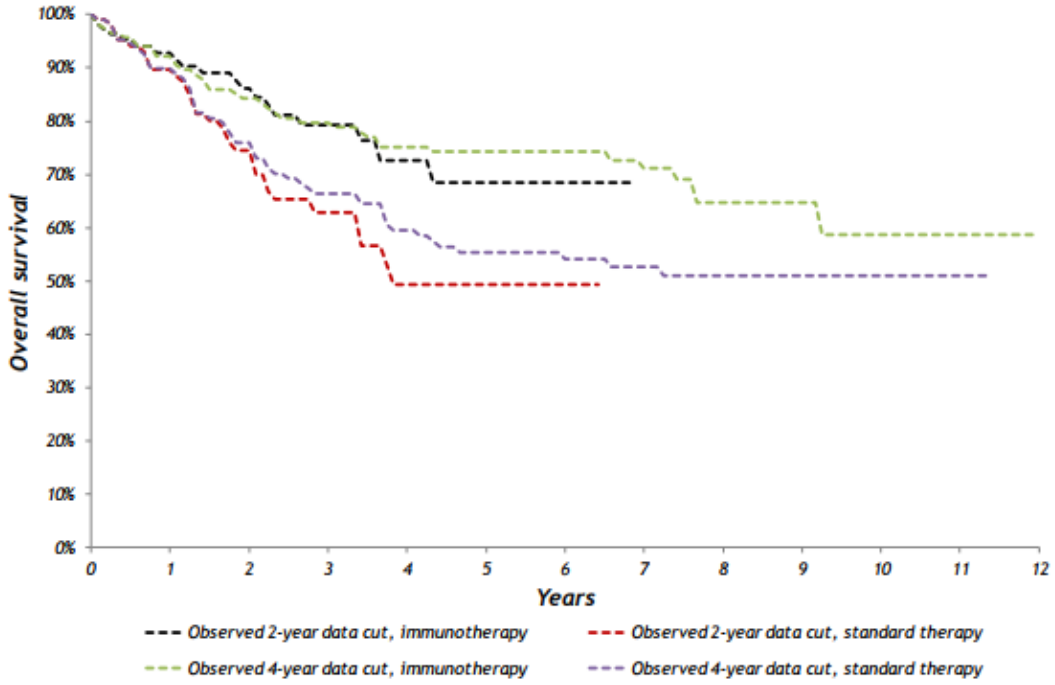


Figure D. Unadjusted EFS curve for dinutuximab beta and estimated unadjusted EFS curve for isotretinoin

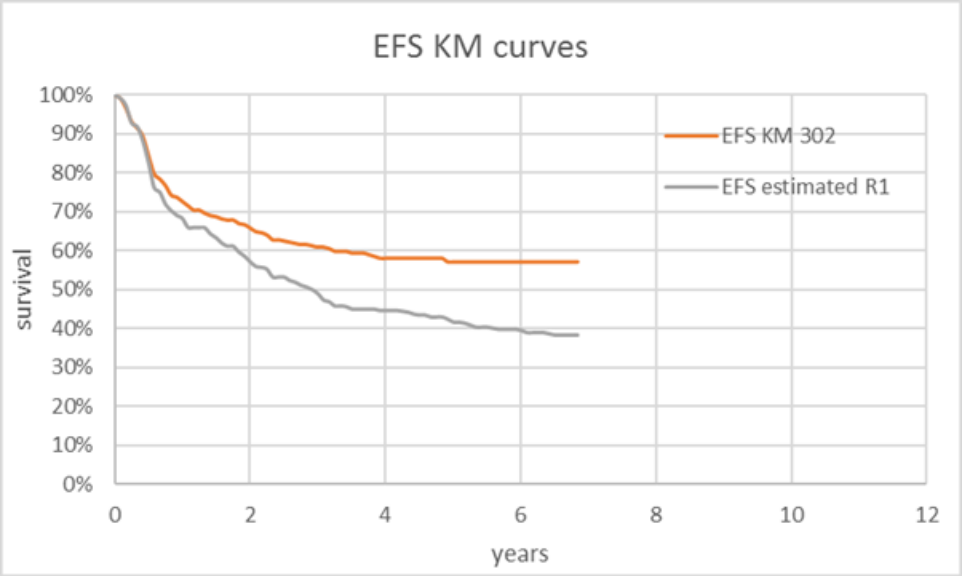
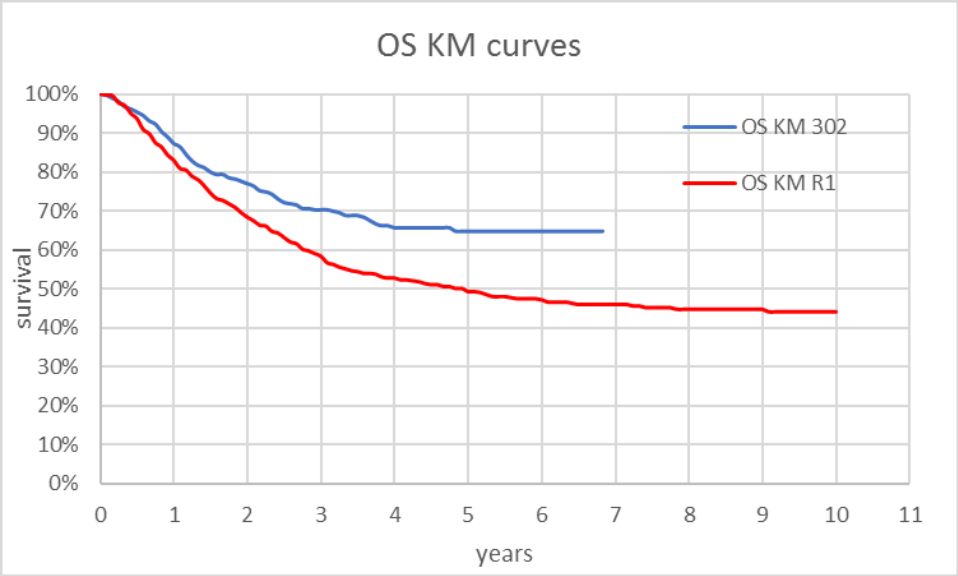


Figure E. Unadjusted OS KM curves

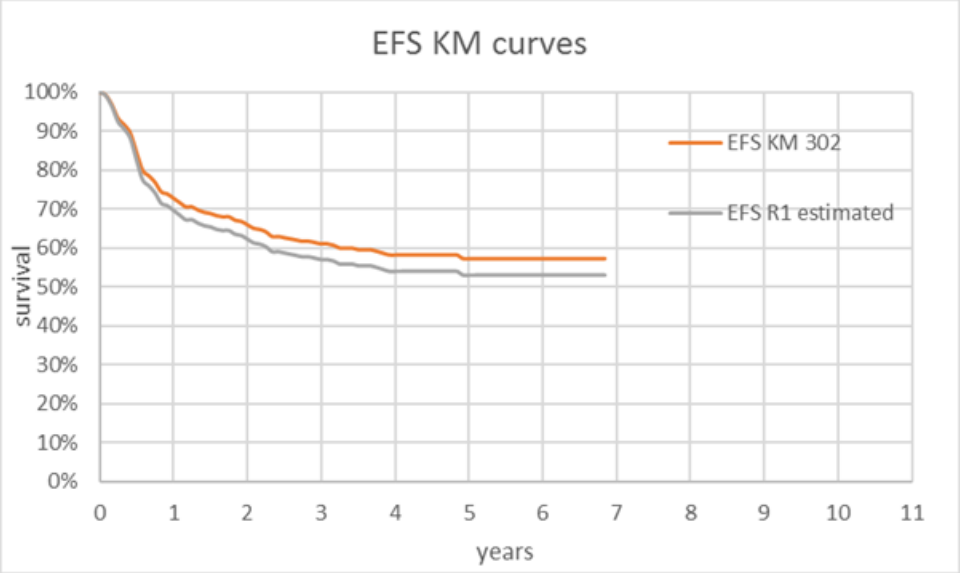


The ERG took the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission and applied it to the adjusted OS HR estimated for dinutuximab beta. The ERG estimated EFS HR for dinutuximab beta compared with isotretinoin is 1.656/1.319*[redacted]=[redacted].

The ERG acknowledges that the underlying assumption in the ERG's approach is that there is a constant relative risk between EFS and OS for dinutuximab alpha, and furthermore, that the latter relationship is also only observed for dinutuximab beta vs isotretinoin. This is a caveat to the ERG's approach as not only are these assumptions strong, but also the ERG has no evidence to corroborate these. However, the ERG notes that these were the best available data to overcome undertaking a naïve analysis of treatment effectiveness in the model.

After applying the HR of [redacted] to estimate the EFS curve for isotretinoin, the ERG arrived at the curves shown in Figure F. At year 7, the EFS curves seem to be separated by approximately 4% (57% vs 53%). This separation, albeit smaller than the 7% shown in Figure B, is likely to be a better approximation of the relative effectiveness of dinutuximab beta compared with isotretinoin than the 20%, shown in Figure D (resulting from non-evidence based assumptions made by the company, as R1 did not provide EFS data). Finally, the separation of the curves is also linked to the use of a HR to estimate the EFS curve for isotretinoin. As previously mentioned, the ERG cannot be certain if this is a correct methodological approach in this case.

Figure F. Unadjusted EFS curve for dinutuximab beta and estimated isotretinoin EFS curve with adjusted HR



The ERG also notes that about 50% of patients in Figure C were event-free at year 11, regardless of having received dinutuximab alpha or not. With regards to the other 50% of patients, who have progressed, it could be hypothesised that dinutuximab alpha delays, rather than prevents a further event. While it would appear that patients receiving isotretinoin experience the majority of their events over the first two years, a considerable number of events experienced by patients receiving dinutuximab alpha occur between year 2 and year 7. The ERG sought clinical expert opinion with regards to the role

of dinutuximab beta in preventing or delaying events. The clinical experts advising the ERG confirmed that dinutuximab beta was expected to delay events, rather than prevent them.

The ERG's proposed alternatives to overcome the several methodological shortcomings of the company's analysis are, to some degree, flawed, when considered in isolation (for example an assumption of proportional hazards in order to use HRs). However, when combined and incorporated in the final analysis, the synergies resulting from the individual changes made by the ERG, contribute to an increase in the level of uncertainty in the analysis. The ERG summarises the main methodological changes undertaken in Table D.

Table D. Summary of fundamental problems in CS and ERG's ammendmants

	Problem in CS	**ERG's amendment**	**Level of mitigation**	**Proposed approach**
	Naïve comparison of OS data	Use of adjusted HR for OS	Problem partially mitigated. Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis. However, the HR estimation method is flawed and it is unlikely that the use of HRs is an appropriate method of analysis.	An indirect comparison of dinutuximab beta versus isotretinoin and versus dinutuximab alpha should be undertaken. The major methods outlined in the DSU TSD18 applicable in this case are an MAIC and/or an STC. The ERG considers that, depending on what assumptions are made on the nature of the data being compared (e.g. whether proportional hazards hold), an MAIC or an STC will be the most appropriate method to use (please see Section 4 for more details)
	Naïve comparison of EFS data + lack of EFS data for isotretinoin in historical control R1	Taking the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission and applying it to the adjusted OS HR estimated for dinutuximab beta.	Problem partially mitigated. Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis, through the adjusted OS HR. However, the EFS HR carries the same flaws as the OS HR. Furthermore, it relies on the naïve comparison of the relative treatment effectiveness of dinutuximab alpha vs isotretinoin and isotretinoin beta vs isotretinoin.	
Robustness of the final analysis	Economic analysis unfit for purpose. Resulting ICERs are meaningless	Economic analysis unfit for purpose	Problem partially mitigated	As above

When applying the OS and EFS HRs to the dinutuximab beta curves, the ERG obtained the curves shown in Figure H. The fact that the relative positioning of the dinutuximab beta curves (Figure G) was maintained, allied to the fact that the OS HR and the EFS HR used in the ERG's analysis come from different data sources (thus different populations), leads to the fact that the final relationship between the isotretinoin OS and EFS curves has different and cumulative layers of embedded uncertainty. This is illustrated by the EFS curve crossing the OS curve at approximately 70 months. The ERG had to subsequently cap the EFS curve by the OS curve in the isotretinoin arm of the model.

In conclusion, the ERG does not consider that the changes made to the company's model are robust enough to provide results suitable for robust decision making. The economic analysis needs reconsideration before a meaningful ICER can be produced.

Figure G. Gompertz OS and EFS curves for dinutuximab beta

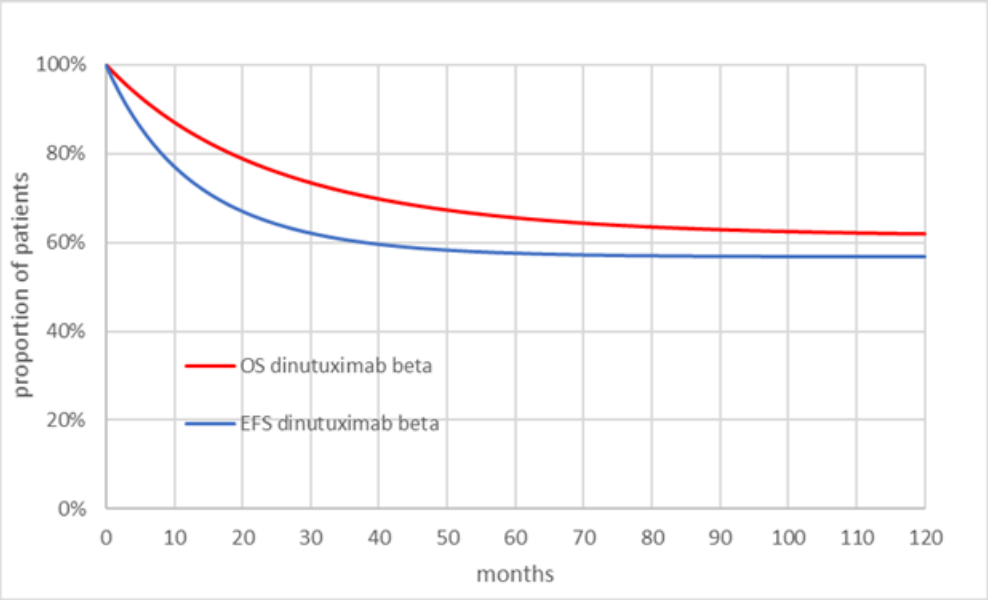
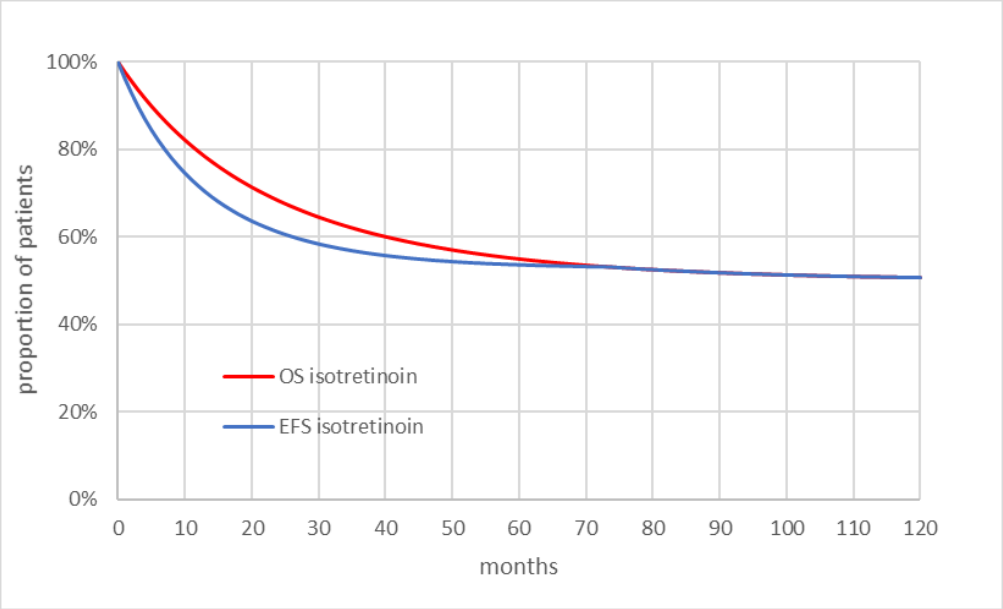


Figure H. Gompertz OS and EFS curves for isotretinoin



The ERG identified issues relating to the estimation of costs and utility values in the economic analysis. These, however, only become relevant once the aforementioned fundamental issues are addressed.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.5.1 Economic

The ERG describes the errors found in the company's analysis throughout Section 5 of the report. The company's base case ICER rose from £22,338 to £31,366 per QALY gained, when the ERG corrections were applied.

As the ERG disagrees with carrying out a naïve analysis of treatment effectiveness, two additional corrections were implemented in terms of relative treatment effectiveness in the model:

1. Restructuring the high-risk economic model to incorporate the use of the OS HR ([redacted]) to estimate OS for isotretinoin.

2. Using the relative difference between the OS HR and the EFS HR (for dinutuximab alpha compared with isotretinoin) in the dinutuximab alpha submission and applying it to the adjusted OS HR estimated for dinutuximab beta of [redacted]. To note is that the EFS HR for dinutuximab alpha vs isotretinoin was found to be not statistically significant in the dinutuximab alpha STA. The ERG's estimated EFS HR for dinutuximab beta compared with isotretinoin is 1.656/1.319*[redacted]=[redacted];

Furthermore, the ERG replaced the dinutuximab beta KM curves for OS and EFS by the fitted and extrapolated Gompertz curves in the short-term model, in order to estimate OS after the 7-year KM OS curve. In doing so, the ERG had to subsequently cap the EFS curve by the OS curve in the isotretinoin arm of the model as the curves cross in the model at approximately 70 months.

Using the Gompertz survival curves and the OS and EFS HRs to estimate relative treatment effectiveness in the model leads to an ICER of £111,858 per QALY gained (with all the ERG's corrections incorporated in the analysis).

The ERG considers that while some of the amendments made to the model provide step changes in the right direction, when combined in the final analysis these produce inconsistent outcomes and introduce a paramount level of uncertainty in the analysis. Therefore, the ERG does not consider that the changes made to the company's model are robust enough to produce an ICER fit for purpose and emphasises that the final ICER of £111,858 is provided for illustrative purposes only.

Given the ERG's assessment that the departing ICER of £111,858 is fundamentally flawed, the ERG did not proceed to implement further scenario analyses as all the resulting ICERs. The ERG lists below the analyses that would be required to explore further uncertainty in the economic model, once the base case ICER is robust enough to be used to carry sensitivity analysis:

1. Changing the assumption that patients entering the failure state of the economic model receive chemotherapy for the rest of their lives. In the base case model, some patients receive chemotherapy for more than 20 years, which is not clinically plausible. Therefore, the partitioned survival model should be changed to estimate newly progressed patients in both the dinutuximab beta and isotretinoin arms of the model. Once newly progressed patients are estimated, an assumption needs to be made for treatment duration. For example, it could be assumed that relapsed patients would stay on treatment for a maximum of one year. An assumption should also be made for the resource use required to manage relapsed patients who have gone off chemotherapy treatment, but are still alive and in the failure state;

2. The cost estimations regarding the chemotherapy regimens used in the failure state should include wastage;

3. The cost of treatment administration in the failure state should use the cost of an inpatient stay (£4,670 for five days), instead of procurement cost for chemotherapy drugs, which is used in the base case model (£2,620.54);

4. Concomitant medication costs in the stable state should include wastage for gabapentin;

4.4.2 Methods

The company evaluated the difference in OS between dinutuximab beta and no dinutuximab beta using the log rank test. Estimates of effect and accompanying 95% CIs were not reported. As part of the clarification process, the ERG requested that, for high-risk neuroblastoma, the company carry out an MAIC using the RCT by Yu *et al*.[80] to inform the comparator group of isotretinoin alone. In case the company considered an MAIC infeasible, as an alternative, the ERG requested HRs and 95% CIs for the indirect comparisons of the relevant APN311 study versus historical control and asked that the HR be adjusted for prior treatment (BuMel vs CEM), MYCN status, and age at diagnosis and INSS stage. As discussed in the paragraph introducing Section 4.4, the company did not carry out the MAIC, instead reporting adjusted HRs, initially adjusted for each individual factor and, after further clarification, adjusted simultaneously for all factors. The company presents p values for chi squared tests for potential association between each prognostic factor and treatment effect. Minimal details on the methods and tools used to generate the HRs are available in the clarification response. Cox proportional hazards regression methods have been implemented to generate multivariate adjusted estimates of effect.

4.4.3 Results

The ERG notes that effect estimates for the indirect comparisons are available for only OS. EFS was not captured during the R1 phase of APN311-302 or in Garaventa, and so evaluation of EFS is not feasible. Given that the ERG evaluating dinutuximab alpha raised the point that the immunotherapy might be delaying rather than preventing events, together with the relatively short length of follow-up available for APN311-302, the ERG considers that the lack of availability of EFS estimates results in an incomplete representation of the short- and long-term clinical effectiveness of dinutuximab beta-containing regimens versus isotretinoin.

Figure 9. Deleted by ERG

4.4.3.1 High-risk neuroblastoma

As the company highlights in the CS, mean OS was substantially longer in those receiving isotretinoin alone (2,447.1 days) compared with those receiving dinutuximab beta plus isotretinoin with or without IL-2 (1,359.4 days; Table 30). Similarly, there was variation between groups in median OS, with a median OS of 1,869 days for those receiving isotretinoin and median OS yet to be reached in the group receiving the dinutuximab beta-containing regimen: estimation of the median OS time was not possible in the group receiving dinutuximab beta-containing regimen as <50% of patients had died at the time of analysis. The company proposes that the large difference in mean OS between the groups is likely due to those in the isotretinoin group being followed for longer. The ERG considers that data from the combined analysis for APN311-302 is immature and has concerns about the disparity in length of follow-up between the two studies.

The company reports that the difference in OS between the two groups was statistically significant when evaluated using the log rank test ($p < 0.0001$; unadjusted HR not available; Table 30) and favoured treatment including dinutuximab beta: unadjusted KM curves for OS are presented in Figure 10. The company reported that Cox regression models had been investigated and that INSS stage at initial diagnosis (combined stage 2 vs stage 4S, stage 3 vs stage 4S and stage 4 vs stage 4S) and prior myeloablative consolidation therapy (BuMel vs CEM) were identified as having statistically significant associations with all-cause mortality ($p = 0.0011$ for INSS stage and $p = 0.001$ for prior myeloablative

- [redacted] compared with isotretinoin alone [redacted]): the reported HR is adjusted for age, INSS stage at initial diagnosis, MYCN status, and prior myeloablative therapy.

- In relapsed neuroblastoma, [redacted]. For example, OS estimate for [redacted] with dinutuximab beta-based treatment [redacted].

- Data on the adverse effect profile of dinutuximab beta are primarily derived from a safety database comprising 514 people who have undergone treatment with the immunotherapy, with a focus on 98 people who received dinutuximab beta as a continuous infusion over 10 days. Administration of dinutuximab beta is known to be associated with pain, hypersensitivity reactions, and capillary leak syndrome. Each person in APN311-202 and APN311-303 experienced a TEAE. The company reported that, although the number of TEAEs decreased substantially with each treatment cycle, the proportion of people experiencing a TEAE remained high throughout the study (data not presented).

4.5.1 Clinical issues

- Methods implemented to search and appraise the literature for clinical effectiveness undermine the robustness of the company's systematic review process, including omission of index terms for neuroblastoma from the search strategies, review of abstract and full text publications by one reviewer, potential non-validation of data extraction.

- Potential sources of bias associated with design and conduct of APN311-302 include uncertainty around concealment of allocation, open label design of the study and lack of masked independent assessment of EFS, and the possible disparity within the study in timing of follow-up and recording of clinical effectiveness outcomes.

(instead of using just the tail) but decided to use KM data (instead of the fitted curve) for the period of time where KM data were available.

Despite these technical shortcomings, the ERG notes that estimated survival data are only used for a maximum of 3 years in the company's base case model, for the dinutuximab beta arm of the model, when the 10-year cure threshold is used. Nonetheless, the ERG disagrees with the approach of using OS and EFS KM data for dinutuximab beta for seven years, and then using estimated survival data for three years. To note is that this approach was not justified by the company. The ERG discusses the issues related with the KM data for OS and EFS in APN311-302 in the next section.

5.4.5.2.1 Kaplan–Meier data from APN311-302

Figure 17 presents the OS and EFS curves for APN311-302, while Figure 18 shows the FS curve, derived by estimating OS-EFS. The ERG is concerned with the fact that the company did not provide numbers at risk to accompany the unadjusted KM data for APN311-302 and R1, despite the ERG's requests for these data at the clarification stage.

Figure 17. Kaplan-Meier curves for OS and PFS in APN311-302

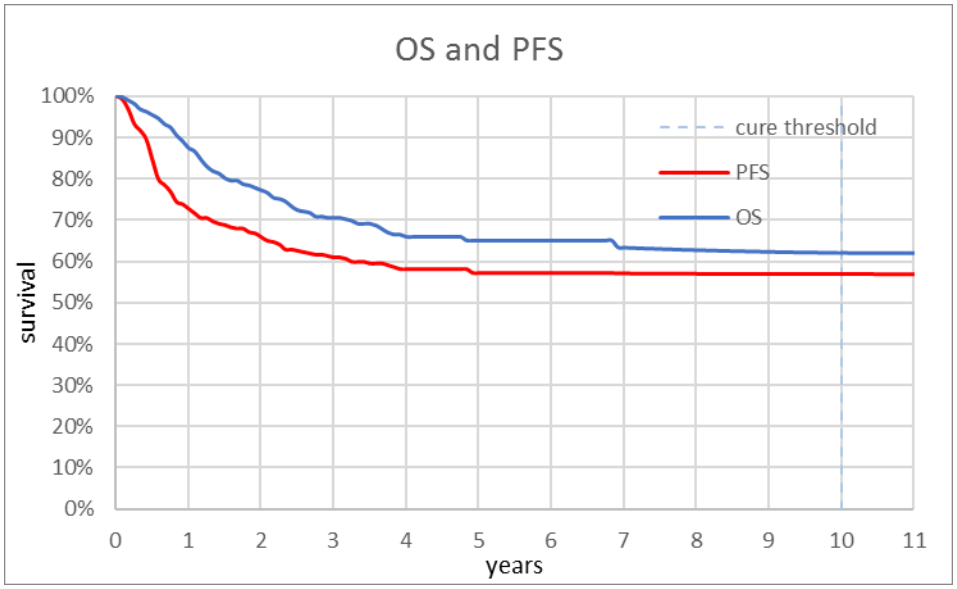
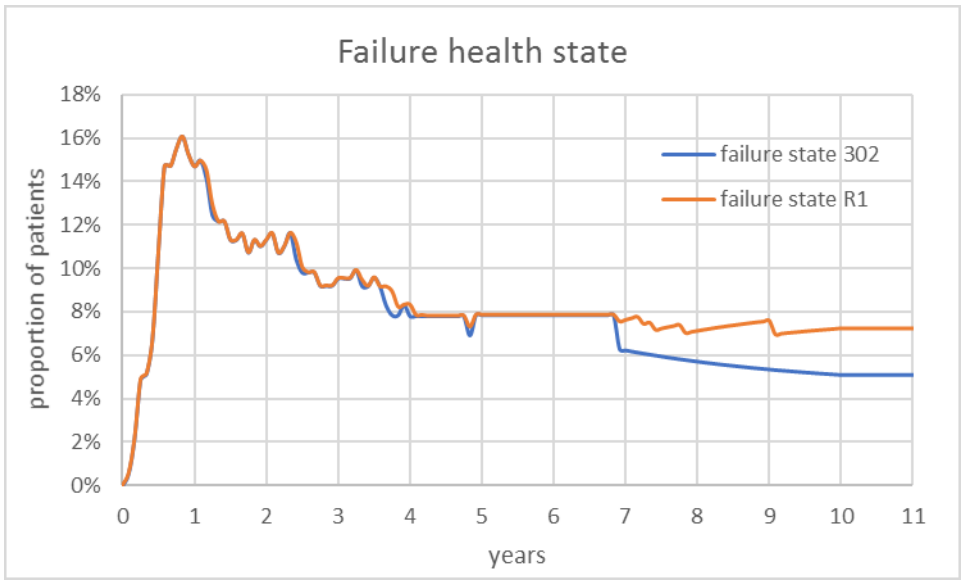


Figure 18. Failure state KM data



The ERG considers that using fitted curves for the 10-year analysis is a more robust approach. Figure 20 shows the unadjusted OS and EFS KM curves for dinutuximab beta, along with the fitted Gompertz curves, and Figure 21 shows the OS KM curves for isotretinoin taken from R1 and the estimated EFS data for R1 (using APN311-302 data), along with the fitted Gompertz curves.

In terms of assessment of fit, the ERG can only rely of visual fit and the measure of variance provided by the company. Both seem to suggest that the Gompertz, lognormal and log-logistic models are the more suitable models to fit the KM data for APN311-302. The same is true for the Gompertz curves fitted to the OS data from R1 and the estimated EFS data for isotretinoin.

The ERG is concerned with the fact that the company's model relies on the naïve (unadjusted) analysis of dinutuximab beta's effectiveness, compared with isotretinoin. As reported in NICE DSU TSD 18, in the case of a disconnected network of evidence, a naïve (unadjusted) indirect comparison will include sampling error plus systematic error due to the imbalance in both prognostic factors and effect modifiers. The guidance adds that the size of this systematic error can be reduced, and probably substantially, by appropriate use of a matching-adjusted indirect comparison (MAIC).[79]

As part of the clarification process, the ERG requested that the company carry out an MAIC. Furthermore, the ERG proposed that an MAIC of the full trial population in APN311-302 versus the group receiving isotretinoin alone in the RCT published by Yu *et al*.[29] (with the updated follow-up data from the dinutuximab alpha submission) would have constitute a better comparison than using R1 (and would have provided a source EFS data for the comparator arm). The company decided against carrying out an MAIC, and instead provided adjusted HRs. The ERG disagrees with the company's arguments for deciding against an MAIC and considers this to have been a most robust method of analysis in this case (details on the company's justification and ERG's views on the latter can be found in Section 4 of the ERG report).

As an alternative, the company provided HRs and 95% confidence intervals (CIs) for the indirect comparisons of OS in the APN311-302 study versus historical control R1, adjusting for prior treatment (BuMel vs CEM), MYCN status, and age and INSS stage at diagnosis. Hazard ratios were initially adjusted for each individual factor and, after further clarification, adjusted simultaneously for all factors. The company presented p-values for chi-squared tests for potential association between each prognostic factor and treatment effect. Cox proportional hazards regression methods have been implemented to generate multivariate adjusted estimates of effect. These are reported in Table 31 below. However, the

Table 38. Summary of fundamental problems in CS and ERG's ammendments

	Problem in CS	ERG's amendment	Level of mitigation	Proposed approach
	Naïve comparison of OS data	Use of adjusted HR for OS	Problem partially mitigated. Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis. However, the HR estimation method is flawed and it is unlikely that the use of HRs is an appropriate method of analysis.	An indirect comparison of dinutuximab beta versus isotretinoin and versus dinutuximab alpha should be undertaken. The major methods outlined in the DSU applicable in this case are an MAIC and/or an STC. The ERG considers that, depending on what assumptions are made on the nature of the data being compared (e.g. whether proportional hazards hold), an MAIC or an STC will be the most appropriate method to use (please see Section 4 for more details).
	Naïve comparison of EFS data + lack of EFS data for isotretinoin in historical control R1	Taking the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission and applying it to the adjusted OS HR estimated for dinutuximab beta.	Problem partially mitigated. Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis, through the adjusted OS HR. However, the EFS HR carries the same flaws as the OS HR. Furthermore, it relies on the naïve comparison of the relative treatment effectiveness of dinutuximab alpha vs isotretinoin and isotretinoin beta vs isotretinoin.	
Robustness of the final analysis	Economic analysis unfit for purpose. Resulting ICERs are meaningless	Economic analysis unfit for purpose	Problem partially mitigated	As above

When the ERG replaced the OS and EFS KM dinutuximab beta curves by the Gompertz curves in the model, it became apparent that the intrinsic problematic relationship between the OS and the EFS KM curves for dinutuximab beta (Figure 29) were carried to the isotretinoin OS and EFS curves (Figure 30), as HRs were applied to the OS and EFS dinutuximab beta curves to estimate isotretinoin curves.

Using the extrapolated Gompertz curves in the short-term model for OS and EFS, is an attempt to minimise the structural issues found in the KM data from APN311-302. However, given that the underlying KM data is flawed (and the Gompertz curves seems to be a considerable good fit to the shape of the KM curves), the shape of the Gompertz curves carries the same problems as the KM curves. Even though the ERG cannot anticipate the direction or the extent of the error in the shape of the curves, it is known that the OS and EFS curves should have a wider gap, as there is either an underestimation

of events being captured in the EFS curve, or an overestimation of deaths captured in the OS curve.

When applying the OS and EFS HRs to the dinutuximab beta curves (Figure 29), the ERG obtained the curves shown in Figure 30. The fact that the relative positioning of the dinutuximab beta curves was maintained, allied to the fact that the OS HR and the EFS HR used in the ERG's analysis come from different data sources (thus different populations), leads to the fact that the final relationship between the isotretinoin OS and EFS curves has different and cumulative lawyers of embedded uncertainty. This is illustrated by the EFS curve crossing the OS curve at approximately 70 months. The ERG had to subsequently cap the EFS curve by the OS curve in the isotretinoin arm of the model.

Furthermore, given the possibility that immunotherapy might be delaying rather than preventing events, or simply that immunotherapy works in a different way from isotretinoin, therefore altering the disease pathway, it might be inappropriate to assume a constant HR between immunotherapy and conventional chemotherapy. It is uncertain if the plateau typically observed for immunotherapy agents is likely to be observed for dinutuximab beta, and how this compares to isotretinoin.

Consequently, the ERG considers that while some of the amendments made to the model provided step changes in the right direction, when combined in the final analysis these produce inconsistency and introduce a paramount level of uncertainty in the analysis. In conclusion, the ERG does not consider that the changes made to the company's model are robust enough to produce an economic model fit for robust decision making. Nonetheless, and for inclusiveness, the ERG provides the results of implementing the changes listed in Table 38 in the final ICER in Section 6. However, the ERG emphasises that these results are provided purely for illustrative purposes.

9. The discounting factor being applied in the model was estimated on a monthly basis instead of an annual basis. For example, at 1.5 years in the model, instead of using an annual discount factor of 1, the company used a discount factor of 1.5. The ERG corrected this to reflect annual discounting in the analysis.

The company's base case results with the implemented ERG's corrections are presented in Table 56 below. The company's base case ICER rose from £22,338 to £31,366 per QALY gained, when the corrections were applied.

Table 56. Company's corrected base case results – high-risk population

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£172,236	13.61	—	—	£31,366
Dinutuximab beta + isotretinoin	£36,172	18.83	£163,808	5.22	
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.					

As discussed in Section 5.4.5, the ERG does not consider that a naïve comparison of APN311-302 and R1 data is a reliable method for estimating treatment effectiveness. Therefore, the ERG used the only available evidence providing an alternative to the company's analysis. This consisted on the following:

1. Restructuring the high-risk economic model to incorporate the use of the OS HR ([redacted]) to estimate OS for isotretinoin.

2. Using the relative difference between the OS HR and the EFS HR (for dinutuximab alpha compared with isotretinoin) in the dinutuximab alpha submission and applying it to the adjusted OS HR estimated for dinutuximab beta of [redacted]. The ERG notes that the EFS HR for dinutuximab alpha vs isotretinoin was found to be not statistically significant in the dinutuximab alpha STA (GID-TAG507). The ERG's estimated EFS HR for dinutuximab beta compared with isotretinoin is 1.656/1.319*[redacted]=[redacted];

As discussed in Section 5.4.5, the ERG replaced the dinutuximab beta KM curves for OS and EFS by the fitted and extrapolated Gompertz curves in the short-term model, in order to estimate OS after the 7-year KM OS curve. In doing so, the ERG had to subsequently cap the EFS curve by the OS curve in the isotretinoin arm of the model as the curves cross in the model at approximately 70 months.

The company's base case results with the implemented ERG's corrections and the applied HRs to estimate isotretinoin curves are presented in Table 57 below. Using HRs to estimate relative treatment effectiveness in the model leads to an ICER of £111,858 per QALY gained (with all the ERG's corrections incorporated in the analysis).

the comparison, the ERG considers the results of the naïve indirect comparisons in OS to be unreliable and advises that the results are interpreted with extreme caution.

The ERG has serious concerns with the robustness of the economic analysis undertaken by the company. The second (updated) version of the company's model provided to the ERG incorporated paramount changes, which were only accompanied by a brief document as a reply to the ERG's clarification questions. Thus, most of the ERG's critique is based on the inspection of the economic model and not on written evidence submitted by the company. The ERG notes that several calculations and assumptions were changed in the updated model, without being reported or justified by the company (or requested by the ERG during the clarification stage). The consequences of this are twofold: the ERG cannot guarantee that some aspects of the economic analysis and/or economic model were not missed; and there were several instances where the ERG had to make assumptions with regards to what was the company's approach. The ERG identified implementation and formulae errors in the updated economic model (described throughout the report). The ERG is concerned that this reflects a poor level of internal quality assessment of the model by the company.

Overall, the company's modelling approach and model structure is unnecessarily burdensome and removes transparency from the formulae and calculations within the model. It is the ERG's view that the use of a decision-tree to estimate short-term outcomes was unnecessary, especially when the cohort data populating the decision-tree structure is taken from the cohort-based partitioned survival model. The decision-tree model is extremely difficult to navigate and has several circular references in its data implementation. All this makes the ERG's review unnecessarily complex. This also leads to a higher probability of errors in formulae, and a lower probability of all errors being identified during the ERG's review process. In total, the company's model was structured in three different model engines, the decision-tree model, the short-term partitioned survival model and the long-term partitioned survival model. The company could have simplified the model structure, and have a single cohort-based partitioned survival model, which would have been more efficient and transparent, and potentially avoided formulae, and calculation errors.

The ERG has severe concerns with the estimation of treatment effectiveness in the economic analysis. These, stem mainly from two overarching issues. The first one is related to the lack of maturity of OS data and the non-existence of EFS data in historical control R1. The second issue relates to the naïve (unadjusted) analysis of the relative treatment effectiveness of dinutuximab beta, when compared with isotretinoin

The ERG's proposed alternatives to overcome the methodological shortcomings of the company's analysis are, to some degree, flawed, when considered in isolation. However, when combined and

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Qarziba (dinutuximab beta) [ID910]

Additional Analyses and Clarification for the Second Appraisal Committee Meeting

Version 2

Date of preparation: 31 January 2018

File name	Version	Contains confidential information	Date
ID910 Additional Analyses and Clarification for the Second Appraisal Committee Meeting[noACIC]	**2**	**No [noACIC]**	**31 January 2018**

Executive summary:

EUSA Pharma has revised the CEA model for dinutuximab beta in high-risk neuroblastoma in accordance to all NICE and ERG requests. The highlights of the changes implemented compared to the previous model submission are as follows:

1- Indirect comparison of dinutuximab beta vs isotretinoin using various scenarios of MAIC analyses were conducted
2- An assumption was made for the resource use required to manage relapsed patients alive but in the failure state
3- Adjustment was made for wastage in the cost estimates for the chemotherapy regimens used in the failure state
4- A weighted analysis of costs taking into consideration the proportion of patients falling into different BSA categories was conducted
5- Logistic regression is replaced with the published multiple regression to estimate age-specific UK EQ-5D in the model (Ara et al. (2010))
6- The use and costs of IL-2 use were removed as there is no clinical justification confirmed by expert clinical opinion and the literature

The revised model containing all the recommended changes above now constitutes the Base Case scenario submitted. In this revised Base Case model:

- The most significant driver of the ICER is the MAIC analyses. Here, the incremental cost-effectiveness ratio (ICER) for dinutuximab beta compared with isotretinoin is **£24,661 per QALY** gained for the high-risk population when, all the predictive variables are included in the MAIC analyses as requested by the ERG, and in line with NICE DSU Technical Support Document 18. (see Table 6)

- In exploring uncertainties around all requested clinically plausible and expert validated assumptions, following various scenario analyses, only variance in the combination of the predictive baseline co-variates included in the MAIC appear to significantly influence the ICER generated by the model, with the ICER ranging from £22,378 to £29,089 (see Table 10)

- Similarly, the agreed and clinically validated cure rate threshold of 10 years produced an ICER of £24,661 per QALY. Shorter timeframes which were dismissed by clinical expert opinion as implausible did produce increasing higher ICERS. (see Table 9)

- Finally, a closer assessment of the cost profile of the isotretinoin treatment arm in the model does suggest that zero costs assigned to treatment costs, monitoring costs and potentially favours isotretinoin compared to dinutuximab beta. These Zero cost assumptions are confirmed by clinical experts as implausible. It was not considered necessary at this stage to amend these cost items in the Base Case model as they were not part of the adjustments requested by NICE and the ERG. (see Table 7)

EUSA Pharma has revised the CEA model for Qarziba (dinutuximab beta) in high-risk neuroblastoma as suggested by NICE in the letter "specification of further work following the Appraisal Committee meeting on 23th November 2017", as follows:

Note:
- The revised CEA model is attached to the submission and all changes compared to previous submission are highlighted in light yellow.
- The name of Dinutuximab beta EUSA has been changed to Qarziba

1) *An indirect comparison of dinutuximab beta versus isotretinoin and versus dinutuximab alpha using a matching-adjusted indirect comparison or simulated treatment comparison approach, as described in the Decision Support Unit's technical support document 18, (particularly sections 2.3, 4.1.4 and 4.2.4 which focus on an unanchored comparison). Further guidance and a worked example, with appropriate code, is available on the DSU website.*

As requested, the assessment of the efficacy of immunotherapy with dinutuximab beta was performed by an indirect comparison (matching-adjusted indirect comparison (MAIC)) to the group receiving isotretinoin alone of another randomized clinical trial published by Yu et al[1]. However, the analysis was not run versus dinutuximab alpha since dinutuximab alpha was not considered as a relevant comparator following MA withdrawal.

The MAIC was carried out using the methods described in Decision Support Unit's technical support document 18[2], in order to compare EFS and OS for dinutuximab beta+isotretinoin+/- IL-2 (full population of APN311-302) versus isotretinoin alone[1]. As APN311-302 arms (+/- IL-2) did not report any significant difference in OS and EFS, all the people in APN311-302 were included to maximise the number of people available for analysis.

Summary of MAIC method
The first step in the process identified and excluded those patients in the APN311-302 dataset who would not have qualified for inclusion in the Yu et al study[1]. Following this, baseline characteristics of the patients in both studies were examined, in order to identify those factors that were predictive of the outcomes of interest and which could potentially vary between studies.

Selection of prognostic factors was based on:

1. Availability of parameters from individual patient datasets for study APN311-302

2. Availability of the parameters that were also available for the published comparator study (Yu et al, 2010[1])

3. Determination which of those variables were potentially predictive of EFS or OS was based on:

    a. A preliminary screen based on those baseline characteristics that were demonstrated in the Yu study to be potentially predictive, based on a p-value of <0.2 for either EFS or OS (Table 1, p.1328, Yu et al[1])

    b. Discussion with a clinical advisor (Dr Juliet Gray; Associate Professor in paediatric oncology, Southampton NHS Trust) in order to identify which of the candidate variables were likely to be clinically relevant predictors in the patient group likely to be considered for treatment with dinutuximab beta.

Propensity weighting was then applied to the APN311-302 patient set, in order to allow comparison with the Yu et al study for the MAIC.

Adjusted results are presented for OS and PFS (KM curves, HR + 95% CI) for both the combined dinutuximab treatment arms (regardless of IL2 treatment) and also for the two arms separated out according to whether IL2 was given or not.

The R-code used for this analysis are attached as an appendix to this submission (Appendix 1).

The OS and EFS have been extracted from their respective Kaplan Meier curves. To compute the Hazard Ratios (HRs) and confidence intervals, we assumed that OS and EFS follow an exponential distribution.

Results

Populations

The only clinically relevant difference in inclusion criteria between the two studies was the prior treatment response before autologous stem cell transplant. In the case of the Yu et al study[1], patients were required to have at least a partial response, while in the APN311-302 study this was not a requirement.

Examination of the APN311-302 dataset revealed 16 patients who had shown less than a partial response to prior therapy and 10 patients for whom this information was missing. These 26 patients were therefore excluded from the dataset taken forward for the MAIC.

Prognostic variables

The candidate prognostic variables used are summarised in Table 1, together with the rationale for their inclusion/exclusion. The final variable set used in the CEA model base case was:

- Age
- INSS stage
- Tumour MYCN status
- Response to treatment before ASCT

Table 1: Baseline variables considered for inclusion in the MAIC and CEA model base case

Predictor variable	Yu et al*	Study APN311-302	Clinician opinion	Outcome
Age (<18 months)	No significant effect	Data available	Felt to be important despite negative finding in Yu et al	Included
Gender	Not analysed	Data available	Not felt to be predictive of outcome	Not included
INSS stage	Significant for EFS + OS	Data available	Agreed to be clinically relevant	Included
Tumour MYCN status	Significant for OS	Data available	Agreed to be clinically relevant	Included
Tumour histological features	Significant for EFS + OS	Data not available	Felt not to be clinically relevant in population with metastatic disease in whom dinutuximab beta would be considered	Not included
Tumour ploidy	Significant for EFS + OS	Data not available	Felt not to be clinically relevant in population with metastatic disease in whom dinutuximab beta would be considered	Not included
Response before ASCT	Significant for EFS + OS	Data available	Agreed to be clinically relevant	Included
No of ASCTs	No significant effect	Data not available	Not felt to be relevant to UK practice	Not included
Number of purged infusions	No significant effect	Data not available	Not felt to be relevant to UK practice	Not included

** "significant" implies p<0.2 for either EFS or OS*

MAIC results

The intention-to-treat population in APN311-302 included 370 patients assigned to Myeloablative therapy plus interleukin-2 (IL-2) plus isotretinoin (N = 190) or Myeloablative therapy plus isotretinoin (N = 180). After excluding 26 patients with an achievement worse than a partial response after completion (see above), the dataset of MAIC included was 344 patients.

Table 2: Baseline characteristics pre- and post-matching

Baseline Characteristics[a]	APN311-302 study sample		
Yu et al study	Pre-match	Post-match	As reported
Age			
< 18 Mo	6.75	4	4
≥18 Mo	93.25	96	96
INSS stage			
2	0.27	0.0	0.0
3	9.18	15	15
4S	1.89	0.0	0.0
4	88.65	85	85
Tumour MYCN status[b]			
Not amplified	48.92	45.2	45.2
Amplified	41.08	39.8	39.8
Unknown	10	15	15
Response before ASCT[c]			
Complete response	55.68	34	34
Very good partial response	25.41	43	43
Partial response	11.89	23	23
Less than partial response	4.3	-	-
Missing/NE	2.7	-	-

Notes:

[a] Reported as percentages in the table

[b] The distribution of Tumour MYSN status in Yu study was recomputed to include those with unknown status

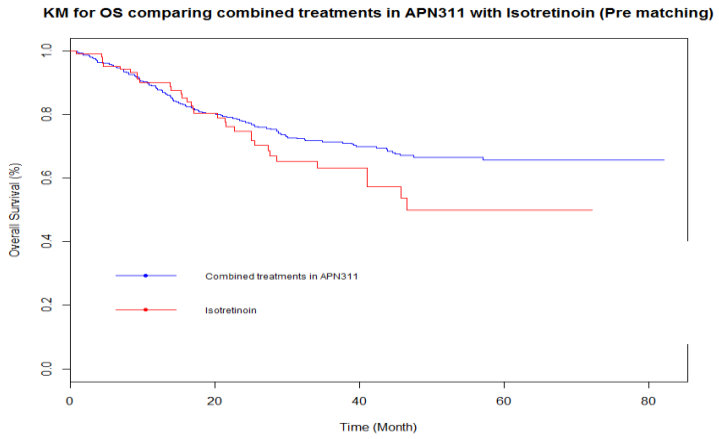
[c] A total of 26 patients were from the APN311 study, 10 with missing/NE value and 16 achieving less than PR

Table 3 Comparisons of event-free survival and overall survival

Comparison	After matching	
	HR	(95% CI)
Event-free survival		
Dinutuximab beta + CT vs. Isotretinoin alone at 24 Months	0.553	0.51 - 0.63
Dinutuximab beta + CT vs. Isotretinoin alone at 48 Months	0.672	0.61 - 0.79
Dinutuximab beta + CT vs. Isotretinoin alone at 70 Months	0.681	0.62 - 0.8
Overall Survival		
Dinutuximab beta + CT vs. Isotretinoin alone at 24 Months	0.886	0.78 - 1.16
Dinutuximab beta + CT vs. Isotretinoin alone at 48 Months	0.620	0.53 - 0.85
Dinutuximab beta + CT vs. Isotretinoin alone at 70 Months	0.629	0.54 - 0.86

Figure 1. Kaplan Meier curve for Overall Survival (OS)

A. Pre-matching



B. Post-matching

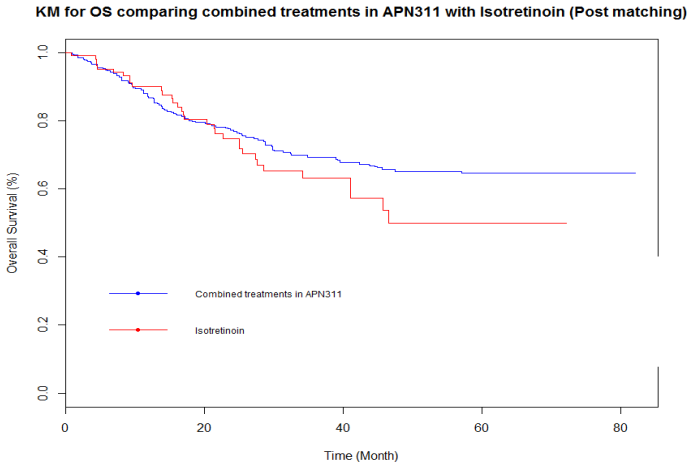
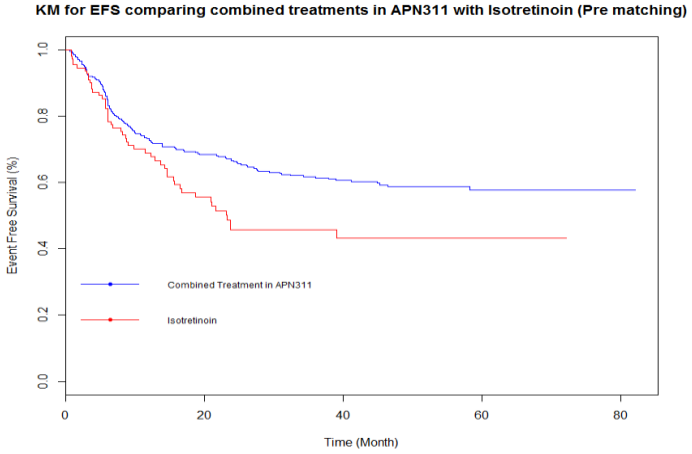
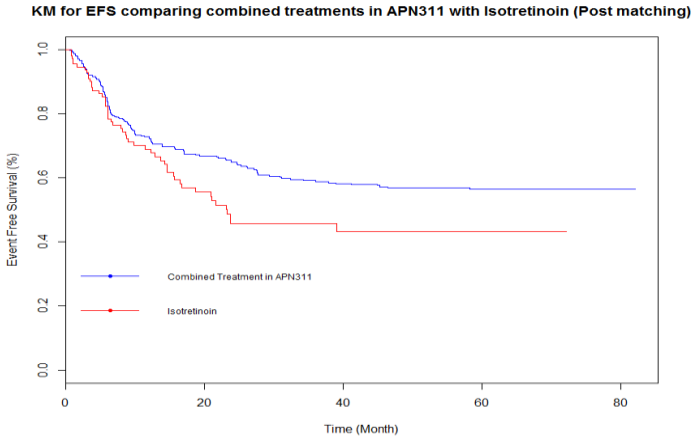


Figure 2. Kaplan Meier curve for Event-free Survival (EFS)

A. Pre-matching



B. Post-matching



2) A revised fully executable economic model and cost-effectiveness analyses that incorporates:

a) *The indirect comparison (as specified above)*

The monthly OS and EFS have been extracted from their Kaplan Meier curves through MAIC analysis (Appendix 2) and used as input in the revised CEA model (Sheet called "MAICSurvivalFunction"). The dataset of MAIC was used also for calculating the percentage of newly progressed patients per month (revised model sheet called "Dataset_DB_MAIC").

Treatment effectiveness within the updated short-term model was implemented through a partitioned survival method, which used the OS and EFS data from MAIC to determine mortality and disease progression for each cycle of the economic model, respectively. The use of survival analysis in the model depends on the cure threshold assumed for the analysis. EFS and OS data from MAIC were used for the time period where data were available (70 months), and then used a parametric curve fitted to available data with Gompertz models for both clinical outcomes to extrapolate the clinical data for the rest of the short-term model's time horizon (71 months to cure threshold).

b) *Weighted average costs taking into account the proportion of people in different body surface area categories in trial APN311-302.*

Individual patient data from APN311-302 were used to define BSA categories and to calculate the weighted average number of vials for each administration of dinutuximab beta. Please find below the calculations (as well as in the revised model excel file sheet called "InputFL"):

Table 4 – BSA categories in APN311-302 and weighted average number of vials of dinutuximab beta

BSA category	>0 - ≤0.4m2	>0.4m2 - ≤0.8m2	>0.8m2 - ≤1.2m2	>1.2m2 - ≤1.6m2	>1.6m2 - ≤2.0m2	>2.0m2 - ≤2.4m2
Number of vials per admin of 50mg/m2	1 vial(s)	2 vial(s)	3 vial(s)	4 vial(s)	5 vial(s)	6 vial(s)
Total number of patients with BSA data	285					
Total number of patients within each BSA category	4	242	32	6	1	0
Proportion of patients within each BSA category (%)	1.40%	84.90%	11.20%	2.10%	0.40%	0.00%
Weighted average number of vials for each admin at 50mg/m2	2.1509					

c) *Two assumptions in the failure health state:*

i. The model needs to estimate newly progressed patients in both the dinutuximab beta and isotretinoin arms of the model. Once newly progressed patients are estimated, an assumption needs to be made for treatment duration (for example, it could be assumed that relapsed patients would stay on treatment for a maximum of one year)

APN311-302 individual patient data weighted post-MAIC were used to derive the percentage of non-fatal events per month (i.e. newly progressed patients), as calculated in the revised model (sheet called "Dataset_DB_MAIC"). The same proportion has been applied to derive the percentage of newly progressed patients in the control arm. These proportions have been used in the "5y10yFL" and "LifetimeFL" worksheets on both dinutuximab and isotretinoin alone arms. Without access to individual patient data from Yu et al on the control arm, we assumed the same proportion of newly progressed patients per month in both arms.

Clinical expert opinions sought by EUSA reported that in the UK, duration of treatment for a child in failure state is difficult to predict as treatments are individualized regarding clinician strategy and level of aggression accepted by families. However, when they consider all their patients in failure state, they agree that one year of treatment is a reasonable assumption.

Based on the APN311-302 individual patient data weighted post-MAIC, the percentage of patients surviving one year of treatment and the percentage of patients on treatment were computed for each month. A logarithmic fit was then applied to calculate the proportion per month of patients surviving an event for at least one year and applied in both arms (worksheet called "Dataset_DB_MAIC").

ii. The resource use needed to manage the disease in people who complete chemotherapy and relapse, but are still alive and are in the failure health state.

Clinical expert opinions sought by EUSA reported that in UK, after one year of treatment post-relapse, costs for those disease-free children and children in stable state post-dinutuximab beta could be assumed similar (i.e. £76.5 per month, Table 68 in the CS).

d) Adjustment for wastage in the cost estimates for the chemotherapy regimens used in the failure state.

Adjustment for wastage has been made in the revised model to select the optimal vial size minimizing wastage considering the weight or the BSA evolutions of children through the CEA model. These changes could be found in the worksheet called "5y10yFL" and "LifetimeFL", highlighted in light yellow (columns J, K, M in "5y10yFL" and columns AC, AD and AF in LifetimeFL).

e) The cost of a hospital day (£934 per day) to calculate the administration costs per cycle, which amounts to a total of £4,670 for 5 days in the hospital (which compares to the chemotherapy procurement cost of £2,620.54 used in the model originally).

In the failure input costs, £934 per hospital day has been applied to calculate the administration costs per cycle (worksheet called "InputGeneral" column I8). The total amount per months or years are computed in the worksheets called "5y10yFL" and "LifetimeFL", respectively, highlighted in light yellow (column L in "5y10yFL" and column AE in LifetimeFL). For example, the cost of administration per month is equal to £6,768.92 (=£934* 5 days/21 days* 365.25 days/12 months).

f) Adjustment for wastage of gabapentin in the concomitant medication costs in the model.

Adjustment for wastage of gabapentin in the concomitant medication costs has been implemented in the revised CEA model (worksheet "DrugCostcalculation", J12).

g) The multiple regression published by Ara et al. (2010) to estimate age-specific UK EQ-5D values in the model.

The previous logistic regression has been replaced with the published algorithm by Ara et al. 2010 to estimate mean EQ-5D HSUVs for individuals in the general population, using a multiple regression including gender, age and age^2 as covariates. The Ara et al equation EQ-5D = 0.9508566 + 0.0212126*male – 0.0002587*age – 0.0000332*age^2 has been used

in the worksheet “5y10yFL” columns AQ and AR, and “LifetimeFL” columns L and M, as well as in the worksheet “UKData”.

Presentation of the base-case incremental cost-effectiveness analysis results

The changes applied to the revised CEA model compared to the previous submission have been summarised in the Table below and highlighted in light yellow in the submitted excel model.

Table 5 – Summary of changes apply to the revised CEA model

Company's approach	ERG's amendment	Company's revised model
OS and EFS data from APN311-302, to overcome the lack of EFS data for the comparator arm R1, the absolute separation (in %) between OS and EFS observed in the active arm is the same for the comparator arm over time	Proposed approach: an indirect comparison of dinutuximab beta vs isotretinoin using a MAIC analysis	Revised model includes ERG proposed approach, the monthly MAIC OS and EFS as input in the model
Patients entering the failure state of the economic model receive chemotherapy for the rest of their lives.	The partitioned survival model should be changed to estimate newly progressed patients in both the dinutuximab beta and isotretinoin arms of the model. Once newly progressed patients are estimated, an assumption needs to be made for treatment duration. An assumption should also be made for the resource use required to manage relapsed patients who have gone off chemotherapy treatment, but are still alive and in the failure state	Revised model uses APN311-302 individual patient data weighted post-MAIC to derive the newly progressed patients per months in dinutuximab beta arm and the same proportion were assumed for isotretinoin arm. One year of treatment is a reasonable assumption (expert opinions) and was used in the revised model. After one year of treatment post-relapse, costs for those disease-free children could be assumed similar to children in stable state post-dinutuximab beta (i.e. £76.5 per month).
Cost estimates for the chemotherapy regimens in failure state do not include wastage	Adjustment for wastage in the cost estimates for the chemotherapy regimens used in the failure state	Revised model includes the ERG's suggested amendment
Administration cost for failure state was based on procurement cost for chemotherapy drugs (£2,620.54)	Cost of a hospital day (£934/day) should be used to calculate the administration costs	Revised model includes the ERG's suggested amendment
Median BSA from APN311-302 (0.63m2) has been used for most of the cost calculations in the model	Given that BSA is one of the key drivers of costs in the economic model, a weighted analysis of costs taking into consideration the proportion of patients falling into different BSA categories would be advisable	Revised model includes the ERG's suggested amendment, taking into consideration the individual patient data from APN311-302

Company's approach	ERG's amendment	Company's revised model
Cost for gabapentin in the concomitant medication costs does not include wastage	Adjustment for wastage of gabapentin in the concomitant medication costs in the model	Revised model includes the ERG's suggested amendment
Age-specific UK EQ-5D utilities relies on a logistic regression using published UK EQ-5D general population norms	ERG recommends that the logistic regression is replaced with the published multiple regression to estimate age-specific UK EQ-5D in the model (Ara et al. (2010))	Revised model includes the ERG's suggested amendment
Long-term model has annual cycle	Applied a half-cycle correction in the long-term model	Revised model includes the ERG's suggested amendment
5.6 increase in mortality factor applied to only female mortality (formulae error)	Applied to weighted male and female mortality in the UK population	Revised model includes the ERG's suggested amendment
Company included cost of treatment with IL- 2 in the isotretinoin arm of the model	ERG does not see a clinical justification for this, please removed the costs of IL-2	Revised model includes the ERG's suggested amendment
Used 7.5 hospital days for the first cycle and 2.5 days for the second cycle	Included 10 days for hospitalisation in the first cycle and 5 days in the second cycle	Revised model includes the ERG's suggested amendment
100% of patients in the dinutuximab arm assumed to receive IL-2	Changed the 100% assumption to 51% of patients (based on proportion in APN311-302)	Revised model includes as a base case 0% IL-2 and other scenarios have been run (41% and 51%, please see section scenario above)
Not included the administration costs associated with treatment with IL-2	Included it	Revised model includes the ERG's suggested amendment
Undiscounted total costs for the stable and failure states of the short-term model	Replaced these with discounted costs	Revised model includes the ERG's suggested amendment
First row of costs and QALYs in the Excel model wasn't included	Included it in the model	Revised model includes the ERG's suggested amendment
No probabilistic sensitivity analyses of varying relative treatment effectiveness	Probabilistic sensitivity analyses to incorporate the impact of varying relative treatment effectiveness estimates on the incremental cost-effectiveness ratios (ICERs)	Revised model includes the ERG's suggested amendment, by applying a multiplication variable that follows a normal distribution
Mean body weight from APN311-302	No specific request	The median was used instead of the mean body weight from APN311-302 to follow the use of median age and BSA inputs

Company's approach	ERG's amendment	Company's revised model
Discounting factor estimated on a monthly basis instead of an annual basis	Corrected this to reflect annual discounting in the analysis	Revised model includes the ERG's suggested amendment
-	-	A distinction between Pyrexia/infection and grade 3-4 infections wad added to the model as follow: in the active arm, 54.9% of patients experience Pyrexia or grade 1-2 infections, 26.2% (48/183 patients) of patients experience grade 3 infection and 1.1% (2/183 patients) grade 4 infection (page 70 of the APN311-302 CSR). In the comparator arm, 15% of patients experience Pyrexia or grade 1-2 infections and 7% grade 3-4 infections as reported in Yu et al 2010.
-	-	Revised event rates of severe capillary syndromes were also considered as follow: 3.3% in the active arm (page 70 of the APN311-302 CSR), and 0% in the isotretinoin arm.

As a summary, please find below the main assumptions considered for the base case economic model:

- Continuous infusion over the first 10 days, 2 administrations for 10 days infusion (as suggested in the pharmacy manual)
- After 10yrs in EFS a patient assumed cured (cure threshold, expert opinions)
- A 1.5% discount on costs and benefits
- Mortality rate in cured state: 5.6 factor applied to the age and gender-matched mortality in the UK general population
- EFS and OS data post-MAIC from both treatment arms were used for the time period where data were available (70 months), and then used a parametric curve fitted to available data with Gompertz models (best visual and minimized fit) for both clinical outcomes to extrapolate the clinical data for the rest of the short-term model's time horizon (71 months to cure threshold).
- Adverse Events: assumed that utility values for each health state do not differ by treatment arm.
- HRQoL: A decrement utility value of 12.5% (Portwine et al, 2016) for high-risk and neuroblastoma patients compared to general population
- To reflect clinical practice in UK, 0% of IL-2 has been used. "The official position of both the European Neuroblastoma research network (SIOPEN) and the UK Children's Cancer and Leukaemia Group (CCLG) is that the antibody should be given alone (without IL-2), even in the context of residual disease. The exception of this would be in the context of a clinical trial (e.g the current SIOPEN HR-1 study, for which Dinutuximab beta is provided as part of the trial). This will remain the position unless any new information emerges to support benefit of giving IL-2. This guidance will be followed by UK paediatric oncologists." (Expert opinion, leader from CCLG).

A list of all variables used in the economic analysis is provided in Appendix 3.

According to the revised updated base case analysis, the ICER for dinutuximab beta compared with isotretinoin is £24,661 per QALY gained, for the high-risk population (Table 6). The summary of predicted resource use by category are summarised in the Table 7. As described in the CS document, the input costs have been validated by experts.

Table 6: Base-case results of the revised CEA model

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
Comparator - Isotretinoin alone	£55,923	11.6460	—	—	—
Dinutuximab Beta + isotretinoin	**£225,373**	**18.5172**	**£169,450**	**6.8712**	**£24,661**

Table 7: Summary of predicted resource use by category of cost

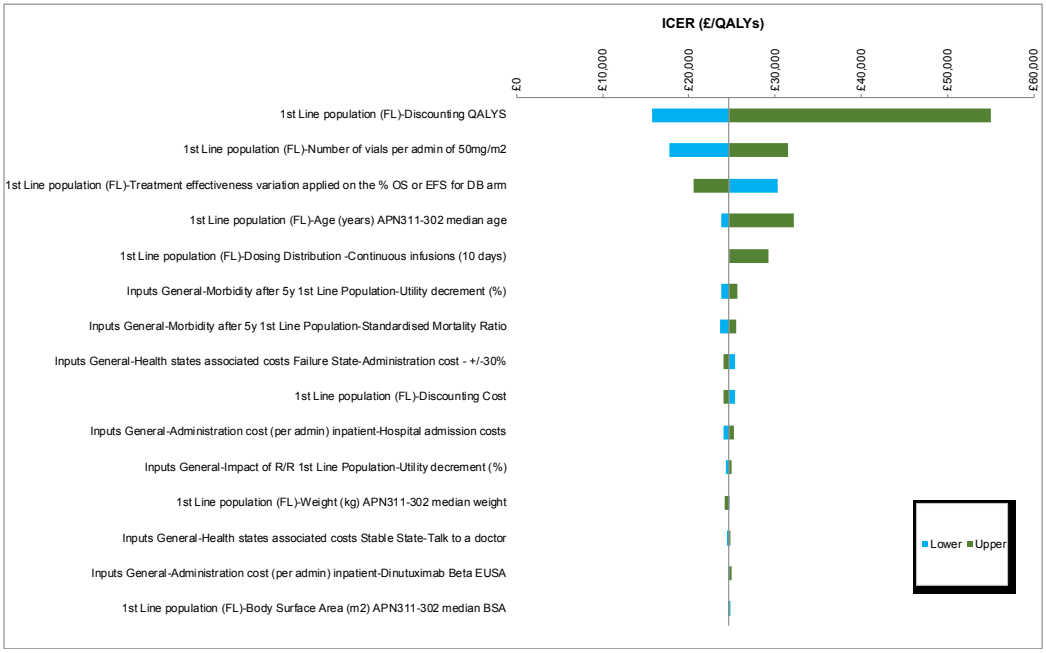
Item	High-Risk Neuroblastoma				
	Cost (£), Dinutuximab	Cost (£), Isotretinoin	Increment	Absolute Increment	% Absolute Increment
Drug Cost	£157,833	£,268	£157,565	£157,565	93.1%
Administration & Hospitalization Costs	£17,247	£,0	£17,247	£17,247	10.2%
Concomitant medication cost	£,946	£,0	£,946	£,946	0.6%
Monitoring cost	£,560	£,0	£,560	£,560	0.3%
Adverse event cost	£2,097	£,392	£1,704	£1,704	1.0%
Failure cost	£27,035	£43,278	-£16,243	£16,243	9.6%
Ongoing healthcare cost	£20,370	£12,886	£7,484	£7,484	4.4%
Total	£226,088	£56,824	£169,263	Total absolute increment	100%

Sensitivity analyses

The table in Appendix 3 summarises the parameters included in the DSA and PSA, with the distributions used to determine their values.

The results of the one-way sensitivity analysis on the revised model are presented in Figure 4. According to the analysis the main drivers of the high-risk model are the discount rate applied to QALYs, the number of dinutuximab beta vials and treatment effectiveness variation.

Figure 4: Tornado diagram for deterministic sensitivity analysis for dinutuximab beta in high-risk



A probabilistic sensitivity analysis (PSA) was performed to assess the joint parameter uncertainty around the updated base case results. The results across 1,000 iterations are presented in Table 8. The PSA results produced a mean ICER of £24,684 per QALY gained for dinutuximab beta+isotretinoin compared to isotretinoin for the high-risk population. The scatterplots, and cost-effectiveness acceptability curves are presented in Figure 5 and Figure 6. All simulation results lie in the north-east and south-east quadrants of the cost-

effectiveness plane, indicating that dinutuximab beta is always more effective than isotretinoin alone. The CEAC shows that dinutuximab beta in the first-line setting has a 71.3% probability of being below the £30,000 willingness to pay threshold when compared with isotretinoin alone.

Table 8: PSA results for dinutuximab beta for the high-risk population

	Immunotherapy				Standard Therapy			
	Mean	Median	Lower 95% Confidence Interval	Upper 95% Confidence Interval	Mean	Median	Lower 95% Confidence Interval	Upper 95% Confidence Interval
Cost (£)	£168,602	£120,672	£158,993	£178,211	£55,590	£45,158	£53,320	£57,860
QALY	18.57	18.58	18.51	18.63	11.68	11.73	11.65	11.71
Mean ICER	£24,684							

Figure 5: Cost-effectiveness plane for dinutuximab beta for the high-risk revised model with a £30,000/QALY threshold

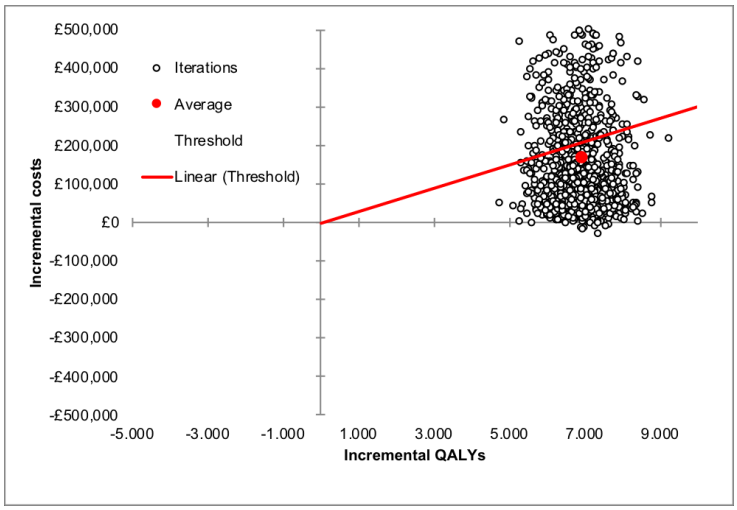
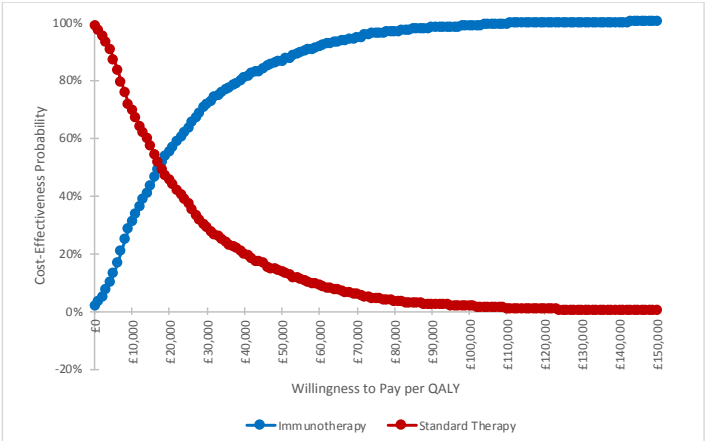


Figure 6: Cost effectiveness acceptability curve for dinutuximab beta for the high-risk revised model



Scenario analyses in the revised model

h) *Scenario analyses exploring the impact on the ICER of different proportions of patient receiving concomitant use of interleukin-2, including any additional time in hospital as a result of infection, to determine incremental differences between the regimens, based on:*

i. Treatment schedule followed in the trial; individual patient data from the APN311-302
ii. What would be done in clinical practice
iii. Reflecting the use of interleukin-2 in line with the marketing authorisation

In addition to the base-case which uses 0% IL-2 (i.e. the clinical practice), these different proportions of patient receiving concomitant use of IL-2 have been computed:

- Reflecting the use of IL-2 in line with the marketing authorisation (i.e. 41% patients had evidence of disease and will take concomitant IL-2 (CS, Appendix E)
- Treatment schedule followed in the randomised trial; individual patient data from the APN311-302 (i.e. 51% of patients in APN311-302 received IL-2)

In terms of additional costs associated with the IL-2 use, grade 3 to 4 infection rates reported in the APN311-302 CSR were used as follows:

- In the NO IL-2 group: [redacted] of patients experience grade 3 infection and [redacted] grade 4 infection (page 70 of the APN311-302 CSR)
- In the IL-2 group: [redacted] of patients experience grade 3 infection and [redacted] grade 4 infection (page 70 of the APN311-302 CSR)

Event rates for Pyrexia and grade 1-2 infections were modified accordingly.
Grade 3 and 4 infection events were associated with an increased cost of £3,980.27 per event corresponding to the currency code: PW16C (Currency Description: Paediatric Major Infections with CC Score 2-4 for each grade 3/4 infection). These costs were validated by experts' opinions sought by EUSA.

In addition to the severe infections, a clear difference was observed in the percentage of severe capillary leak syndromes whether patients are on IL-2 or not.
To reflect this difference, for the purpose of the scenario analyses considering the use of IL-2, different inputs in percentage of severe capillary syndromes were considered and as follow:

- Severe Capillary leak syndrome: [redacted] in the no IL2 group and [redacted] in the IL-2 group infection (page 70 of the APN311-302 CSR) and 0% in the isotretinoin arm

Table 8: scenario analysis outcomes using different proportions of patient receiving concomitant use of interleukin-2

IL-2 Scenario Analyses	High-risk Neuroblastoma Population (Dinutuximab beta + Isotretinoin vs. Isotretinoin) ICER
Base case	**£24,661**
41% of patients in the dinutuximab arm assumed to receive IL-2	**£27,924**
51% of patients in the dinutuximab arm assumed to receive IL-2	**£28,755**

i) Scenario analyses reflecting that the hazard ratios will vary over time and the treatment effect is not maintained indefinitely. For example, the company should explore use of the relative treatment difference between the event-free survival and overall survival hazard ratios from dinutuximab alpha compared with isotretinoin (from the suspended dinutuximab alpha appraisal) and apply it at various cure time points between 5 and 10 years in the dinutuximab beta model.

Different cure thresholds have been tested in the revised CEA model and results are presented in the Table 9.

Table 9: scenario analysis outcomes using different cure threshold

Cure threshold scenario Analyses	High-risk Neuroblastoma Population (Dinutuximab beta+Isotretinoin vs. Isotretinoin) ICER
Base case – cure threshold at 10 years	**£24,661**
Cure threshold at 9 years	**£26,451**
Cure threshold at 8 years	**£28,968**
Cure threshold at 7 years	**£32,699**
Cure threshold at 6 years	**£36,133**
Cure threshold at 5 years	**£41,286**

j) Probabilistic sensitivity analyses to incorporate the impact of varying relative treatment effectiveness estimates on the incremental cost-effectiveness ratios (ICERs).

A multiplication variable that follows a normal distribution (Appendix 3) has been factored-in into the OS and EFS percentages post-fit for dinutuximab beta arm. The results of the PSA have been presented above, in the sensitivity analysis of the base-case.

In addition to the ERG requested scenarios, EUSA pharma has run few extra scenarios to access different methodology in MAIC (impact of the covariates included, Appendix 4) as well as a scenario with three administrations of dinutuximab beta in cycle 1. The last scenario was run as some expert outline that during the first cycle, to minimise vial wastage in case of side effects occurring (i.e. termination of the cycle), they could administer dinutuximab beta in three administrations depending of the BSA of the child.

The ICER results after implementing these scenarios are presented in the Table 10. ICER with different covariates included in the MAIC range from £22,378 to £29,089, being consistent with the submitted base-case and showing that dinutuximab beta is cost-effective in all scenarios.

Table 10: Additional scenario analysis outcomes

Extra Scenario Analyses	High-risk Neuroblastoma Population (Dinutuximab beta+Isotretinoin vs. Isotretinoin) ICER
Base case	**£24,661**
MAIC scenario 1 prognostic variable: Age	**£23,295**
MAIC scenario 2 prognostic variable: INSS stage	**£23,591**
MAIC scenario 3 prognostic variable: MYCN Status	**£22,378**
MAIC scenario 4 prognostic variable: Response to treatment before ASCT	**£25,704**
MAIC scenario 5 prognostic variables: Response to treatment before ASCT + Age	**£25,709**
MAIC scenario 6 prognostic variables: Response to treatment before ASCT + Age + INSS Stage	**£26,375**
MAIC scenario 7 prognostic variables: Response to treatment before ASCT + Age + MYCN Status	**£25,282**
MAIC scenario 8 prognostic variables: Response to treatment before ASCT + INSS Stage + MYCN Status	**£24,618**
MAIC scenario 9 prognostic variables: Response to treatment before ASCT + INSS Stage	**£26,338**
MAIC scenario 10 prognostic variables: Response to treatment before ASCT + MYCN Status	**£24,672**
Three administrations of dinutuximab beta during the first cycle	**£29,089**

References

1. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, *et al*. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *New Eng J Med* 2010;363(14):1324–34.
2. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, NJ W. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016.

Request for further information from the company

MAIC

- Please explain how the source of isotretinoin data was selected for the MAIC, and whether the Yu et al. 2014 data had also been considered.
- Please clarify if individual patient data (IPD) was available for isotretinoin. If this is available, please provide it.
- The IPD used for MAIC was included in the economic model (sheet "Dataset_DB_MAIC"). Please clarify
    - What are the variables/columns used in the MAIC?
    - What is the unit for column V(age), AH(EFS) and AI(OS)?
    - For Subject [redacted] (row 3), column O(Die) indicates no, but column U(OS Censored) indicates no. Both can't be true simultaneously. There were 50 rows of data that had this problem. There were 91 rows where both Die and OS Censored status were yes. Please explain the reason for this discrepancy and provide the correct data if needed.
    - Some column names do not match the actual data. For example, column I, J, K, L, M, N. Please provide the correct data.

Survival analysis

- Please provide a full explanation of how the parametric curves were fitted to the Kaplan-Meier data for dinutuximab beta and isotretinoin. Clarify in particular:
    - Was IPD available for dinutuximab beta and isotretinoin?
    - What software and packages were used?
- Please provide a full explanation of the process for selecting the Gompertz parametric curve. Clarify in particular:
    - Were log-cumulative hazard, quantile-quantile or other residual plots produced? If so, please provide them.
    - Was the assumption of proportional hazards tested?
    - Were piecewise or other more flexible models considered?
    - Was external data used to compare the fit of different parametric models?
    - Were the Akaike Information Criterion or Bayesian Information Criterion calculated for the different parametric models?
    - Did clinicians validate the parametric models? If so, please provide a detailed description of this process

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Qarziba (dinutuximab beta) [ID910]

Specific clarification questions from the DSU

Version 1

Date of preparation: 16 March 2018

File name	Version	Contains confidential information	Date
ID910 Request for further information [noACIC]	**1**	**No [noACIC]**	**16 March 2018**

Request for further information from the company

MAIC

- Please explain how the source of isotretinoin data was selected for the MAIC, and whether the Yu et al. 2014 data had also been considered.

The MAIC analysis comparing the isotretinoin treatment arm data (from the Yu et al. 2010, NEJM publication) to the APN311-302 data was performed as requested in the NICE ERG *Clarification Letter – Second Part* from August 24th 2017. In this Clarification Letter, NICE expressly requested the company to "carry out a matching-adjusted indirect comparison (MAIC) comparing APN311-302 (all people analysed) versus those receiving isotretinoin alone from the study by Yu et al. 2010 (1)". In further correspondence with NICE and other clarification requests, the consideration or use of data from Yu et al. 2014 was not mentioned.

Data from Yu et al. 2014 was not considered for multiple reasons:

1) A MAIC analysis with this data was not requested by NICE ERG in the clarification letter from 24 August 2017
2) Additionally, as the 2014 data was presented in a conference abstract/poster and part of the NICE committee papers for the STA of Unituxin, and not a published, peer-reviewed article, we considered the 2010 data to be a more prudent and robust source of data for the MAIC analysis. Furthermore, details around the 2014 study were not available to the Company to evaluate the clinical outcomes and understand some discrepancies in the results.
3) Data from Yu et al. 2014 were analysed after randomisation had been broken, and due to stopping recruitment, the later time points were more prone to bias. Therefore, the integrity of the data is questionable.

Nevertheless, based on a request from NICE that was confirmed on 15.03.2018 to also consider the Yu et al. 2014 data, a quick analysis of MAIC using the Yu et al. 2014 data (the Company had approximately 24 hours to respond to this request) has been presented as a scenario analysis to explore the impact on ICER (see Table 5).

- Please clarify if individual patient data (IPD) was available for isotretinoin. If this is available, please provide it.

IPD data for the isotretinoin-only arm from Yu et al. 2010 was not available to the company. Using curves from the Yu et al. 2010 publication, and the technique from Patricia Guyot et al. 2012 (doi.org/10.1186/1471-2288-12-9), which describes an algorithm to map digitized curves back to KM data, we were able to derive individual patient "Time-to-Event" data for use in the MAIC.
The KM curves for EFS and OS in Yu et al. 2010 study were first digitized using the following software: DigitizeIt Version 2. 0. Then, following the technique by Guyot et al. 2012, individual patient "Time-to-Event" data for isotretinoin for OS and EFS was reconstructed. Therefore, we only have access to the estimated individual patient "Time-to-Event" data, which is a close approximation to the actual data, but not the original data for the isotretinoin arm of Yu et al. 2010.

- The IPD used for MAIC was included in the economic model (sheet "Dataset_DB_MAIC"). Please clarify
    - What are the variables/columns used in the MAIC?

All the variables used in the MAIC were reported in the previous submission: Additional Analyses and Clarification for the Second Appraisal Committee Meeting, Table 2: Baseline characteristics pre- and post-matching) and also reported below in Table 1.

Table 1: Baseline characteristics pre- and post-matching

Baseline Characteristics[a] Yu et al. study (2)	APN311-302 study sample		
	Pre-match (%)	Post-match (%)	As reported (%)
Age			
<18 Mo	6.75	4	4
≥18 Mo	93.25	96	96
INSS stage			
2	0.27	0.0	0.0
3	9.18	15	15
4S	1.89	0.0	0.0
4	88.65	85	85
Tumour MYCN status[b]			
Not amplified	48.92	45.2	45.2
Amplified	41.08	39.8	39.8
Unknown	10	15	15
Response before ASCT[c]			
Complete Response	55.68	34	34
Very Good Partial Response	25.41	43	43
Partial Response	11.89	23	23
Less than Partial Response	4.3	-	-
Missing/Not Evaluable (NE)	2.7	-	-

Notes:
[a] Reported as percentages in the table
[b] The distribution of Tumour MYCN status in Yu study was recomputed to include those with unknown status
[c] A total of 26 patients were excluded from the APN311-302 study, 10 with missing/NE value and 16 achieving less than PR

During the last round of aesthetic changes to the excel file, an error was produced in the final revised version of the model. Columns I to P were improperly labeled, therefore, please use the following revised labels: “Gender” (column I), “Death date” (column J), “Died?” (column K), “Date last known to be alive” (column L), “Age (years) at initial diagnosis” (column M), “INSS Stage at initial diagnosis” (column N), “MYCN amplification at initial diagnosis” (column O), “Response before ASCT” (column P). These columns were not used in the output of the CEA model, thus did not have an impact on the final results. The IPD data used for the MAIC analysis did not have any errors in the column labels.

- What is the unit for column V(age), AH(EFS) and AI(OS)?

The units in the columns V (age), AH(EFS) and AI(OS) are months.

- For Subject ID ES-0291 (row 3), column O(Die) indicates no, but column U (OS Censored) indicates no. Both can’t be true simultaneously. There were 50 rows of data that had this problem. There were 91 rows where both Die and OS Censored status were yes. Please explain the reason for this discrepancy and provide the correct data if needed.

Column O is the ‘MYCN amplification at initial diagnosis’ (yes/no). As discussed above, the column name was not correctly labeled. These columns were not used in the CEA model and thus did not impact the model results. The correct data are reported in the revised CEA model.

- Some column names do not match the actual data. For example, column I, J, K, L, M, N. Please provide the correct data.

Please see the attached Excel file with the corrected column names. Corrections were made in Columns I to P: “Gender” (column I), “Death date” (column J), “Died?” (column K), “Date last known to be alive” (column L), “Age (years) at initial diagnosis” (column M), “INSS Stage at initial diagnosis”

(column N), “MYCN amplification at initial diagnosis” (column O), “Response before ASCT” (Column P).

Survival analysis

- Please provide a full explanation of how the parametric curves were fitted to the Kaplan-Meier data for dinutuximab beta and isotretinoin. Clarify in particular:
    - Was IPD available for dinutuximab beta and isotretinoin?

As described above, true IPD data was not available for isotretinoin, but a close approximation was derived from KM data using the algorithm described by Guyot et al. 2012.
True IPD data for dinutuximab beta from study APN311-302 was available from EUSA Pharma.

    - What software and packages were used?

The MAIC analysis has been performed using the following statistical software: R Version 3. 1. 3. The code was shared, and libraries were presented within the code (please refer to the last submission in January 2018).
The KM curves for EFS and OS in Yu et al. 2010 study have been digitized using the following software: DigitizeIt Version 2.0.
The parametric curves were fitted to KM curves after MAIC (using the Microsoft Excel add-in Solver) in the submitted CEA model. A confirmation of the best fit using IPD data as well as the log-cumulative hazard and quantile-quantile plots were performed using the statistical R software (Version 3.1.3, survival package).

- Please provide a full explanation of the process for selecting the Gompertz parametric curve. Clarify in particular:
    - Were log-cumulative hazard, quantile-quantile or other residual plots produced? If so, please provide them.
    - Was the assumption of proportional hazards tested?
    - Were piecewise or other more flexible models considered?

A multi-step approach was taken to identify the most appropriate parametric model types as explained below:

Step 1) Investigation of log-cumulative hazard plots and quantile-quantile to allow initial selection of appropriate models

The log-cumulative hazard and quantile-quantile plots were generated for OS and EFS for immunotherapy and isotretinoin arms (Figures 1 to 4). These plots have been prepared using the survival fit from the KM curves. The log-cumulative hazard and quantile-quantile plots were also generated for all parametric models (Appendix 1).

Figure 1: Log-cumulative hazard plot for OS

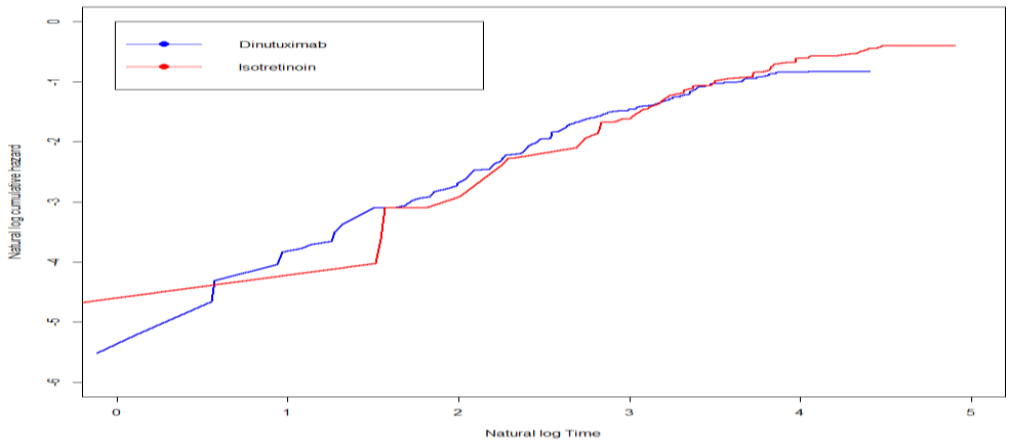


Figure 2: Log-cumulative hazard plot for EFS

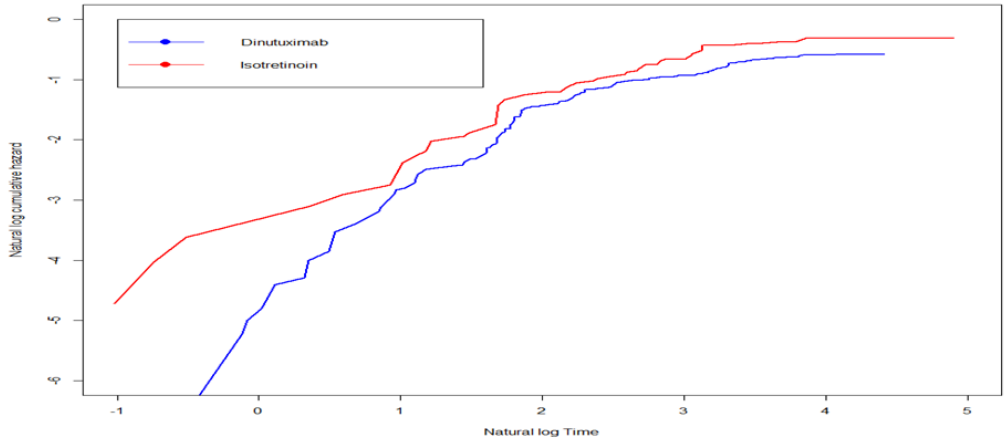


Figure 3: Quantile-quantile plot for OS

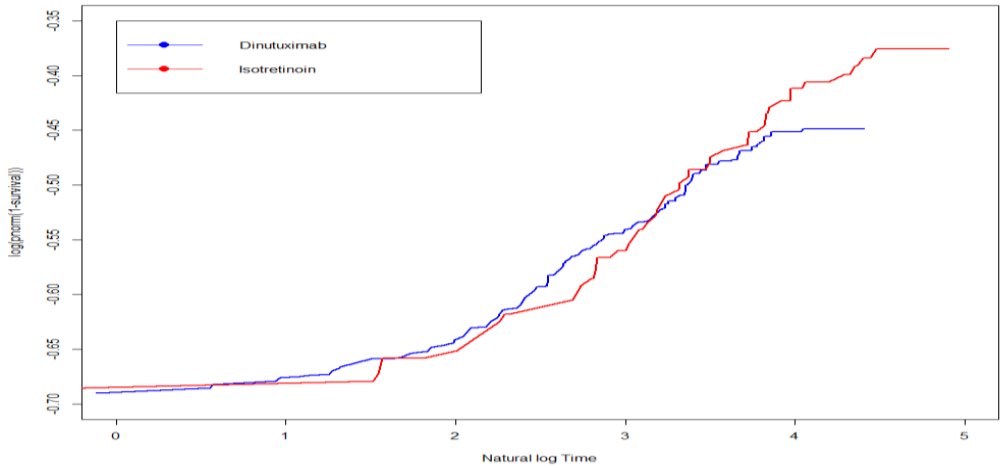
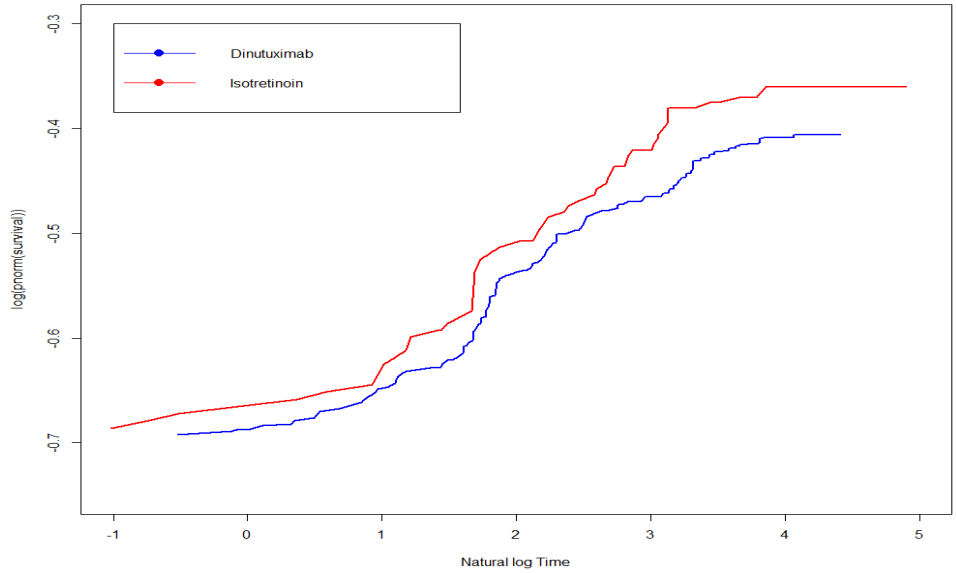


Figure 4: Quantile-quantile plot for EFS



Step 2) Assessment of proportional hazards assumption

The log-cumulative hazard and quantile-quantile plots do not support the assumption of proportionality of the hazards for OS and EFS as the curves are not parallel and deviate from the straight line. Individual model fitting for each treatment arm were undertaken using a suitable model. As the log-cumulative hazard plots were not approximately straight lines, particularly in the case of OS, a more flexible approach was considered as a base-case in the CEA model.

Step 3) Visual and statistical inspection of different parametric models compared to observed data

The KM curves were fitted to non-linear, exponential, Weibull, Gompertz, log-logistic, and log-normal parametric models using Excel and the Solver add-in to minimize the sum of squares (Figure 5 to 8, red dotted lines represent the actual KM curves from MAIC). The coefficients for these models along with Akaike's information criterion (AIC) and Bayesian information criterion (BIC) statistics are provided in Table 2 and Table 3 with two minimization methods.

As shown in Figures 5 to 8, the Gompertz model provided a better visual fit for both the OS and EFS data of dinutuximab beta, and the EFS data of isotretinoin. This was supported by the AIC and BIC statistics (Table 2 and Table 3).
As shown in Figure 7, the Gompertz, the log-normal and the log-logistic models were the best visual fits for the OS of isotretinoin. The AIC and BIC show similar findings in terms of ranking the best fitted models to the empirical data, with a small preference for the log-logistic model. As suggested in the DSU technical report 14, it is better to use the same "type" of model if the parametric models are fitted separately to individual treatment arms, and according to these guidelines, the Gompertz model will be used as a base-case for extrapolating the different treatment arms.

The log-cumulative plot for Gompertz OS data shows that the parametric fit has almost the same pattern as KM curves (Appendix 1). However, the log-logistic models for EFS represents a better pattern (crossing around the same time) and following the same separation as KM curves. The use of the log-logistic model for OS dinutuximab beta was not supported by the best

AIC and BIC. To assess the uncertainty of using the best statistical function (i.e. Gompertz), a scenario is presented using the log-logistic parametric function with isotretinoin OS.

Figure 5: Parametric models for OS of dinutuximab beta

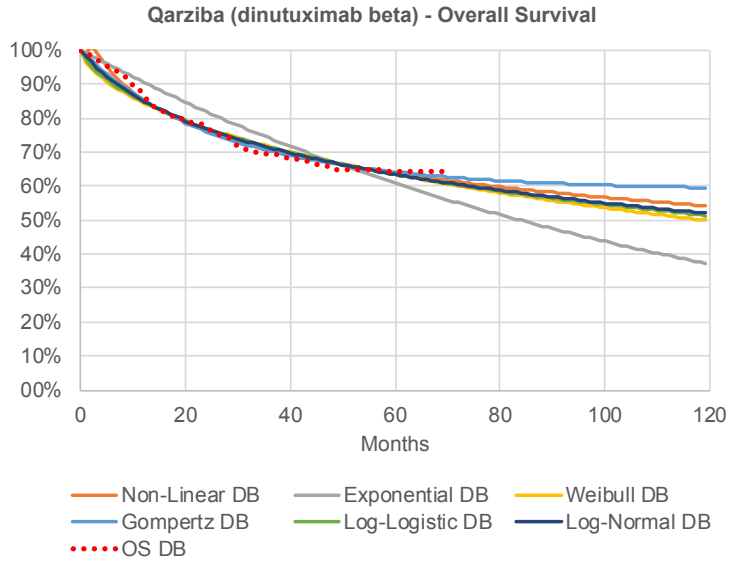


Figure 6: Parametric models for EFS of dinutuximab beta

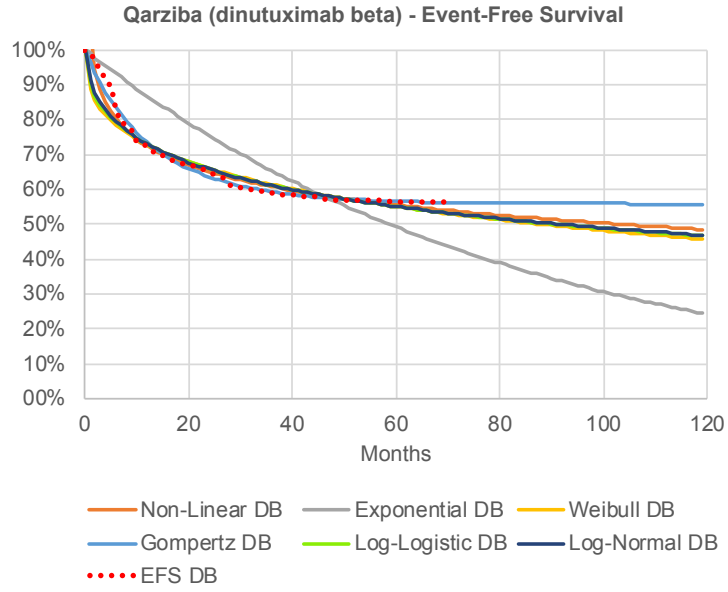


Figure 7: Parametric models for OS of isotretinoin

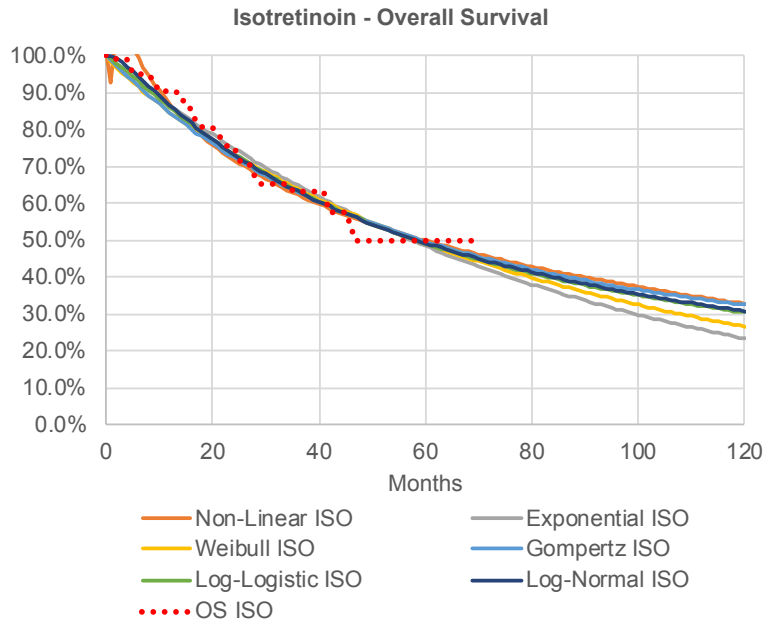


Figure 8: Parametric models for EFS of isotretinoin

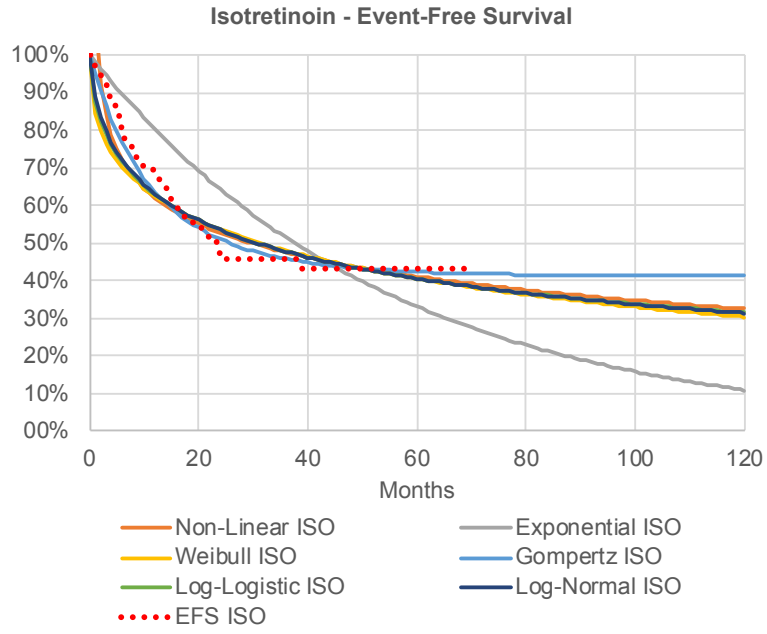


Table 2: Coefficients for different parametric function fits for dinutuximab beta

Residual sum of normalized squared approach:

OS DB	1st parameter (a)	2nd parameter (b)	3rd parameter (c)	AIC Statistic	BIC Statistic
Non-Linear	1.2291	-0.2361	-0.1432	-345.69	-336.64
Exponential	0.0083			-190.54	-186.02
Weibull	0.0365	0.6162		-282.89	-276.11
Gompertz	0.0158	-0.0297		-364.11	-357.32
Log-Logistic	-3.5156	0.7235		-295.74	-288.96
Log-Normal	4.9011	2.3302		-308.94	-302.15

EFS DB	1st parameter (a)	2nd parameter (b)	3rd parameter (c)	AIC Statistic	BIC Statistic
Non-Linear	0.9677	0.0886	-0.1012	-303.13	-294.08

Exponential	0.0118			-74.55	-70.02
Weibull	0.1195	0.3933		-243.08	-236.29
Gompertz	0.0366	-0.0626		-394.00	-387.21
Log-Logistic	-2.2138	0.4915		-255.09	-248.30
Log-Normal	4.5130	3.3073		-262.33	-255.54

Residual sum of squared errors approach:

OS DB	1st parameter (a)	2nd parameter (b)	3rd parameter (c)	AIC Statistic	BIC Statistic
Non-Linear	1.2419	-0.2553	0.0289	-437.53	-428.48
Exponential	0.0084			-288.96	-284.44
Weibull	0.0307	0.6616		-383.22	-376.43
Gompertz	0.0152	-0.0277		-478.09	-471.30
Log-Logistic	-3.6923	0.7704		-393.58	-386.79
Log-Normal	4.8408	2.2084		-402.55	-395.76

EFS DB	1st parameter (a)	2nd parameter (b)	3rd parameter (c)	AIC Statistic	BIC Statistic
Non-Linear	1.0070	0.0278	0.0561	-430.68	-421.63
Exponential	0.0123			-215.74	-211.21
Weibull	0.0998	0.4420		-383.69	-376.90
Gompertz	0.0362	-0.0618		-680.67	-673.88
Log-Logistic	-2.4098	0.5453		-392.24	-385.45
Log-Normal	6.0521	11.6690		-396.03	-389.25

Table 3: Coefficients for different parametric function fits for isotretinoin

Residual sum of normalized squared approach:

OS ISO	1st parameter (a)	2nd parameter (b)	3rd parameter (c)	AIC Statistic	BIC Statistic
Non-Linear	1.5520	-0.6268	-0.2545	-225.58	-216.53
Exponential	0.0121			-204.38	-199.85
Weibull	0.0179	0.8983		-209.84	-203.06
Gompertz	0.0149	-0.0084		-221.80	-215.01
Log-Logistic	-4.6321	1.1392		-227.04	-220.25
Log-Normal	4.0686	1.4385		-233.56	-226.77

EFS ISO	1st parameter (a)	2nd parameter (b)	3rd parameter (c)	AIC Statistic	BIC Statistic
Non-Linear	0.9049	0.2027	-0.1215	-167.83	-158.78
Exponential	0.0184			-14.38	-9.85
Weibull	0.1724	0.4043		-142.61	-135.83
Gompertz	0.0528	-0.0597		-250.93	-244.14
Log-Logistic	-1.9440	0.5683		-155.17	-148.38
Log-Normal	3.4213	2.8145		-156.95	-150.16

Residual sum of squared errors approach:

OS ISO	1st parameter (a)	2nd parameter (b)	3rd parameter (c)	AIC Statistic	BIC Statistic
Non-Linear	1.5362	-0.6089	-0.2493	-346.98	-337.93
Exponential	0.0121			-317.00	-312.47
Weibull	0.0130	0.9803		-318.35	-311.56
Gompertz	0.0133	-0.0042		-332.58	-325.79
Log-Logistic	-4.9295	1.2159		-333.63	-326.84
Log-Normal	4.0597	1.3653		-338.52	-331.73

EFS ISO	1st parameter (a)	2nd parameter (b)	3rd parameter (c)	AIC Statistic	BIC Statistic
Non-Linear	1.0369	-0.0042	-0.1554	-340.01	-330.96
Exponential	0.0194			-175.91	-171.38

Weibull	0.1191	0.5032		-313.99	-307.20
Gompertz	0.0486	-0.0537		-468.49	-461.70
Log-Logistic	-2.3622	0.6822		-323.24	-316.45
Log-Normal	3.4617	2.3650		-324.96	-318.18

Step 4) Expert opinion

A clinical expert (a UK paediatric oncologist) was approached to validate the parametric models via a telephone call guided by figures displaying the outputs of the model with different parametric fits in a presentation. With respect to the EFS curves, the clinical expert advised that the Gompertz fit most accurately represented the available data for both the isotretinoin and dinutuximab beta extrapolated curves. This feedback is also in agreement with our expectations of which fit is the best for the data set (meaning this fit has the smallest difference from the actual data).

With respect to the OS curves, the clinical expert was again in agreement that the Gompertz fit was most accurate for the dinutuximab beta extrapolation curve, however was in disagreement about the form of any of the extrapolated fits for the isotretinoin curve (including Gompertz). Their anticipated form of the extrapolated curve was a line that tracks more in parallel with the dinutuximab beta Gompertz extrapolation curve, remaining mostly flat with a very shallow descent. They also expressed concern over the fact that when the 10 year curve threshold is applied, the extrapolated EFS and OS curves for isotretinoin cross at approximately 80 months (6.67 years), which is clinically unrealistic, but is actually an artifact of the statistical analysis based on the available data source. To assess this uncertainty, we have run a scenario fixing the difference between OS and EFS isotretinoin curves over the period of extrapolation to ensure that the curves remain parallel and thus closely mirroring what the clinical expert would anticipate in the real-world.

Step 5) External data

Identifying external data for extrapolation of survival beyond the APN311-302 trial presented a challenge due to the rarity of the disease. In the SLR results, two studies were identified with OS and EFS outcomes using isotretinoin in the maintenance treatment: CCG-3891 (Matthay et al, 1999; Matthay et al., 2009 and Park et al, 2009) and COG ANBL0032 (Yu et al, 2010). The R1 historical control population (patients who only received myeloablative therapy from the HR-NBL-1 trial) can also serve as a relevant source for comparison since these patients did not receive immunotherapy either. When comparing the Gompertz parametric flexible model for each data source, both EFS and OS were the closest to the observed data in Yu et al. 2010 and R1, but lower than the values reported in Matthay et al. 2009 and Yu et al. 2014 studies.

Table 4: Five year survival comparison from external data sources, APN311-302 data, and associated parametric models

	EFS	**OS**
Yu et al. 2010 (observed data; isotretinoin arm)	43.5%	49.3%
Yu et al. 2014 (observed data; isotretinoin arm)	48.3%	57%
Matthay et al (2009) (isotretinoin after bone marrow transplant)	50%	59%
R1 historical control (from R1 randomization of SIOPEN HR-NBL-1 trial, isotretinoin)	N/A	50%
Parametric Fit on isotretinoin arm from Yu et al. 2010 (flexible model)		
Non-linear	41.3%	50.4%
Exponential	33.7%	49.0%
Weibull	40.8%	49.7%

Gompertz (*best fit EFS, but also for OS to keep the same model type*)	**42.4%**	**50.1%**
Log-logisitic	40.8%	49.7%
Log-normal (*best fit OS*)	40.8%	49.8%
Dinutuximab beta (observed data from APN311-302)	56.5%	64.6%
Yu et al. 2014 (observed data; Dinutuximab arm)	56.5%	74.2%
Parametric Fit Type on dinutuximab beta (flexible model)		
Non-linear	55.6%	64.1%
Exponential	49.7%	61.4%
Weibull	55.2%	63.8%
Gompertz (*best fit for both OS & EFS*)	**56.6%**	**64.4%**
Log-logisitic	55.2%	63.8%
Log-normal	55.2%	63.8%

Step 6) Choice of final parametric models

As the log-cumulative hazard plots were not approximately straight lines, a more flexible approach was used: KM curves were used when survival data were available, and then the Gompertz models for extrapolation of the curve were used until the cure threshold (i.e. 10 years). When patients reach the cure threshold in the model, the proportion of patients in the EFS and the failure state (FS) can only move to the death state, as patients cannot progress or enter remission in the model anymore. From this point onwards in the analysis, patients in the EFS and in FS states die at different rates, to model the fact that some patients are considered cured while others will become relapsed patients (as described in CS).

For EFS and OS, the use of a full Gompertz extrapolation was tested in a scenario. The uncertainty around the parametric survival model for OS isotretinoin was tested using the log-normal model. Furthermore, a scenario fixing the difference between OS and EFS isotretinoin curves were tested over the period of extrapolation to take into consideration feedback coming from a clinical expert.

The ICER results after implementing these scenarios are presented in the Table 5. The EFS and OS curves in the short term and long term models are presented for the base-case as well as the different scenarios in Figures 9 to 20. The base-case result was presented in the previous submission (31th January 2018).

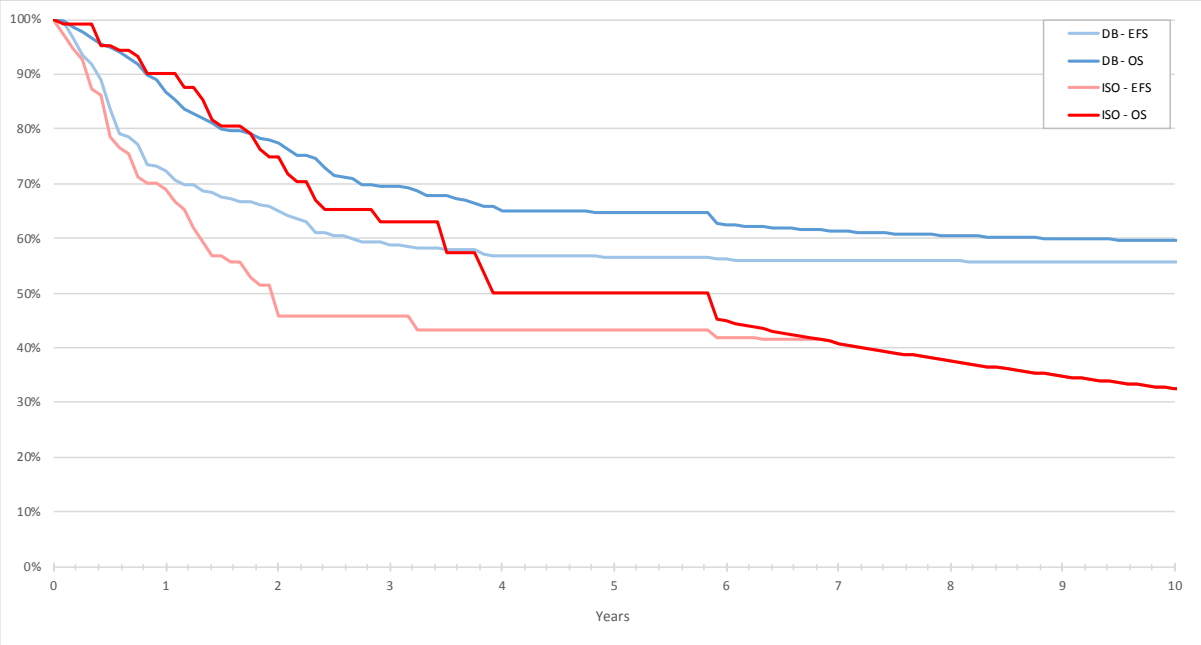
The results of MAIC analysis using Yu et al. 2014 data are presented in Appendix 2. The log-cumulative and quantile-quantile plots as well as the assessment of the best statistical parametric fits are presented in Appendix 3.

Table 5: scenario analysis outcomes

Cure threshold scenario Analyses	**High-risk Neuroblastoma Population (Dinutuximab beta+Isotretinoin vs. Isotretinoin) ICER**
Base case – cure threshold at 10 years, flexible approach (KM+Gompertz), MAIC Yu et al 2010 (31th January submission)	**£24,661**
Scenario 1- Full Gompertz extrapolation	£24,033
Scenario 2- log-logistic models for OS Isotretinoin (Gompertz for the other treatment arms)	£23,080
Scenario 3- Log-logistic model for EFS Isotretinoin and dinutuximab beta	£27,805

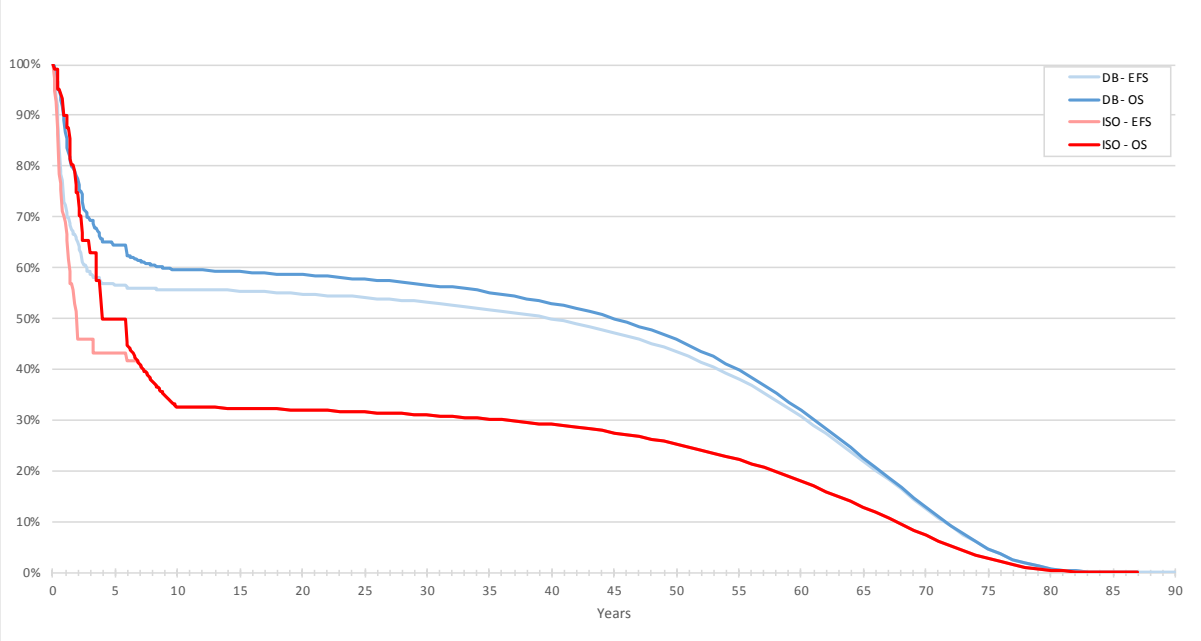
Scenario 4- Flexible approach (KM+Gompertz) with fixing difference between OS and EFS in isotretinoin arm	£36,500
Scenario 5- MAIC analysis using Yu et al 2014	£43,308

Figure 9: Short term OS and EFS in the economic analysis (base-case)



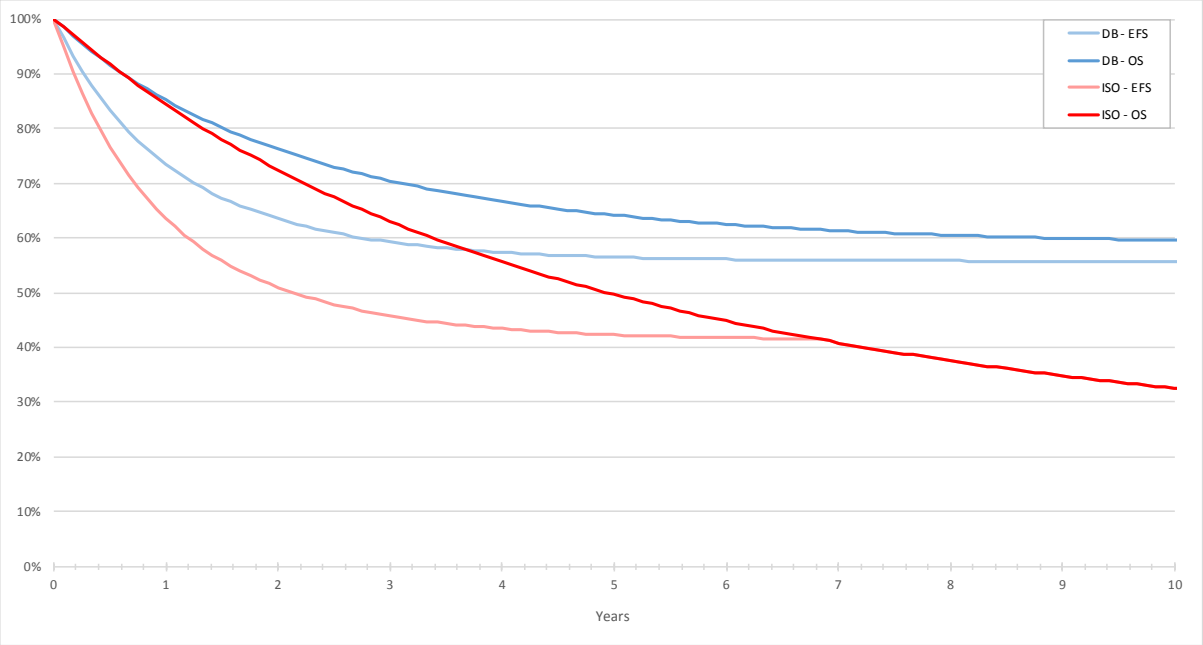
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 10: Long term OS and EFS in the economic analysis (base-case)



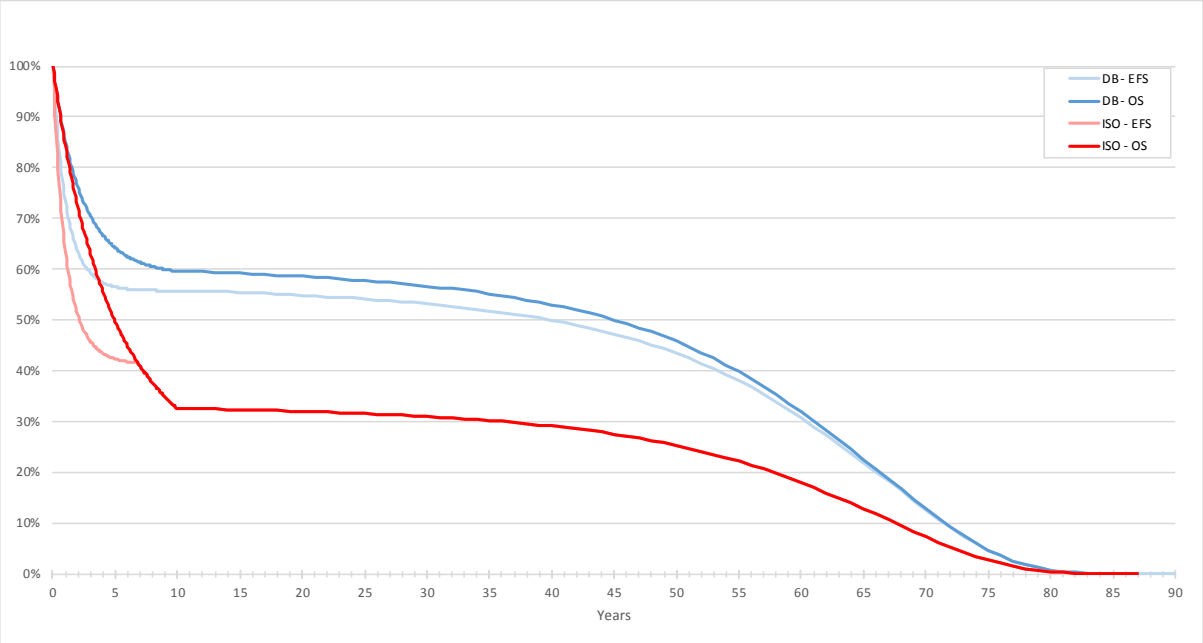
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 11: Short term OS and EFS in the economic analysis (Scenario 1)



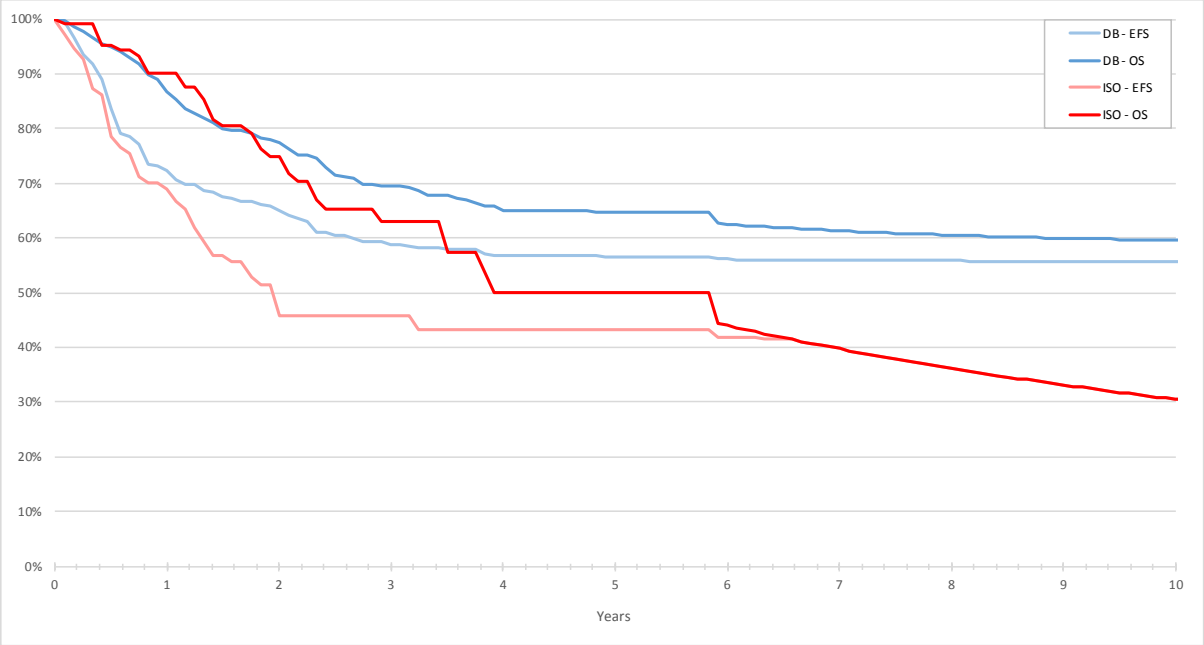
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 12: Long term OS and EFS in the economic analysis (Scenario 1)



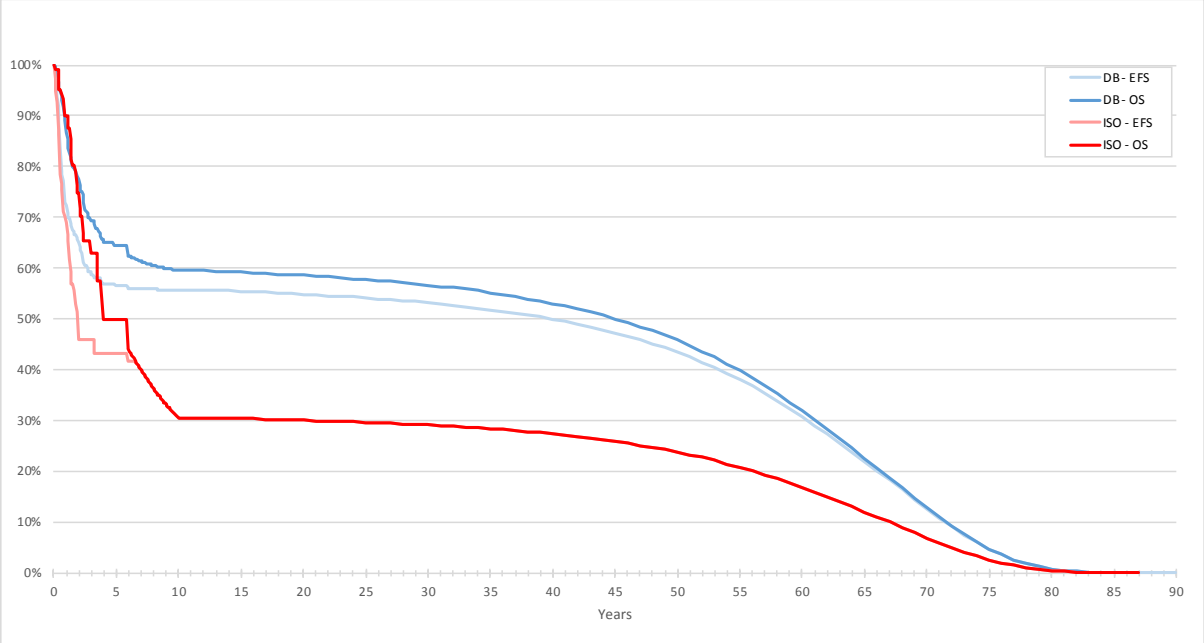
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 13: Short term OS and EFS in the economic analysis (Scenario 2)



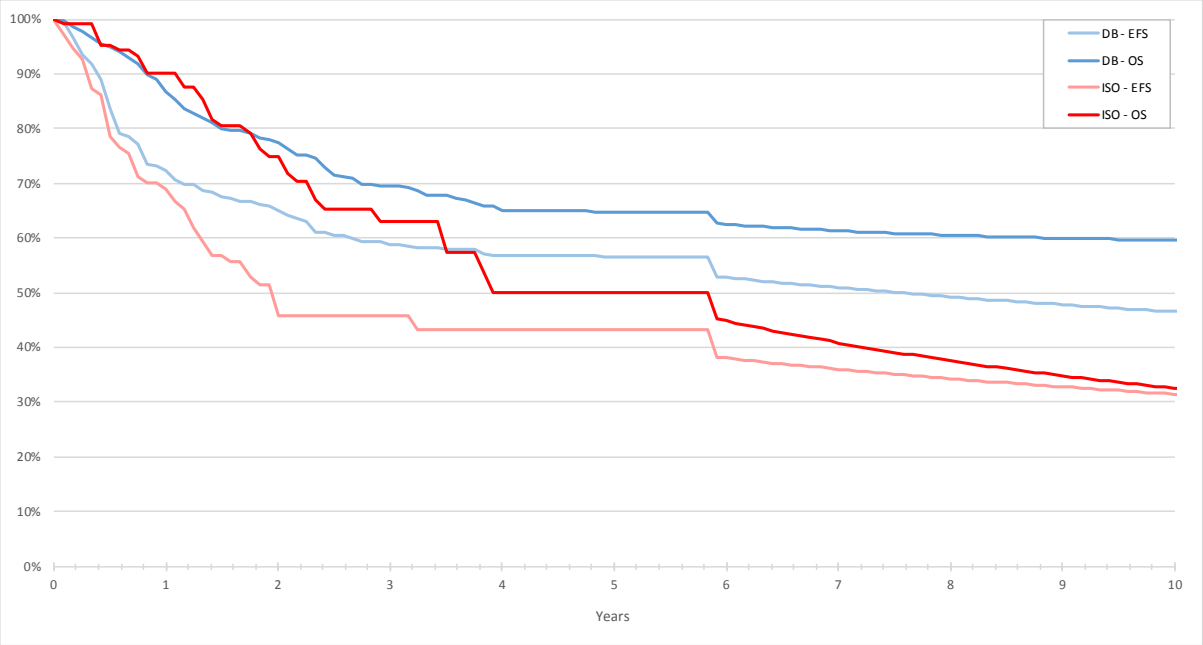
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 14: Long term OS and EFS in the economic analysis (Scenario 2)



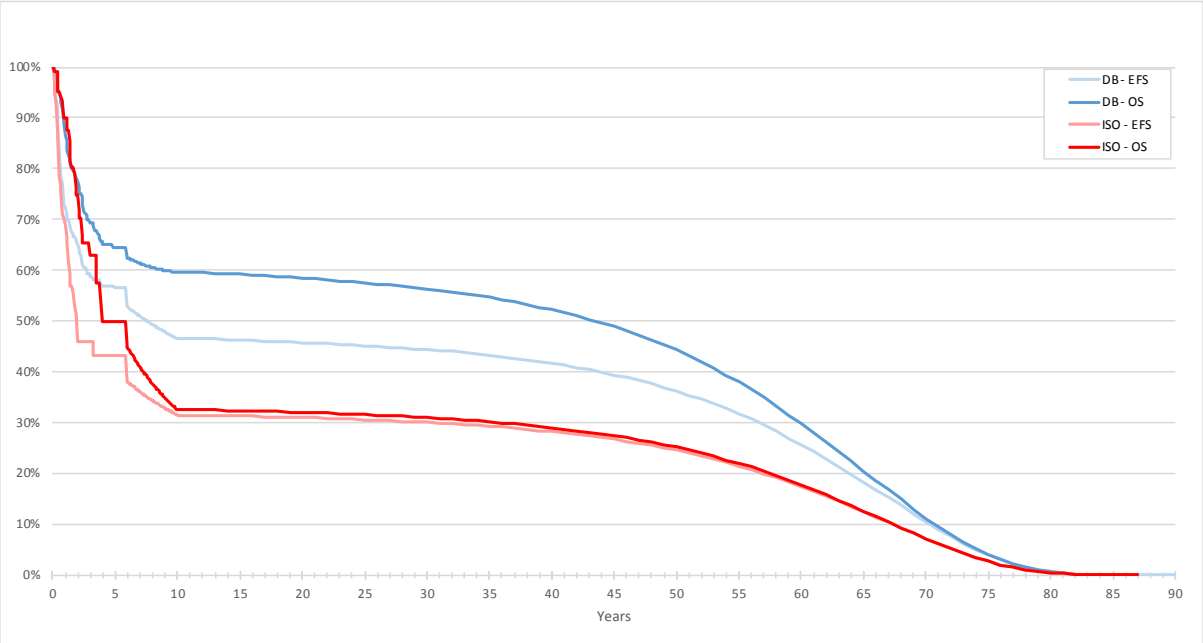
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 15: Short term OS and EFS in the economic analysis (Scenario 3)



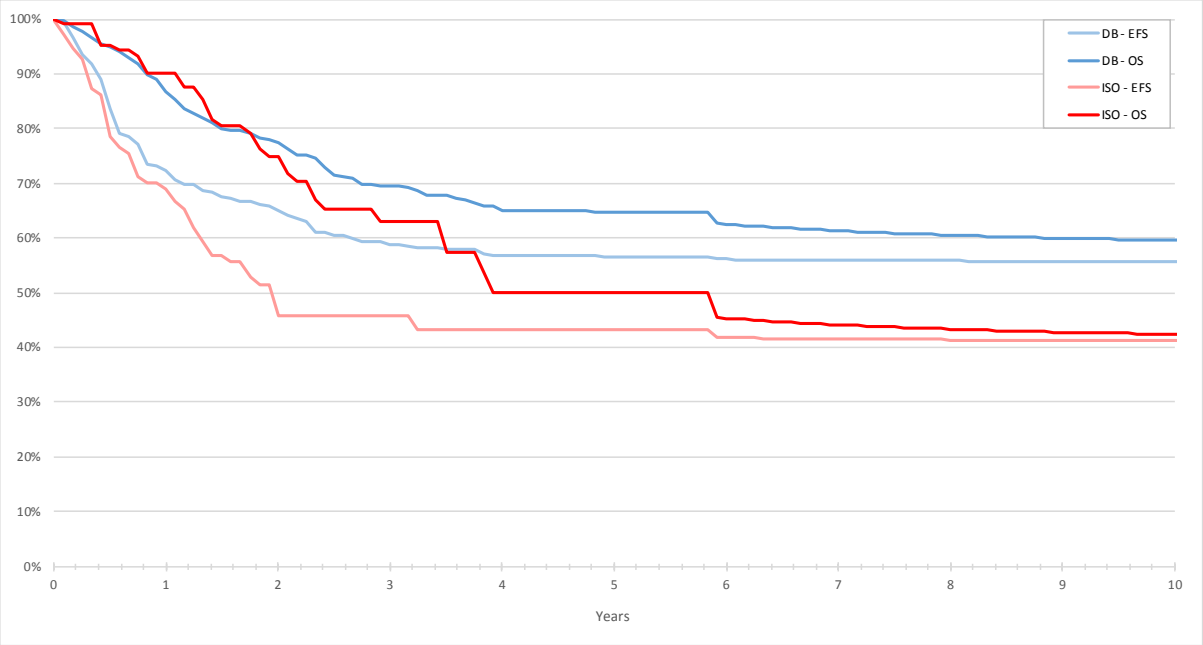
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 16: Long term OS and EFS in the economic analysis (Scenario 3)



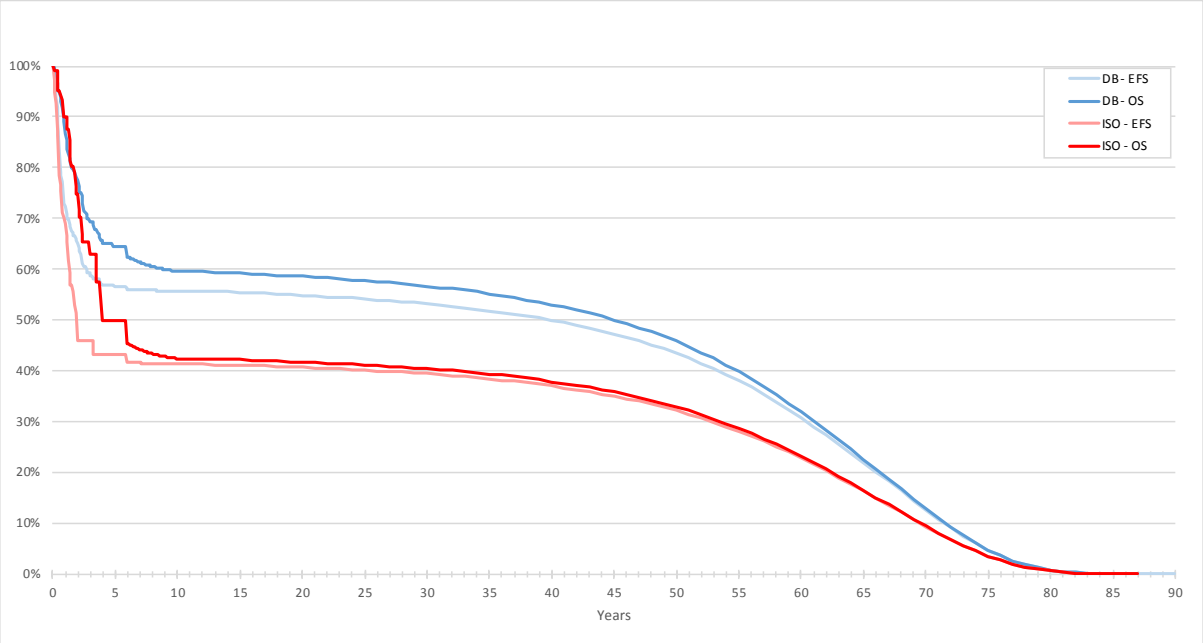
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 17: Short term OS and EFS in the economic analysis (Scenario 4)



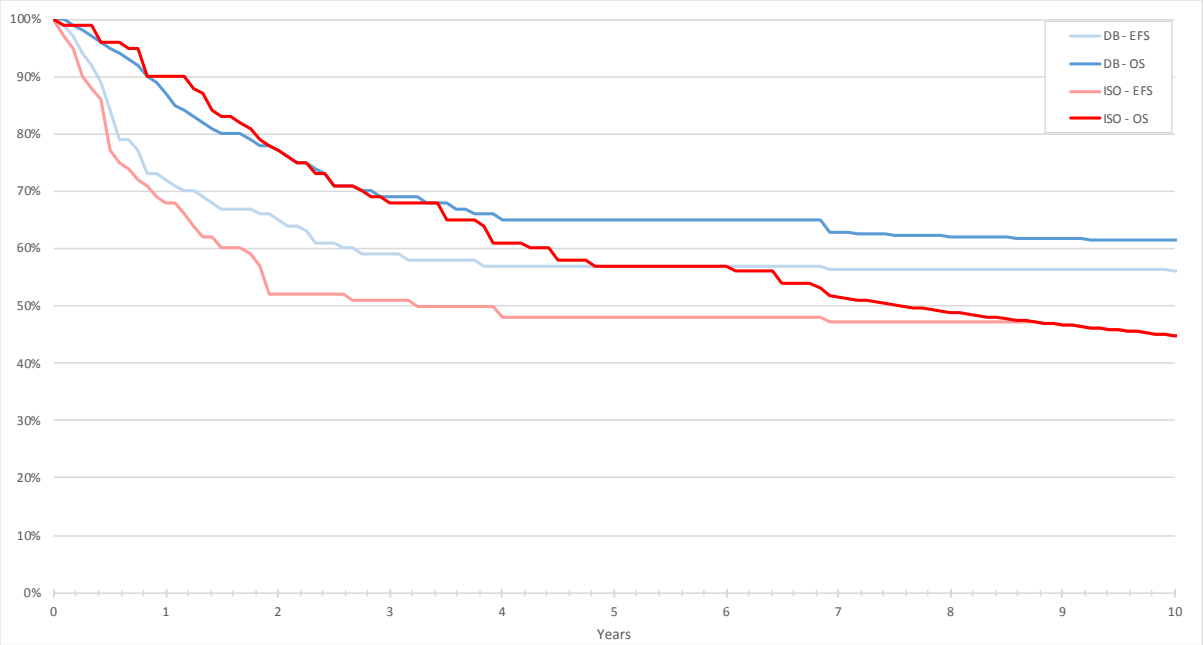
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 18: Long term OS and EFS in the economic analysis (Scenario 4)



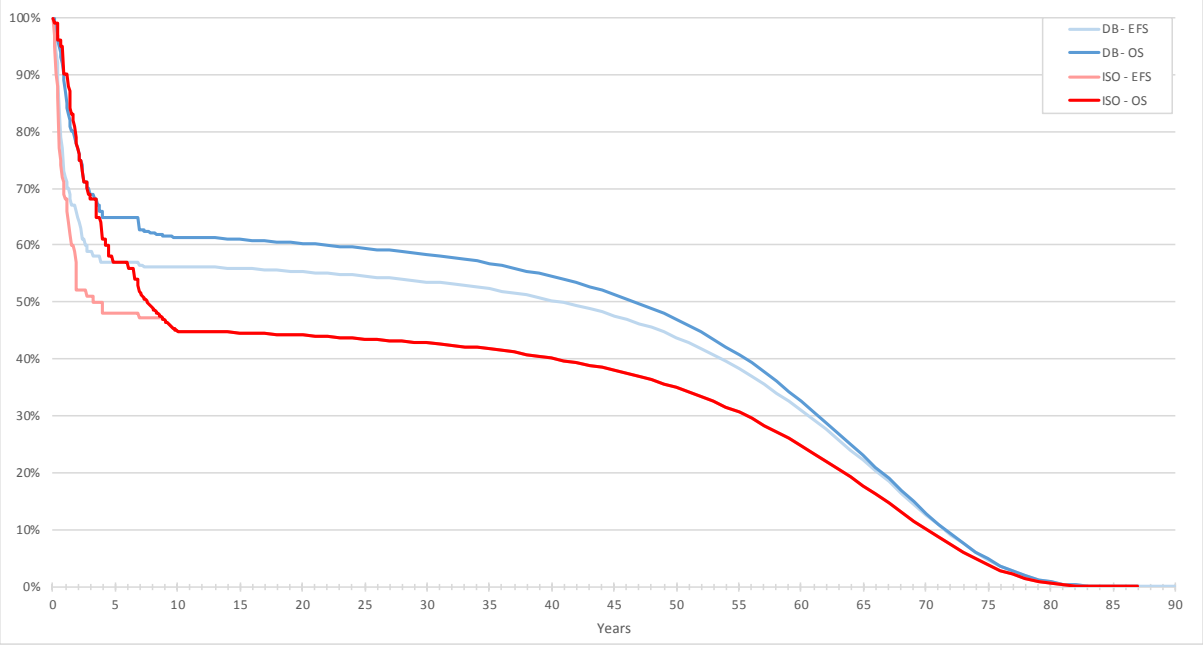
Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 19: Short term OS and EFS in the economic analysis (Scenario 5)



Legend: DB- dinutuximab beta; ISO- isotretinoin

Figure 20: Long term OS and EFS in the economic analysis (Scenario 5)



Legend: DB- dinutuximab beta; ISO- isotretinoin

References:

1. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010;363(14):1324-34.

2. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. New England Journal of Medicine. 2010;363(14):1324-34.

3. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.

DINUTUXIMAB BETA FOR TREATING HIGH-RISK NEUROBLASTOMA: REVIEW OF COMPANY'S ADDITIONAL ANALYSIS

REPORT BY THE DECISION SUPPORT UNIT

6 April 2018

Becky Pennington[1], Shijie Ren[1]

[1]School of Health and Related Research, University of Sheffield

Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street Sheffield, S1 4DA

Tel (+44) (0)114 222 0734
E-mail dsuadmin@sheffield.ac.uk
Website www.nicedsu.org.uk
Twitter @NICE_DSU

ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by the National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk.

The production of this document was funded by NICE through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

Acknowledgements

The authors wish to thank Dr Juliet Gray and Dr Martin Elliot for their time discussing clinical assumptions; Prof Allan Wailoo, Prof Matt Stevenson and Dr Paul Tappenden (all from ScHARR, University of Sheffield) for helpful contributions during the development of this report; Prof Steve Palmer (University of York) for providing peer review; and Dr Claire Rothery and Dr Pedro Saramago Goncalves (University of York) for providing information.

EXECUTIVE SUMMARY

The National Institute for Health and Care Excellence (NICE) appraisal committee were unable to make a decision about dinutuximab beta for neuroblastoma as there was insufficient evidence to inform their considerations relating to clinical and cost-effectiveness, and so further analyses were requested from the company. The company has responded to this request and provided analyses and information, including a matching-adjusted indirect comparison (MAIC) to compare dinutuximab beta to isotretinoin and revised cost-effectiveness analyses. The Decision Support Unit (DSU) has reviewed and critiqued the company's additional analysis and performed its own additional analyses.

MAIC is a reweighting approach that adjusts the population in a study where individual patient-level data (IPD) are available to match aggregate data (AD) from another study. In the company's MAIC, they selected four prognostic factors to adjust for: age, INSS stage, tumour MYCN status and response to treatment before ASCT. The DSU had identified some errors in the data and model used in the company's MAIC, so has undertaken a new MAIC analysis, correcting for these errors. In the DSU's MAIC analysis, the same four factors were included as the company's MAIC The results of the DSU's MAIC are similar to those of the company's MAIC, which are similar to the observed data.

The company used 6-year data for isotretinoin (Yu et al. 2010[1]) in the revised economic model. The DSU considered that the more recent analysis with 12 years of data for isotretinoin from the same dataset (Yu et al. 2014[2]) is more appropriate.

The data for dinutuximab beta was limited to 70 months so it was necessary to extrapolate this to the modelled cure point of 10 years. The DSU considered that the company's method for performing survival analysis using optimisation was inappropriate and so conducted additional survival analysis using the DSU's MAIC data for dinutuximab beta.

The DSU considered that many of the changes in the company's revised analysis were appropriate and correct, and made minor revisions to others. However, using the longer-term data for isotretinoin (Yu et al. 2014[2]), and the DSU's survival analysis of the data from the

DSU's MAIC increased the incremental cost-effectiveness ratio (ICER) for dinutuximab beta substantially.

The DSU recognises that there is uncertainty associated with extrapolating overall survival and event-free survival for dinutuximab beta and presented analyses using different distributions for modelling these. The DSU considers that a flexible spline model is most plausible for modelling event-free survival, and that the Gompertz or flexible spline models may be most appropriate for modelling overall survival. Using these models, the ICERs are estimated to lie in the range of £76,000 - £108,000 per quality adjusted life year (QALY). In scenarios considering the Generalised gamma model for dinutuximab beta overall survival (which converges towards isotretinoin overall survival), the range of ICERs increases to £89,000 - £140,000 per QALY.

Probabilistic sensitivity analysis demonstrated that for all scenarios for overall survival and event-free survival, the probability that dinutuximab beta is cost-effective is below 5% for thresholds of up to £50,000 per QALY.

Scenario analyses demonstrated that the ICERs decrease when a cure point of 5-9 years is used, with ICERs ranging from £61,000 - £72,000 per QALY using the most favourable assumptions for event-free survival and overall survival, or £63,000 - £110,000 per QALY using the least favourable assumptions.

CONTENTS

1. INTRODUCTION 9

1.1. BACKGROUND 9

1.2. THIS REVIEW 9

2. MATCHING-ADJUSTED INDIRECT COMPARISON 10

2.1. SUMMARY AND CRITIQUE OF THE MAIC APPROACH 10

OVERALL SURVIVAL 17

2.2. ADDITIONAL WORK ON THE MAIC ANALYSIS BY THE DSU 18

3. REVISED COST-EFFECTIVENESS ANALYSIS 20

3.1. INDIRECT COMPARISON 21

3.2. ACCOUNTING FOR THE PROPORTION OF PEOPLE IN DIFFERENT BODY SURFACE AREA CATEGORIES 21

3.3. ASSUMPTIONS IN THE FAILURE HEALTH STATE 22

3.3.1. Number of newly progressed patients and their treatment duration 22

3.3.2. Resource use for people who complete chemotherapy 23

3.4. ADJUSTMENT FOR WASTAGE IN COST ESTIMATES FOR CHEMOTHERAPY 23

3.5. ADMINISTRATION COSTS 24

3.6. ADJUSTMENT FOR WASTAGE OF GABAPENTIN 24

3.7. MULTIPLE REGRESSION BY ARA ET AL (2010) FOR AGE-SPECIFIC EQ-5D VALUES 24

3.8. SCENARIO ANALYSES EXPLORING DIFFERENT PROPORTIONS OF PATIENTS RECEIVING INTERLEUKIN-2 24

3.8.1. Treatment schedule followed in the trial 25

3.8.1. What would be done in clinical practice 25

3.8.2. Marketing authorisation 25

3.9. SCENARIO ANALYSES REFLECTING THAT HAZARD RATIOS VARY OVER TIME AND THE TREATMENT EFFECT IS NOT MAINTAINED INDEFINITELY 25

3.10. PROBABILISTIC SENSITIVITY ANALYSIS 27

3.11. COMPANY'S REVISED BASE CASE 28

3.12. ADDITIONAL WORK ON THE ECONOMIC MODEL UNDERTAKEN BY THE DSU 28

3.12.1. Adjusting for topotecan wastage 29

3.12.2. Correcting the uncertainty in the number of vials 29

3.12.3. Incorporating the longer term isotretinoin data 29

3.12.4. Extrapolation for dinutuximab beta 31

3.13. RESULTS FROM THE DSU'S REVISED ECONOMIC MODEL 41
3.13.1. Deterministic results *41*
3.13.2. Probabilistic results *43*
3.13.3. Scenario analysis varying the cure point *44*
3.13.4. Scenario analyses varying the proportion receiving concomitant IL-2 ..... *45*
3.13.5. Scenario analyses varying the duration of chemotherapy *45*
4. CONCLUSIONS 46
5. REFERENCES 47
6. APPENDIX – CHANGES TO THE ECONOMIC MODEL 48
6.1. ADJUSTMENT FOR COST OF TOPOTECAN 48
6.2. ADDITION OF NEW DATA 48
6.2.1. Isotretinoin data *48*
6.2.2. DSU MAIC *48*
6.3. CHANGES TO THE PROBABILISTIC SENSITIVITY ANALYSIS 48

TABLES

Table 1: Summary of prognostic factors in APN311-302 and Yu et al. study *13*
Table 2: Hazard ratio estimates of event-free survival and overall survival (reproduced) *17*
Table 3: MAIC scenario analysis and effective sample size *18*
Table 4: Company's revised base case results *28*
Table 5: ICER with corrected topotecan wastage *29*
Table 6: ICER with corrected topotecan wastage and longer-term isotretinoin data *30*
Table 7: Summary of goodness-of-fit of overall survival *33*
Table 8: ICER with corrected topotecan wastage, longer-term isotretinoin data and DSU Gompertz overall survival dinutuximab beta *36*
Table 9: ICER with corrected topotecan wastage, longer-term isotretinoin data and DSU spline k=1, scale=hazards overall survival dinutuximab beta *37*
Table 10: ICER with corrected topotecan wastage, longer-term isotretinoin data and DSU spline k=2, scale=hazards overall survival dinutuximab beta *37*
Table 11: Summary of goodness-of-fit of event-free survival *38*
Table 12: DSU results: EFS spline k=1, scale=odds *42*
Table 13: DSU results: EFS Generalised gamma *43*
Table 14: Probabilistic results *44*
Table 15: Scenario analysis varying the cure point *45*
Table 16: Scenario analyses varying concomitant IL-2 usage *45*
Table 17: Scenario analyses varying the duration of chemotherapy *46*

FIGURES

Figure 1: Pre- and post-matching Kaplan-Meier curve for overall survival (reproduced) *15*
Figure 2: Pre- and post-matching Kaplan-Meier curve for event-free survival (reproduced) *16*
Figure 3: The comparison of observed and MAIC data in APN311-302 ..... *19*
Figure 4: Company submitted versus DSU EFS and OS data for Isotretinoin *30*
Figure 5: Overall survival for dinutuximab beta: Kaplan-Meier curve vs. fitted models *32*
Figure 6: Comparison of survival curves to isotretinoin Kaplan-Meier data *34*
Figure 7: Overall survival for dinutuximab alpha and isotretinoin (reproduced from ERG report) *35*
Figure 8: Comparison of company and DSU overall survival data *36*
Figure 9: Event-free survival Kaplan-Meier curve vs. fitted models *39*
Figure 10: Event-free survival for dinutuximab alpha and isotretinoin (reproduced from ERG report) *40*
Figure 11: Comparison of company and DSU event-free survival data *41*

ABBREVIATIONS AND DEFINITIONS

AIC	Akaike information criterion
AD	Aggregate data
ASCT	Autologous stem cell transplant
BIC	Bayesian information criterion
BSA	Body surface area
BuMel	Busulfan and melphalan hydrochloride
CC	Complication and comorbidity
CEM	Carboplatin, etoposide and melphalan
DSU	Decision Support Unit
EFS	Event-free survival
EQ-5D	EuroQol 5 Dimension
ERG	Evidence review group
ICER	Incremental cost-effectiveness ratio
IL-2	Interleukin-2
IPD	Individual patient-level data
INSS	International Neuroblastoma Staging System
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
MYCN	N-myc proto-oncogene protein
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
QALY	Quality-adjusted life-year
TSD	Technical Support Document

1. INTRODUCTION

1.1. BACKGROUND

The appraisal committee was unable to make a recommendation for dinutuximab beta, in combination with isotretinoin within its marketing authorisation for treating high-risk neuroblastoma in people aged 12 months and over who have had induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplant. This was because there was not enough information to make a decision about the clinical and cost effectiveness of dinutuximab beta for high-risk neuroblastoma for the following reasons:

- there was no evidence directly comparing dinutuximab beta with isotretinoin,
- the evidence for dinutuximab beta was relatively immature, potentially at risk of bias and the dosing schedule did not represent that used in NHS practice,
- a naïve indirect comparison, using a historical cohort of the trial to represent the control arm, did not produce robust estimates of treatment effect for overall survival, and did not capture event-free survival,
- the modelled treatment effect assumed proportional hazards which were not supported by data from the dinutuximab alpha appraisal, for which more mature evidence was available (after 5 years the initial separation of the survival curves diminished),
- several cost assumptions in the model were considered inappropriate,
- the cure threshold in the model was 10 years; an appeal hearing for the appraisal of dinutuximab alpha recommended that other cure thresholds be explored.

The committee therefore requested further clarification and analyses from the company. The company has now provided a matching-adjusted indirect comparison (MAIC) and a revised cost-effectiveness analyses.

1.2. THIS REVIEW

This document reviews the methods and assumption in the clarification and analyses from the company, to determine if there is now sufficient evidence to inform the committee's conclusion on the clinical and cost-effectiveness of dinutuximab beta. Additionally, this document describes the methods and results of additional analyses undertaken by the Decision Support Unit (DSU).

2. MATCHING-ADJUSTED INDIRECT COMPARISON

2.1. SUMMARY AND CRITIQUE OF THE MAIC APPROACH

MAIC is a reweighting approach that allows matching the observed imbalance in the patient baseline characteristics between the two studies, where the individual patient-level data (IPD) are available in one study and aggregate data (AD) in another. It adjusts the population in the IPD study so that it matches to the population in the AD study. As with other approaches that rely on matching methods, the method relies on sufficient overlap in the two populations. The unanchored MAIC, where there is no common comparator between the two studies, also relies on strong assumptions that all effect modifiers and prognostic variables are adjusted in the reweighting of the patients. The MAIC approach does not adjust for unobserved confounding. Further information on the MAIC approach is available in NICE DSU Technical Support Document 18[1,3].

In the absence of head-to-head trials comparing dinutuximab beta to isotretinoin or to dinutuximab alpha (which was compared to isotretinoin in a head-to-head trial[1]), the company conducted an unanchored MAIC analysis to estimate the relative effectiveness of dinutuximab beta versus isotretinoin on event-free survival (EFS) and overall survival (OS). No analysis was performed for dinutuximab beta versus dinutuximab alpha because dinutuximab alpha was not considered as a relevant comparator.

In the unanchored MAIC analysis, both arms of APN311-302 (dinutuximab beta plus isotretinoin with and without interleukin-2 (IL-2)) were combined to inform the dinutuximab beta group; the isotretinoin arm in the Yu et al. (2010)[1] study was used to inform the isotretinoin group. The NICE committee previously noted that there was no statistically significant difference in OS or EFS between the two arms of APN311-302, and concluded that "…based on the analyses, concomitant administration of interleukin-2 does not improve event-free survival and overall survival." Our clinical experts advised that combining the two arms from APN311-302 is appropriate, as there is no difference between groups in terms of outcome.

The company selected prognostic factors to be included in the MAIC based on:

1. the inclusion and reporting of factors in both APN311-302 and the Yu et al (2010) study,

2. statistical significance of predicting either EFS or OS based on Yu et al (2010), and
3. expert judgment.

Four prognostic factors were considered in the MAIC:

- age (<18 months and ≥ 18 months),
- International Neuroblastoma Staging System (INSS) stage (2, 3, 4 and 4S),
- tumour N-myc proto-oncogene protein (MYCN) status (not amplified, amplified and unknown) and
- response before autologous stem cell transplant (ASCT) (complete response, very good partial response and partial response).

In the evidence review group (ERG) report for this appraisal, it was noted that the type of consolidation therapy differed between APN311-302 and the Yu et al. (2010)[1] study: the majority of the patients in APN311-302 received BuMel (busulfan and melphalan hydrochloride) as the consolidation therapy, but all patients received CEM (carboplatin, etoposide and melphalan) in the Yu et al (2010)[1] study. As explained in the ERG report, in the UK, BuMel is now the standard of care in high-risk neuroblastoma, and CEM is very rarely used given that BuMel is considered a more effective consolidation therapy than CEM. A published randomized controlled trial comparing BuMel and CEM reported that 3-year EFS was 50% for BuMel and 38% for CEM (p=0.0005).[4] The DSU's clinical advisors also confirmed that in the UK, BuMel is widely used whilst CEM is not, and that BuMel is considered more effective.

The summary of included prognostic factors in APN311-302 and Yu et al (2010)[1] study is presented in Table 1. The DSU identified errors in the company submission when presenting the summary of the prognostic factors in both APN311-302 and Yu et al. (2010)[1] study:

- The total number of patients used in calculating the percentages in APN311-302 was incorrect.
    - In APN311-302 N=370 was used for calculating the percentages for age category, INSS stage and tumour MYCN status. However, the number of patients included in the MAIC was 344, since the company excluded 26 patients in the MAIC because Yu et al. study requires patients to have at least

a partial response and 16 patients had not shown at least partial response and 10 patients had missing information in APN311-302.

    - There were three patients in the MAIC dataset had missing information on either on the OS or EFS, which should be excluded.
- The company ignored that five patients' INSS stage status were unknown in Yu et al. study when calculating the percentages.

The company included the IPD used in the MAIC analysis in the submitted economic model. The DSU corrected the errors in calculating the percentages using the given IPD, which resulted in some changes in the summary of the prognostic factors. The results are presented in Table 1.

Baseline characteristics for the patient population in APN311-302 (N=341) and Yu et al. (2010)[1] are similar in terms of age, INSS, tumour MYCN status. More patients had complete response before ASCT in APN311-302 than in Yu et al. (60.12% vs. 33.63%). More patients received BuMel as the consolidation therapy in APN311-302 than in Yu et al. (2010)[1] study (91.74% vs. 0%).

Table 1: Summary of prognostic factors in APN311-302 and Yu et al. study

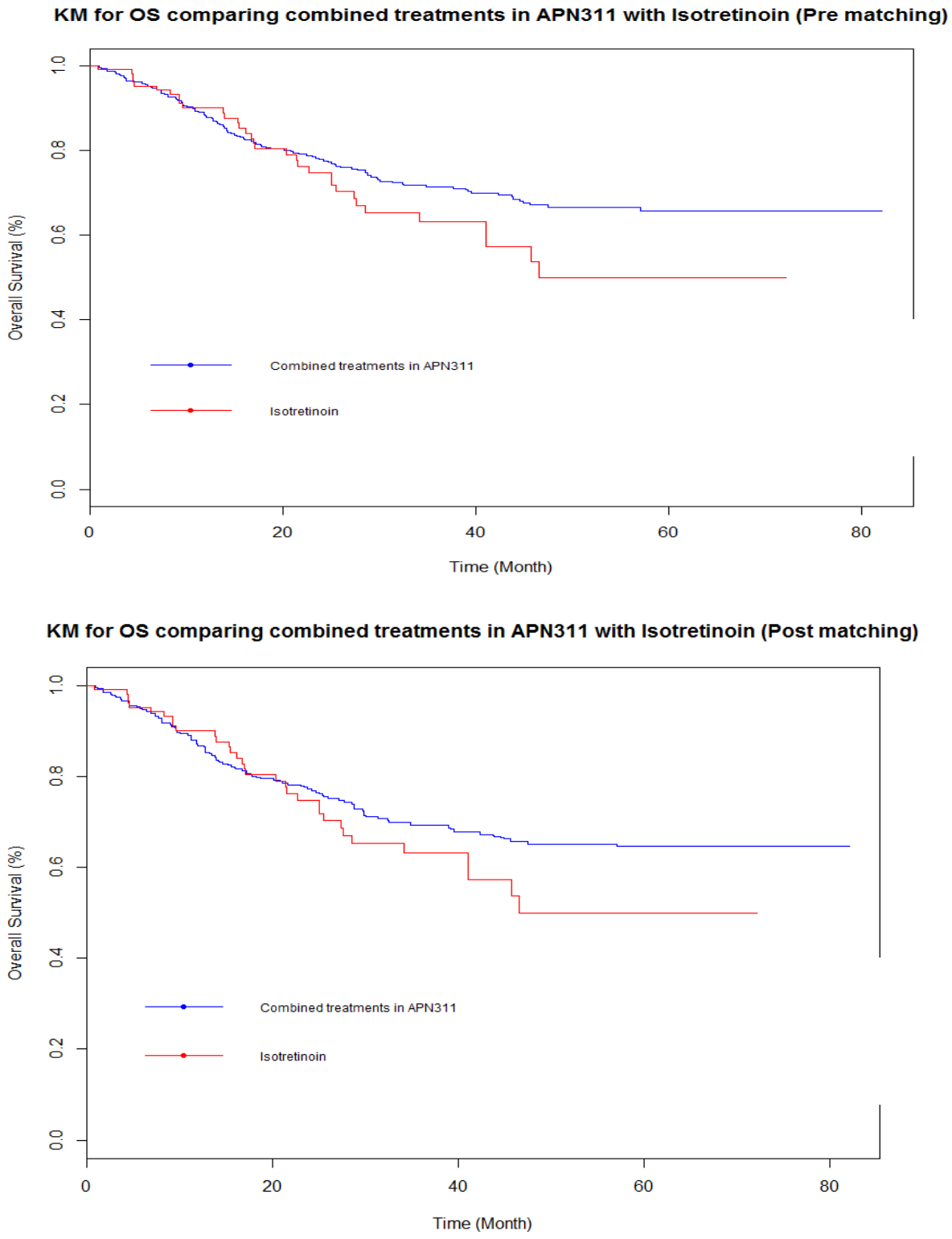
Baseline variable	APN311-302 (Dinutuximab beta) N=344[a]	Yu et al. (Isotretinoin) N=113	APN311-302 (Dinutuximab beta) N=341[b]	Yu et al. (Isotretinoin) N=113
	Company's submission		DSU's calculation	
Age				
<18 months	6.75%	3.54%	7.04%	3.54%
≥ 18 months	93.25%	96.46%	92.96%	96.46%
INSS stage				
2	0.27%	0	0.29%	0
3	9.18%	15%	9.38%	14.16%
4	88.65%	85%	88.27%	81.42%
4S	1.89%	0	2.05%	0
Tumour MYCN status				
Amplified	41.08%	39.82%	41.94%	39.82%
Not amplified	48.92%	45.13%	49.56%	45.13%
Unknown	10%	15.04%	8.50%	15.04%
Response before ASCT				
Complete response	55.81%	33.63%	60.12%	33.63%
Very good partial response	25.58%	43.36%	26.98%	43.36%
Partial response	11.92%	23.01%	12.90%	23.01%
Type of consolidation therapy				
BuMel	-	0	91.74%[c]	0
CEM	-	100%	8.26%[c]	100%

BuMel: busulfan and melphalan hydrochloride, CEM: carboplatin, etoposide and melphalan

a: the company used N=370 for age, INSS stage and tumour MYCN status.
b: the DSU's calculation excludes three patients with missing information on either overall survival or event-free survival.
c: the DSU's calculation excludes additional two patients with either missing information on the type of consolidation therapy or no consolidation therapy was used (N=339).

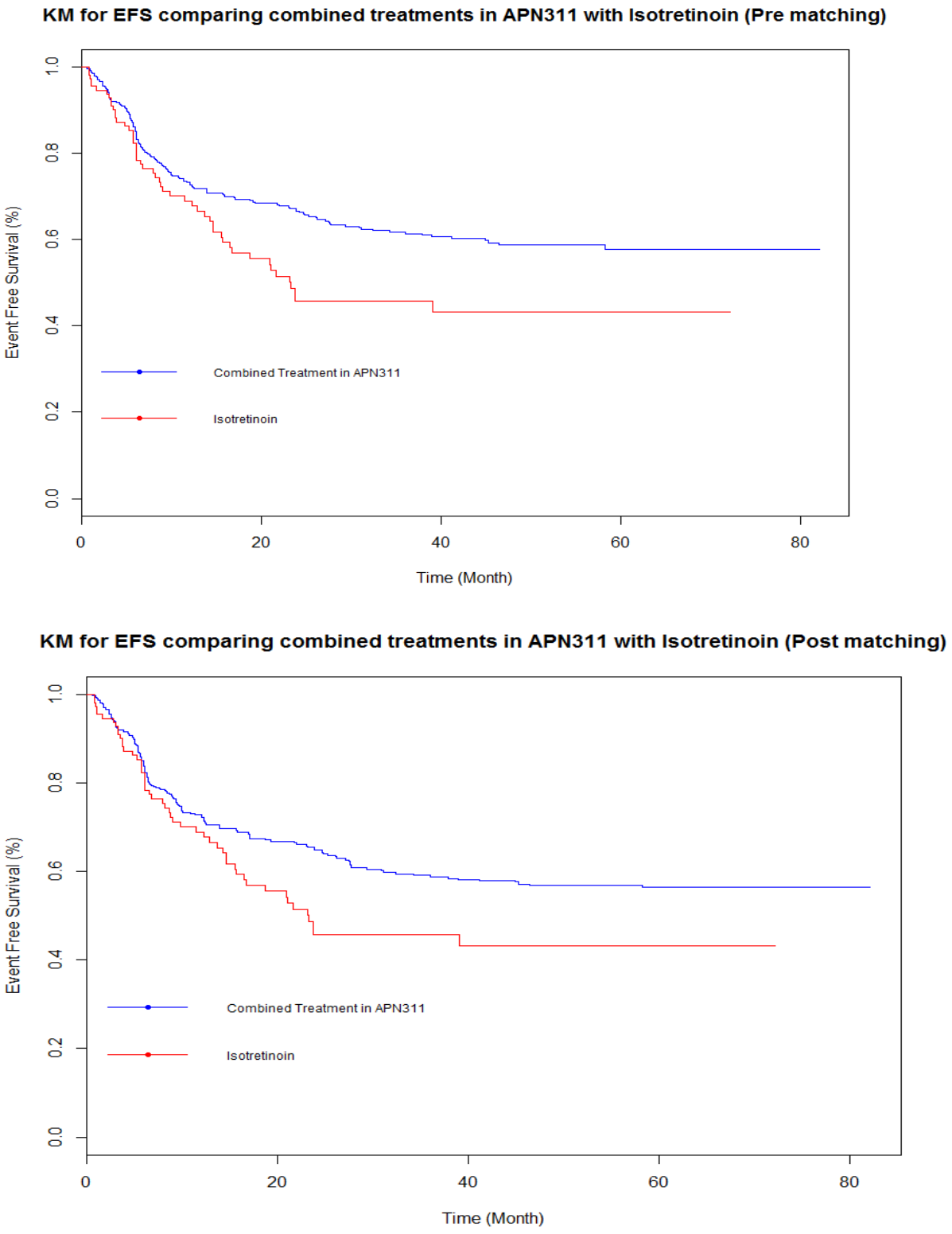
The company presented the pre- and post-matching OS and EFS (reproduced in Figure 1 and Figure 2). The MAIC adjusted Kaplan-Meier (KM) curve for both OS and EFS were very similar to the observed KM curves in APN311-302.

Figure 1: Pre- and post-matching Kaplan-Meier curve for overall survival (reproduced)



KM: Kaplan-Meier, OS: overall survival

Figure 2: Pre- and post-matching Kaplan-Meier curve for event-free survival (reproduced)



KM: Kaplan-Meier, EFS: event-free survival

The DSU has identified a few errors in the company's MAIC procedure. The wrong summary of the Yu et al. (2010)[1] study was used in the adjustment as discussed earlier. Three patients with missing data on either OS or EFS were included in the analysis and subsequently were assigned weights. The company's MAIC model did not have a reference case for INSS stage, tumour MYCN status and response before ASCT. In theory, this would induce perfect collinearity and cause problems in obtaining the weights for the matched population. However, since the company has used an optimization approach (because only IPD are available from one study), it is unclear whether this does cause problems in their MAIC.

The company used the adjusted KM for OS and EFS to calculate the hazard ratio at 24, 48 and 70 months assuming the data follow an exponential distribution (see Table 2). The uncertainty associated with the hazard ratios was calculated using the upper and lower 95% confidence interval (CI) of the KM data. No pre-matching hazard ratios were reported.

The DSU advises that the reported hazard ratios and their 95% CIs in Table 2 should be interpreted with caution. The company's approach assumes that data is piecewise exponential with monthly cut-off points. The estimates of the hazard ratios would vary according to how the interval is chosen. The company also used the 95% CI of the KM data to calculate the 95% CI of the hazard ratio directly, which is not an appropriate approach to estimate uncertainty because the KM function is not a linear function. The DSU notes that the calculated HRs were not used in the economic model.

Table 2: Hazard ratio estimates of event-free survival and overall survival (reproduced)

Comparison	**After matching HR (95% CI)**
Event-free survival	
Dinutuximab beta + CT vs. Isotretinoin alone at 24 Months	0.553 (0.51 – 0.63)
Dinutuximab beta + CT vs. Isotretinoin alone at 48 Months	0.672 (0.61 – 0.79)
Dinutuximab beta + CT vs. Isotretinoin alone at 70 Months	0.681 (0.62 – 0.80)
Overall Survival	
Dinutuximab beta + CT vs. Isotretinoin alone at 24 Months	0.886 (0.78 – 1.16)
Dinutuximab beta + CT vs. Isotretinoin alone at 48 Months	0.620 (0.53 – 0.85)
Dinutuximab beta + CT vs. Isotretinoin alone at 70 Months	0.629 (0.54 – 0.86)

CI: confidence interval, CT: consolidation therapy, HR: hazard ratio

The company also conducted 10 MAIC scenario analyses varying the included prognostic factors. The effective sample size (ESS) for each of the scenario analysis is reported in Table 3. As expected, when the number of included prognostic factors increases, the ESS decreases. All the scenario analyses provide similar adjusted KM curves as compared with the observed KM data from APN311-302.

Table 3: MAIC scenario analysis and effective sample size

MAIC analysis	Effective sample size
Four prognostic factors (Base case)	
Age + INSS stage + tumour MYCN status + response to treatment before ASCT	236
One prognostic factor	
Age	339
INSS stage	325
MYCN Status	329
Response to treatment before ASCT	268
Two prognostic factor s	
Response to treatment before ASCT + Age	267
Response to treatment before ASCT + INSS Stage	252
Response to treatment before ASCT + MYCN Status	251
Three prognostic variables	
Response to treatment before ASCT + Age + INSS Stage	252
Response to treatment before ASCT + Age + MYCN Status	250
Response to treatment before ASCT + INSS Stage + MYCN Status	236

ASCT: autologous stem cell transplant, INSS: international neuroblastoma staging system, MAIC: matching-adjusted indirect comparison, MYCN: N-myc proto-oncogene protein

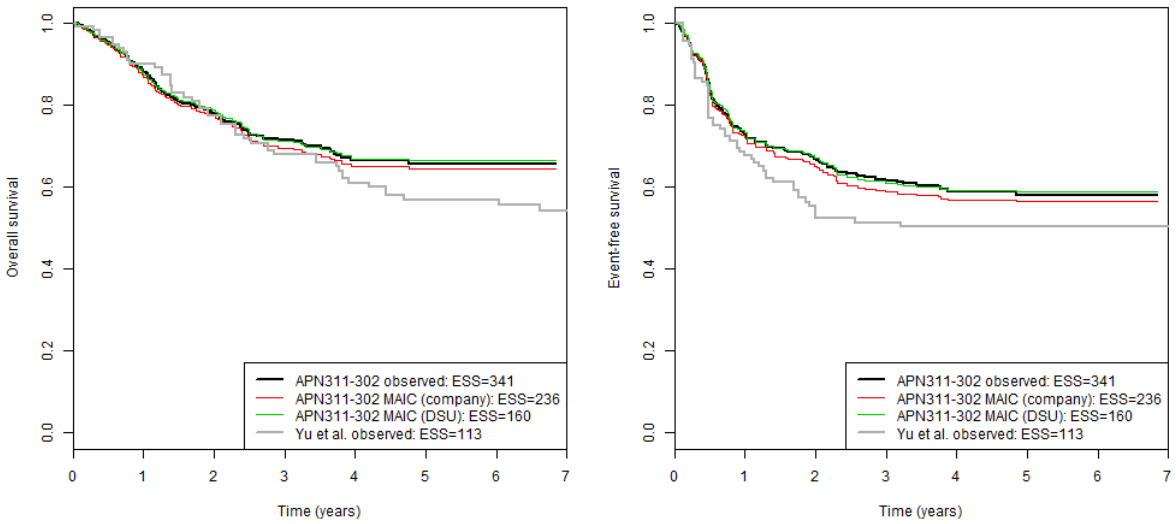
2.2. ADDITIONAL WORK ON THE MAIC ANALYSIS BY THE DSU

Additional work on the MAIC analysis performed by the DSU includes:

- excluding three patients who had missing data on either OS or EFS,
- re-calculating the percentages of the INSS stage in Yu et al. study so that the patients with unknown stages are considered in the calculation,
- amending the company's MAIC approach so that each categorical variable has a reference case.

The results of the DSU's MAIC are presented in Figure 3. The DSU's MAIC adjusted KM for both OS and EFS were similar to the company's adjusted KM curves, which were also similar to the observed data in APN311-302 (N=341).

Figure 3: The comparison of observed and MAIC data in APN311-302



DSU: Decision Support Unit, ESS: effective sample size, MAIC: matching-adjusted indirect comparison

The DSU notes that the type of consolidation therapy received was not adjusted in the company's MAIC. The DSU considered the potential to include adjustment for the type of consolidation in their MAIC, but deemed that this was not appropriate for the following reasons:

- the lack of population overlap, as the percentage of patients who have received BuMel is 91.74% and 0% in APN311-302 and Yu et al. (2010)[1] study, respectively;
- the adjusted comparison would match to the population in Yu et al. (2010)[1], where all the patients received CEM which is not standard practice in the UK;
- the effective sample size would reduce to 8 due to the very low number of patients in APN311-302 that received CEM;;
- following this adjustment, it requires the assumption that the relative effect of dinutuximab beta is the same when following BuMel as it is when following CEM in the economic model;
- the DSU's clinical advisers also noted that induction therapy prior to the consolidation therapy differs in APN311-302 and Yu et al. (2010)[1] study, which may result in a different effect of CEM in these two studies.

3. REVISED COST-EFFECTIVENESS ANALYSIS

The company's revised cost-effectiveness analysis incorporates the following changes requested by the Committee:

a) The indirect comparison.
b) Weighted average costs to account for the proportion of people in different body surface area (BSA) categories in trial APN311-302.
c) Two assumptions in the failure health state:
    i. to estimate newly progressed patients in both the dinutuximab beta and isotretinoin arms of the model. Once newly progressed patients are estimated, an assumption needs to be made for treatment duration (for example, it could be assumed that relapsed patients would stay on treatment for a maximum of one year),
    ii. The resource use needed to manage the disease in people who complete chemotherapy and relapse, but are still alive and are in the failure health state.
d) Adjustment for wastage in the cost estimates for the chemotherapy regimens used in the failure state.
e) The cost of a hospital day (£934 per day) to calculate the administration costs per cycle, which amounts to a total of £4,670 for 5 days in the hospital (which compares to the chemotherapy procurement cost of £2,620.54 used in the model originally).
f) Adjustment for wastage of gabapentin in the concomitant medication costs in the model.
g) The multiple regression published by Ara et al. (2010)[5] to estimate age-specific UK EQ-5D values in the model.
h) Scenario analyses exploring the impact on the incremental cost-effectiveness ratio (ICER) of different proportions of patient receiving concomitant use of interleukin-2, including any additional time in hospital as a result of infection, to determine incremental differences between the regimens, based on:
    i. Treatment schedule followed in the trial; IPD from the APN311-302,
    ii. What would be done in clinical practice,
    iii. Reflecting the use of interleukin-2 in line with the marketing authorisation.
i) Scenario analyses reflecting that the hazard ratios will vary over time and the treatment effect is not maintained indefinitely.

j) Probabilistic sensitivity analyses to incorporate the impact of varying relative treatment effectiveness estimates on the incremental cost-effectiveness ratios.

Each of these changes is reviewed in turn by the DSU.

3.1. INDIRECT COMPARISON

The company has revised the Excel model to use the data from their MAIC in modelling EFS and OS for dinutuximab beta, and the data from Yu et al. (2010)[1] for isotretinoin. For both dinutuximab beta and isotretinoin group, the KM data are used for months 0-70 and parametric survival functions (fitted to the entirety of the KM data) are used beyond this.

The company fitted exponential, Weibull, Gompertz, log logistic and log normal distributions, and a nonlinear model by applying a least squares approach (i.e., minimising sums of squares) using the solver add-in in Microsoft Excel. The company has chosen the Gompertz model for EFS and OS for both dinutuximab beta and isotretinoin as the base case. In the model, the Gompertz was reported to be the best fit, according to least squares. In response to request for clarification, the company provided further information on the process used to fit and select survival curves, including assessment of proportional hazards using the log-cumulative hazard and quantile-quantile plots, visual and statistical inspection of different parametric curves to the observed data, expert opinion and use of external data.

The DSU considers an important limitation of the analysis presented by the company is the use of least squares to fit parametric models to KM data as this approach ignores the fact that the data used are time-to-event (effectively ignoring the fact these are survival data), and does not rely on any formal statistical methods for making inferences. The DSU has therefore performed additional survival analysis, described in Section 3.12.4.

3.2. ACCOUNTING FOR THE PROPORTION OF PEOPLE IN DIFFERENT BODY SURFACE AREA CATEGORIES

The company has categorised IPD from APN-3112 by BSA according to the number of vials required for each administration of dinutuximab beta. The mean number of vials per

administration has increased from 2 in the original submission to 2.15. This has been implemented correctly.

3.3. ASSUMPTIONS IN THE FAILURE HEALTH STATE

3.3.1. Number of newly progressed patients and their treatment duration

The company has assumed that after progression, patients are treated with chemotherapy for one year. The company state that clinical experts agreed this assumption was reasonable, despite an individualised approach in the UK. Our clinical experts agreed that this was reasonable, but noted that some patients may receive later lines of treatment. This is explored further in Section 3.13.5.

The company has analysed IPD from APN311-302, using the weighting from the MAIC, to estimate the proportion of patients in the failure state each cycle who are receiving treatment with chemotherapy. This is calculated in the model using the following steps each cycle:

1. For both dinutuximab beta and isotretinoin, the model estimates the proportion of patients alive in the failure state by subtracting the cumulative probability of death (from OS) from the cumulative probability of an event or death (from EFS).
2. For both dinutuximab beta and isotretinoin, the model estimates the proportion of patients in the failure state who are alive post-chemotherapy by multiplying the proportion of patients alive in the failure state by the proportion of patients in APN311-302 who survived one year post-chemotherapy.
    - In the first 12 months, the proportion of patients in APN311-302 who survived one year post chemotherapy is calculated as the number of weighted patients in the failure state who survived at least one year after entering the failure state divided by the number of weighted patients in the failure state.
        - The number of weighted patients in the failure state who survived at least one year after entering the failure state is calculated as the sum of the weights in APN311-302 of all uncensored patients who had not died and who had had an event more than one year ago.
        - The number of weighted patients in the failure state is calculated as the sum of the weights in APN311-302 of all uncensored patients who had not died and who had had an event.

- Beyond 12 months, the proportion of patients in APN311-302 who survived one year post chemotherapy is calculated by fitting a logarithmic model to the proportion of patients in APN311-302 who survived one year post chemotherapy (calculated as for the first 12 months).

This assumes that the probability of surviving one year of chemotherapy in the failure state is the same for patients who were treated with dinutuximab beta and isotretinoin. The DSU considers this assumption is reasonable given that IPD linking EFS and OS is not available for isotretinoin.

3.3.2. Resource use for people who complete chemotherapy

The company state that clinical experts advised that costs for children after one year of chemotherapy could be assumed to be similar to those in the stable state, at £76.50 per month. Clinical experts advised the DSU that this is appropriate if the patients disease is under control, but that in the case of uncontrolled disease, patients may receive more intensive palliative care for a short period of time. Since all patients would receive palliative care shortly before dying and all modelled patients die, the only impact this cost would have on the results would be due to discounting – which, at 1.5% per annum would be negligible.

3.4. ADJUSTMENT FOR WASTAGE IN COST ESTIMATES FOR CHEMOTHERAPY

The company has made adjustments to the costs for topotecan, cyclophosphamide and filgrastim. The company's revised model calculates the cost of each drug every cycle, based on the average BSA or weight of the modelled patient. These calculations round up the number of units to include wastage. The calculations for cyclophosphamide and filgrastim are correct, but the calculations for topotecan may overestimate the costs of treatment. There are two vial sizes available for topotecan: 4mg/4ml and 1mg/1ml. The revised model calculates the cost if the small vials are used and the cost if the large vials are used, and uses the minimum. However, the model does not consider that a patient could have a combination of small and large vials which may be cheaper. For example, a patient aged 75 with a BSA of 1.08m^2 requires 4.02mg of topoecan per dose, which rounds up to 5mg. The company assumes two 4mg/4ml vials would be needed, costing £439.40, whereas one 4mg/4ml vial and one 1mg/ml vial would deliver the required dose and cost £349.43.

3.5. ADMINISTRATION COSTS

The company has revised the model to use the administration cost of £4,670 (5 days at £934 per day) per cycle of chemotherapy, as requested by the committee.

3.6. ADJUSTMENT FOR WASTAGE OF GABAPENTIN

The company has revised the model to include wastage for gabapentin, assuming that patients have a new pack of gabapentin for each course of dinutuximab beta.

3.7. MULTIPLE REGRESSION BY ARA ET AL (2010) FOR AGE-SPECIFIC EQ-5D VALUES

The company has revised the model to use the published algorithm by Ara and Brazier (2010)[6] to estimate mean EQ-5D for the general population.

3.8. SCENARIO ANALYSES EXPLORING DIFFERENT PROPORTIONS OF PATIENTS RECEIVING INTERLEUKIN-2

As requested by the Committee, the company has performed scenario analysis assuming that the proportion of patients receiving interleukin-2 concomitantly with dinutuximab beta is 0% (clinical practice), 41% (marketing authorisation) and 51% (APN311-302).

The company has analysed the risk of grade 3 to 4 infection and severe capillary leak syndrome by whether a patient was receiving IL-2 or not and included these in the economic model. The probability of grade 3 to 4 infection is [redacted]% ([redacted]% grade 3 and [redacted]% grade 4) in the no IL-2 group and [redacted]% ([redacted]% grade 3 and [redacted]% grade 4) in the IL-2 group. The company has included a cost for these infections of £3,980.27 per event, from an NHS Reference cost for paediatric major infections with complication and comorbidity (CC) score 2-4, which they state is validated by clinical experts. This cost is for a non-elective long-stay inpatient, with an average stay of 5 days. Our clinical experts advised that a 5-day stay seemed appropriate.

The probability of pyrexia/infection has been recalculated as the probability of pyrexia/infection in the original submission minus the average probability of grade 3 to 4 infection from the IL-2 and no IL-2 patients. The average is not weighted, so assumes 50% of

patients had IL-2 and 50% did not – it would be more accurate to use the 51% of patients who had IL-2 and 49% who did not. In practice this makes little difference to the results.

The probability of capillary leak syndrome is [redacted]% in the no IL-2 group and [redacted]% in the IL-2 group. The cost is unchanged from the original submission.

3.8.1. Treatment schedule followed in the trial

The company provide a scenario where 51% of patients receive IL-2, as analysed from IPD in APN311-302.

3.8.1. What would be done in clinical practice

The company assume in the base case that 0% of patients receive IL-2. The ACD states that "Standard NHS practice does not include concomitant use of interleukin-2 in the majority of patients". Our clinical experts advised that concomitant IL-2 is not recommended in the UK as there is no evidence of benefit.

3.8.2. Marketing authorisation

The company provide a scenario where 41% of patients receive IL-2, which is reported to be in line with the marketing authorisation *"i.e. 41% patients had evidence of disease and will take concomitant IL-2"*.

3.9. SCENARIO ANALYSES REFLECTING THAT HAZARD RATIOS VARY OVER TIME AND THE TREATMENT EFFECT IS NOT MAINTAINED INDEFINITELY

The Appraisal Consultation Document suggests that:

> *"For example, the company should explore use of the relative treatment difference between the event-free survival and overall survival hazard ratios from dinutuximab alpha compared with isotretinoin (from the suspended dinutuximab alpha appraisal) and apply it at various cure time points between 5 and 10 years in the dinutuximab beta model."*

The DSU assumes that this request refers to the variation in the hazard ratios in the dinutuximab alpha appraisal when different time points were used for the data cuts. The hazard ratios for EFS and for OS for dinutuximab alpha versus isotretinoin increased when longer-term data was included, indicating that the relative effectiveness of the intervention decreased. For example, the hazard ratio for EFS was 0.57 using the data from January 2009 and 0.759 using the data from March 2014. The January 2009 data is the Yu et al. (2010)[1] study used by the company in their revised model in this appraisal.

The company did not use hazard ratios in their revised model, but fitted separate parametric curves to the MAIC adjusted dinutuximab beta and isotretinoin data (Yu et al. 2010[1]). The DSU understands that the important element of this request was not that the model should use hazard ratios, but that consideration should be given to longer-term effectiveness data where available, including consideration to the shape of the survival curves (which may converge) and that different cure points should be explored.

The company does provide scenario analysis exploring different cure thresholds from 5 to 10 years. Before the cure threshold, the EFS and OS data from the MAIC (the KM data and then the fitted model, as explained in Section 3.1) are used in the model for dinutuximab beta, and the same approach is used for isotretinoin. Beyond the cure threshold, patients are assumed to no longer be at risk of failure, but are at risk of dying and the probability of dying each cycle is the same for dinutuximab beta and isotretinoin. The company has not used the hazard ratios from dinutuximab alpha compared with isotretinoin from the suspended dinutuximab alpha appraisal. It may have been possible for the company to adjust their analysis to decrease the relative effectiveness of dinutuximab beta versus isotretinoin, to consider that the relative effectiveness may have decreased if longer-term data were used. The company has not done this, but in their response to request for clarification they provided a scenario analysis using the Yu et al. (2014)[2] data for isotretinoin, which increased the ICER for dinutuximab beta versus isotretinoin (see Section 3.12.3).

The DSU believes that the Yu et al. (2014) [2] data are more appropriate as it provides longer-term data on isotretinoin effectiveness, and therefore uses it in their analysis (Section 3.12). Although longer-term evidence is not available for dinutuximab beta, the use of longer-term data for isotretinoin reduces the uncertainty arising from with extrapolation of the comparator arm. The DSU has digitized data for the isotretinoin arm of the Yu et al. (2014) [2] study

(provided by NICE) and used the Guyot algorithm[7] to reconstruct the IPD. Using the 2014 data does not affect the MAIC for dinutuximab beta, as the population is the same as in the Yu et al. (2010)[1] study.

3.10. PROBABILISTIC SENSITIVITY ANALYSIS

The company has incorporated parameter uncertainty for the new parameters (number of vials, duration of chemotherapy, cost post-chemotherapy, failure state costs, infection costs, infection adverse event probabilities) and for treatment effectiveness. The distributions for the new parameters take a similar approach to those of previous parameters, although they are not necessarily rooted in the data.

In the company's deterministic sensitivity analysis, the number of vials appears is the second biggest driver and so appears to be important. However, the number of vials required was varied arbitrarily using ±30%. To avoid this variation adding unnecessary or inappropriate variation into the probabilistic results, the DSU has corrected this. The DSU varied the proportion of patients in each BSA category using a beta distribution, using the number of patients in each category and splitting an extra observation between the five categories to account for low numbers.

Treatment effectiveness is varied by multiplying the EFS and OS for dinutuximab beta by a number sampled from a normal distribution with mean 1 and standard deviation 0.033. This is the third most influential parameter in the tornado diagram. The distribution and range are arbitrary and do not reflect the variation in relative effectiveness reported in the hazard ratios. The model does not incorporate any uncertainty in the estimation of the isotretinoin effectiveness, and the estimates for dinutuximab are limited. Ideally, the model would include:

- Uncertainty in the Kaplan-Meier survival estimates for isotretinoin and dinutuximab beta,
- Uncertainty in the parametric curves fitted for isotretinoin and dinutuximab beta.

Uncertainty in the KM estimates is not reported in Yu et al. (2010)[1]. The DSU considers the uncertainty associated with KM survival estimates and parametric curves in their analysis.

3.11. COMPANY'S REVISED BASE CASE

The company's revised economic model uses the KM data from Yu et al. (2010)[1] for isotretinoin and KM data from their MAIC for dinutuximab beta, extrapolated beyond month 70 using the Gompertz model. The company's revised economic model incorporates further changes requested by the Committee to account for the proportion of people in different body surface area categories, revised assumptions in the failure health state, revised administration costs, adjustment for wastage, Ara et al. (2010)[6] EQ-5D values and 0% concomitant IL-2 usage. The company's revised base case results are reproduced in Table 4.

Table 4: Company's revised base case results

	Total		Incremental		ICER
	Cost	**QALYs**	**Cost**	**QALYs**	
Isotretinoin	£55,923	11.65			
Dinutuximab beta	£225,373	18.52	£169,450	6.87	£24,661

ICER: incremental cost-effectiveness ratio, QALY: quality adjusted life years

3.12. ADDITIONAL WORK ON THE ECONOMIC MODEL UNDERTAKEN BY THE DSU

The DSU considers that the majority of the changes made by the company (Section 3.11) are appropriate and have been incorporated correctly, but believes there are a number of minor errors that should be corrected, longer-term isotretinoin data (Yu et al. 2014[2]) should be used, and that the MAIC needs correcting and new survival analysis should be conducted. As such, the DSU has undertaken additional work. The DSU has made the following changes to the company's revised economic model:

- Adjusting for wastage of topotecan such that the minimal cost is incurred (see Section 3.4).
- Correcting the uncertainty in the number of vials, to use beta distributions, using the number of patients in each category and splitting an extra observation between the five categories to account for low numbers (see Section 3.2).
- Incorporating the longer-term isotretinoin KM data for EFS and OS (see Section 3.9).
- Incorporating the survival distributions for dinutuximab beta EFS and OS generated from the survival analysis of the revised MAIC (see Section 3.12.4).
- Incorporating uncertainty associated with the EFS and OS data for isotretinoin and dinutuximab beta, using a beta distribution for the KM data where alpha is the number

of patients who survived and beta is the number of patients at risk who did not survive each cycle, and using survival probabilities sampled from the appropriate distributions for parametric and non-parametric models.

Details of how the changes have been implemented in the economic model are reported in Section 6.

3.12.1. Adjusting for topotecan wastage

Adjusting the model to use the lowest possible cost does not impact the ICER (Table 5).

Table 5: ICER with corrected topotecan wastage

	Total		Incremental		ICER
	Cost	**QALYs**	**Cost**	**QALYs**	
Isotretinoin	£55,923	11.65			
Dinutuximab beta	£225,373	18.52	£169,450	6.87	£24,661

ICER: incremental cost-effectiveness ratio, QALY: quality adjusted life years

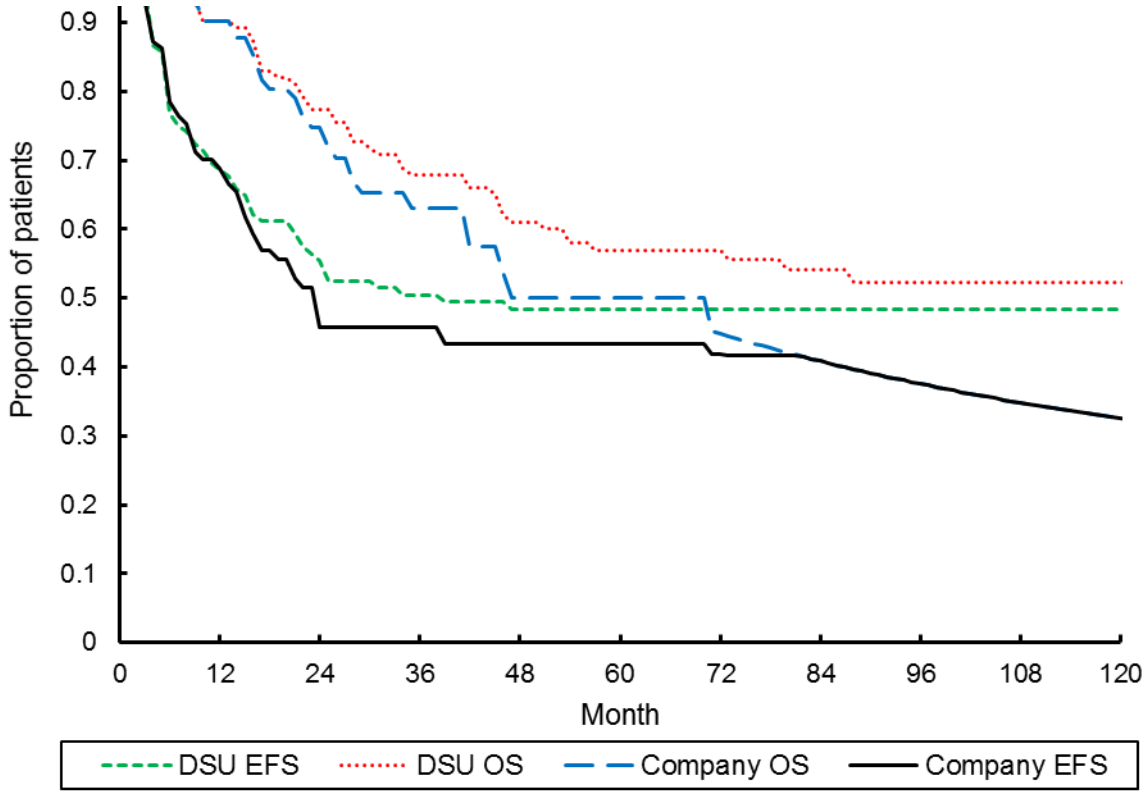
3.12.2. Correcting the uncertainty in the number of vials

Correcting the uncertainty in the number of vials reduces the associated uncertainty – the lower bound is now 2.10 and upper bound is 2.21. The ICER with the lower bound is £24,119 and with the upper bound is £25,291. This is not a key driver of cost-effectiveness results.

3.12.3. Incorporating the longer term isotretinoin data

Incorporating the longer term isotretinoin EFS and OS data removes the need to extrapolate using survival curves for isotretinoin as data is available for the full 10-year period. The company submitted analysis (Yu et al. (2010)[1] KM data to month 70, extrapolated using their fitted Gompertz distribution) and DSU data (Yu et al. (2014)[2] KM data to month 120) are compared in Figure 4. The EFS and OS for isotretinoin are both higher using the DSU's full 2014 data than the company's extrapolated 2010 data, and so the ICER for dinutuximab beta compared to isotretinoin increases, to £79,811 (Table 6).

Figure 4: Company submitted versus DSU EFS and OS data for Isotretinoin



DSU: decision support unit, EFS: event-free survival, OS: overall survival

Table 6: ICER with corrected topotecan wastage and longer-term isotretinoin data

	Total		Incremental		ICER
	Cost	**QALYs**	**Cost**	**QALYs**	
Isotretinoin	£60,459	16.45			
Dinutuximab beta	£225,373	18.52	£164,913	2.07	£79,811

ICER: incremental cost-effectiveness ratio, QALY: quality adjusted life years

In response to a request for clarification, the company provided an analysis using the Yu et al. (2014)[2] data for isotretinoin. This increased their ICER from £24,661 to £43,308. This ICER is still much lower than that produced by the DSU using the 2014 data - it appears that the company fitted parametric curves and extrapolated the data from month 70, as mortality for isotretinoin continues to decrease beyond year 7. The DSU believes that using the KM data directly for isotretinoin for years 0-10 is less uncertain than fitting survival curves and using them for part of the model.

3.12.4. Extrapolation for dinutuximab beta

Extrapolation is required for OS and EFS in the dinutuximab beta group as the dinutuximab beta data are available for only 70 months. The DSU explored the model choice for extrapolation using standard parametric distributions as described in the NICE DSU Technical Support Document (TSD) 14[8] for both OS and EFS using the DSU's MAIC data (with four factors: age, INSS stage, tumour MYCN status and response before ASCT, N=341 and ESS=160).

A more flexible survival modelling approach using the natural cubic spline models by Royston and Parmar[6] with knots=(1, 2, 3) are also explored. Natural cubic spline functions are piecewise cubic polynomials defined to be continuous at knots, and linear beyond boundary knots. This approach is able to model more complex hazard functions, and the complexity of the model is governed by the number of knots. All survival analyses were performed using R package flexsurv[9].

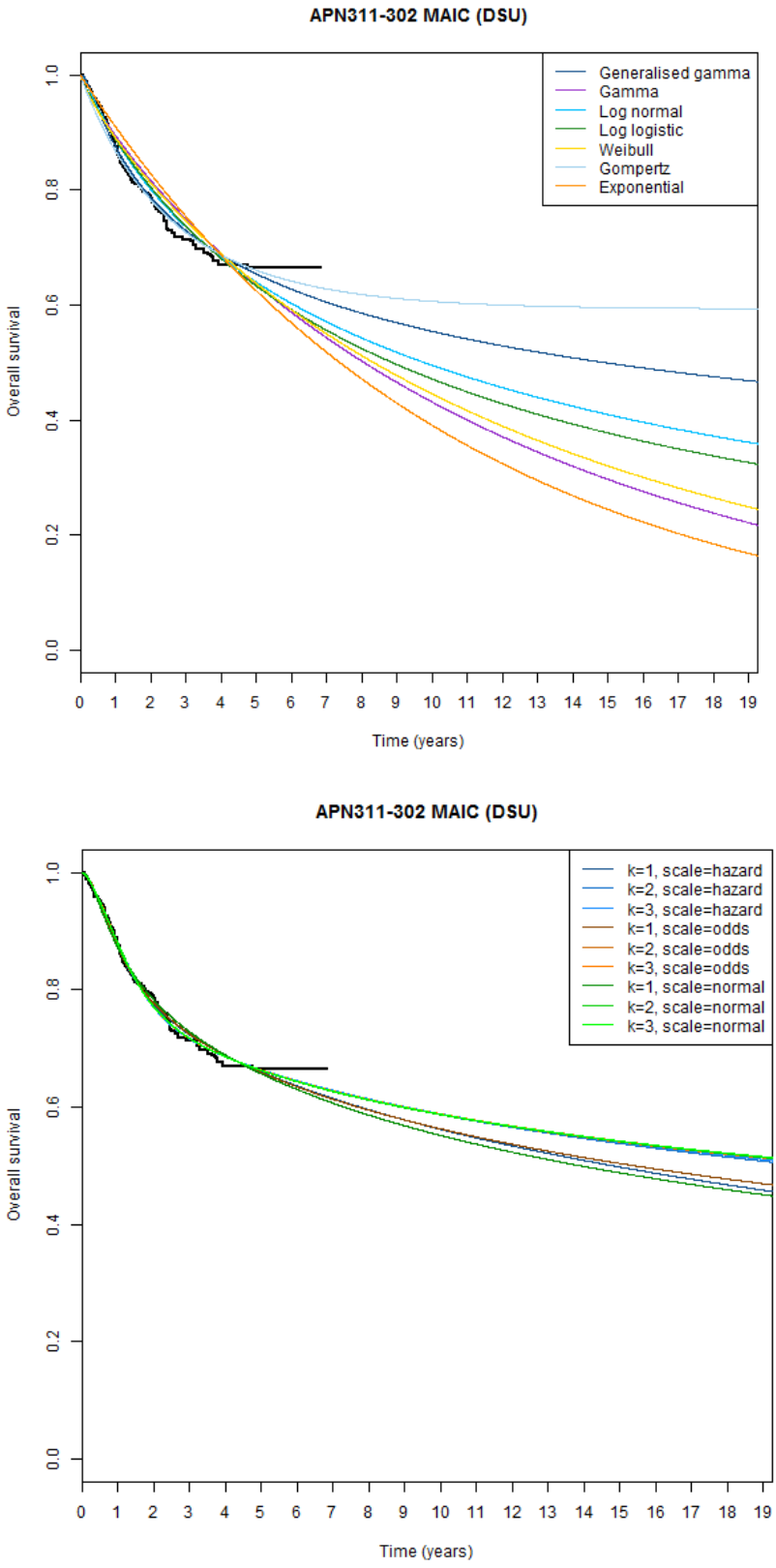
The DSU notes that exploration of cure fraction model may also have been valuable.

3.12.4.1. Overall Survival

The parametric and spline models for OS are shown in Figure 5 (parametric models at the top, spline models beneath). Of the parametric models, the Gompertz model is the most favourable to dinutuximab as it is the highest curve, followed by the Generalised gamma, log normal and log logistic model. The Weibull, gamma and exponential models are the least favourable, as they are the lowest curves. Many of the spline models are very close together, although the three models with only one knot are lower than those with two or three knots.

The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (Table 7) indicate that the best-fitting parametric models are the Generalised gamma, log normal and Gompertz, and that most of the spline models are a good fit. The probability of survival at 10 years varies between the best-fitting parametric models: for the Gompertz this is 61%, for the Generalised Gamma this is 55% and for the log normal this is 50%. The probabilities of survival at 10 years for the spline models with one knot are similar to the Generalised gamma; the survival probability at 10 years for all the other spline models is 59%. Clinical experts advised the DSU that there is uncertainty in predicting long-term overall survival.

Figure 5: Overall survival for dinutuximab beta: Kaplan-Meier curve vs. fitted models



DSU: decision support unit, MAIC: matching-adjusted indirect comparison

Table 7: Summary of goodness-of-fit of overall survival

Model	APN311-302 MAIC (DSU)	
	AIC	BIC
Generalised gamma	**1384.17**	**1395.66**
Gamma	1396.80	1404.46
Log normal	**1386.52**	**1394.19**
Log logistic	1391.99	1399.66
Weibull	1395.91	1403.57
Gompertz	**1385.78**	**1393.44**
Exponential	1396.56	1400.39
k=1, scale=hazard	**1382.95**	**1394.45**
k=2, scale=hazard	**1383.85**	1399.17
k=3, scale=hazard	**1385.53**	1404.69
k=1, scale=odds	**1382.96**	**1394.45**
k=2, scale=odds	**1383.83**	1399.16
k=3, scale=odds	**1385.54**	1404.70
k=1, scale=normal	**1384.03**	**1395.53**
k=2, scale=normal	**1383.63**	1398.96
k=3, scale=normal	**1385.32**	1404.48

AIC: Akaike information criterion, BIC: Bayesian information criterion, DSU: decision support unit, MAIC: matching-adjusted indirect comparison
Bold: best fitting models determined using 5 points rule and visual inspection.

The overall survival curves for the Generalised gamma, Gompertz, log normal and splines with k=1, scale=hazard and k=2, scale=hazard are compared to the isotretinoin KM data from Yu et al. (2014)[2] in Figure 6. The log normal crosses the isotretinoin KM data before month 10 (year 8), and the spline models and Generalised gamma converge towards the isotretinoin KM data at month 144 (year 14), with the spline models just crossing. The Gompertz remains above the isotretinoin KM data. The choice of which survival distribution is most appropriate may depend on which long-term extrapolation scenario is most realistic – whether the survival probabilities for isotretinoin and dinutuximab beta converge, and at what point.

Although there is no longer-term data for dinutuximab beta available, there is longer-term data available for dinutuximab alpha (Figure 7). The exact relationship between dinutuximab

alpha and dinutuximab beta is unknown. However, both treatments are derived from the same antibody and may therefore be expected to be similar. Therefore, the DSU used the dinutuximab alpha data to inform the likely relationship between isotretinoin and dintutuximab beta. The KM data and best-fitting survival curves considered by the ERG (Weibull cure fraction and Royston-Parmar spline model) for the dinutuximab alpha appraisal indicate that OS is higher with dinutuximab than isotretinoin over the 12-year period. The DSU considers that the Gompertz or the spline models appear to be plausible. Two spline models are considered: k=1 and scale=hazards, and k=2 and scale=hazards. The spline with k=1 appears very similar to the Generalised gamma.

Figure 6: Comparison of survival curves to isotretinoin Kaplan-Meier data

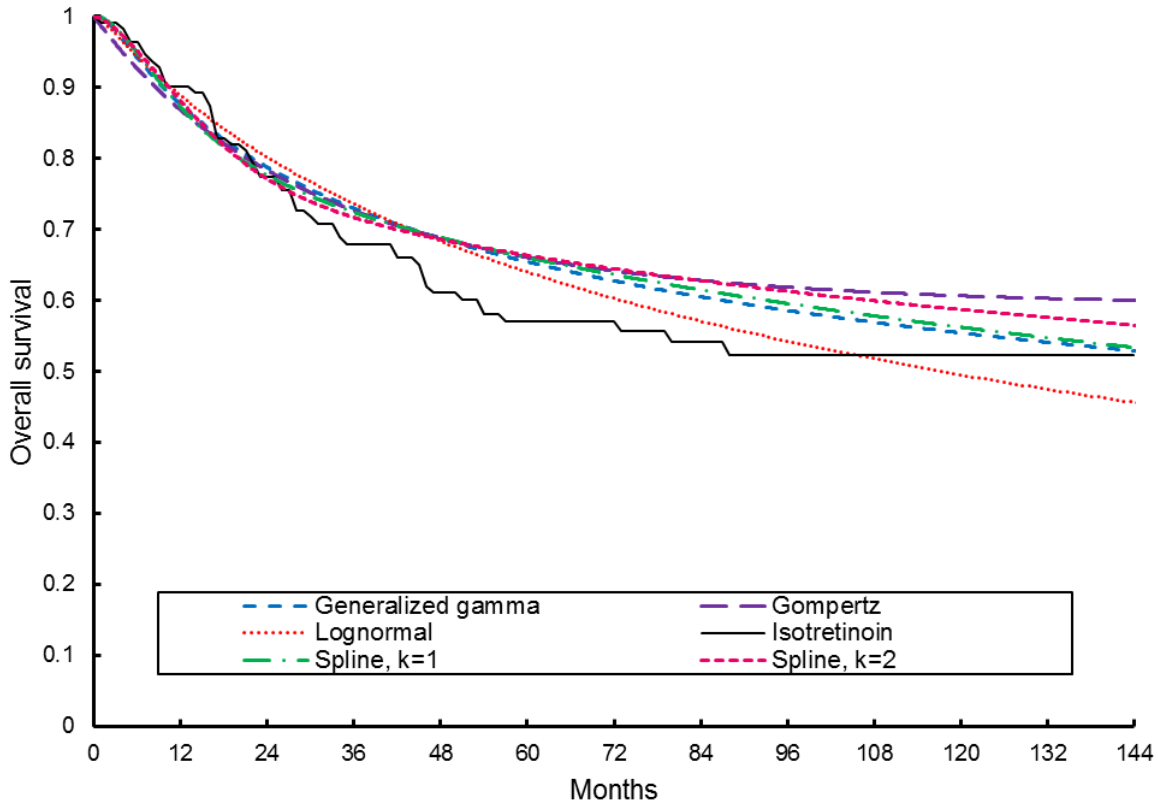
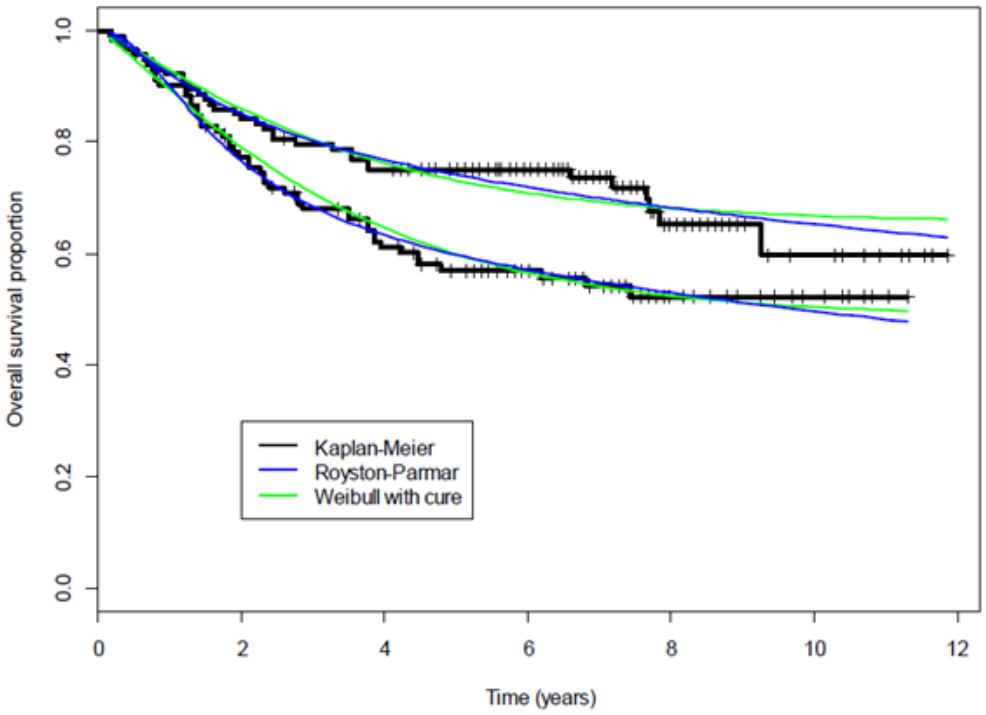


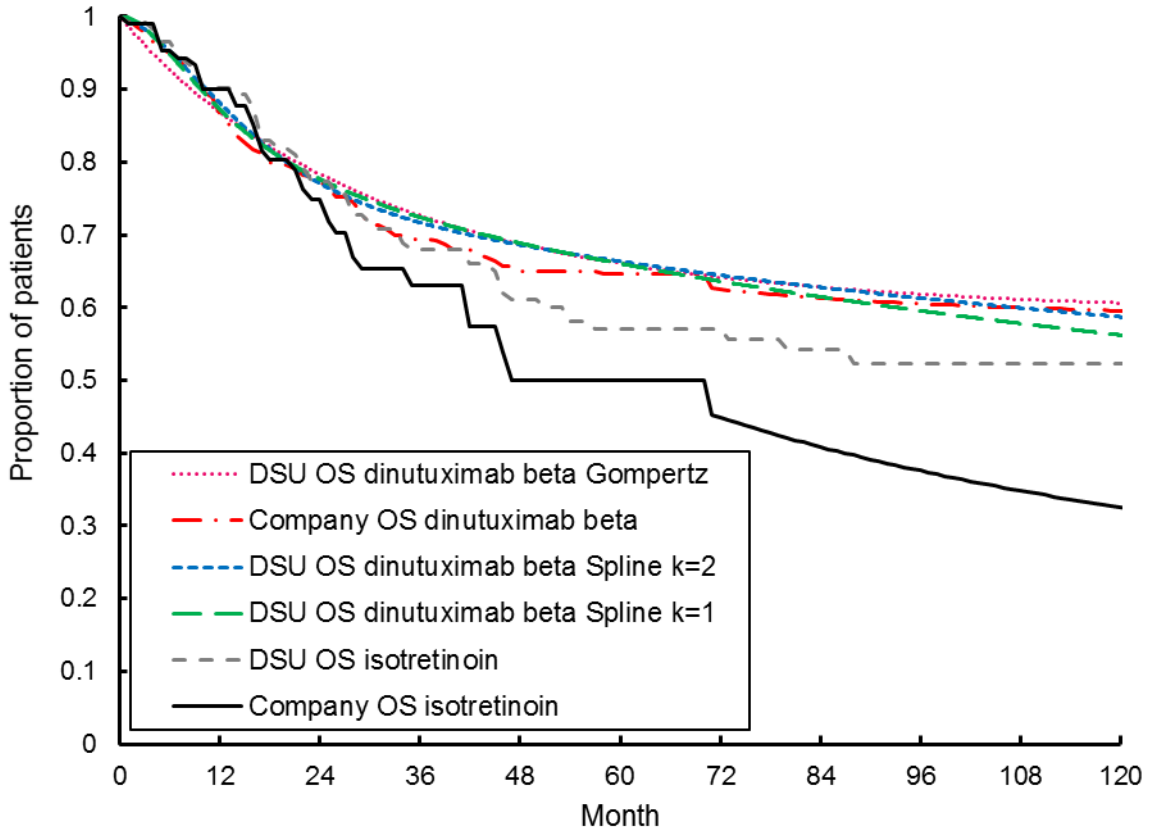
Figure 7: Overall survival for dinutuximab alpha and isotretinoin (reproduced from ERG report)



ERG: evidence review group. Royston-Parmar = spline models.

Figure 8 compares the overall survival for dinutuximab beta and isotretinoin in the company's revised model and DSU's analyses. The DSU's Gompertz lies slightly above the company's OS data, and the two spline models lie slightly below. Using the DSU's Gompertz distribution for dinutuximab beta OS (in combination with other changes including using Yu et al. (2014)[2] KM data for isotretinoin) decreases the ICER from £79,811 (Table 6) to £72,839 (Table 8). Using the DSU's spline model with k=1 and scale=hazards model for dinutuximab beta OS instead (in combination with other changes including using Yu et al. (2014) KM data for isotretinoin) increases the ICER to £101,723 (Table 9). Using the DSU's spline model with k=2 and scale=hazards model for dinutuximab beta OS instead (in combination with other changes including using Yu et al. (2014)[2] KM data for isotretinoin) increases the ICER to £83,131 (Table 10).

Figure 8: Comparison of company and DSU overall survival data



DSU: decision support unit, OS: overall survival

Table 8: ICER with corrected topotecan wastage, longer-term isotretinoin data and DSU Gompertz overall survival dinutuximab beta

	Total		Incremental		ICER
	Cost	**QALYs**	**Cost**	**QALYs**	
Isotretinoin	£60,459	16.45			
Dinutuximab beta	£226,915	18.74	£166,455	2.29	£72,839

ICER: incremental cost-effectiveness ratio, QALY: quality adjusted life years

Table 9: ICER with corrected topotecan wastage, longer-term isotretinoin data and DSU spline k=1, scale=hazards overall survival dinutuximab beta

	Total		Incremental		ICER
	Cost	**QALYs**	**Cost**	**QALYs**	
Isotretinoin	£60,459	16.45			
Dinutuximab beta	£227,030	18.09	£166,571	1.64	£101,723

ICER: incremental cost-effectiveness ratio, QALY: quality adjusted life years

Table 10: ICER with corrected topotecan wastage, longer-term isotretinoin data and DSU spline k=2, scale=hazards overall survival dinutuximab beta

	Total		Incremental		ICER
	Cost	**QALYs**	**Cost**	**QALYs**	
Isotretinoin	£60,459	16.45			
Dinutuximab beta	£227,736	18.46	£167,277	2.01	£83,131

ICER: incremental cost-effectiveness ratio, QALY: quality adjusted life years

3.12.4.2. Event-free Survival

The parametric and spline models for EFS are shown in Figure 9 (parametric models at the top, spline models beneath). Of the parametric models, the Gompertz model is the most favourable to dinutuximab as it is the highest curve, followed by the Generalised gamma, log normal, log logistic, Weibull and gamma model. The exponential model is the least favourable, as it is the lowest curve. Many of the spline models are very close together.

The AIC and BIC (Table 11) indicate that the best fitting models are the Generalised gamma and spline models. Clinical experts advised the DSU that the rate at which people fail treatment is not constant over time. Specifically, most people who relapse do so in the first 1-3 years, and then the rate of relapse decreases and relapse after 5 years is rare. Therefore, we would expect that the most appropriate model has a steep decline in the first few years, and a more gradual decline (but not completely flat) for years 5-10. The spline models fit this description and are the best-fitting according to AIC and BIC. Validation against longer-term data from dinutuximab alpha (Figure 10) indicates that this shape is likely to be appropriate, and we note that the ERG in that appraisal considered the spline model to be a good fit. The

DSU considers that a spline models appear to be most plausible, and consider the spline model with k=1 and scale=odds, as it has the lowest AIC and BIC. The DSU considers the Generalised gamma as a scenario analysis.

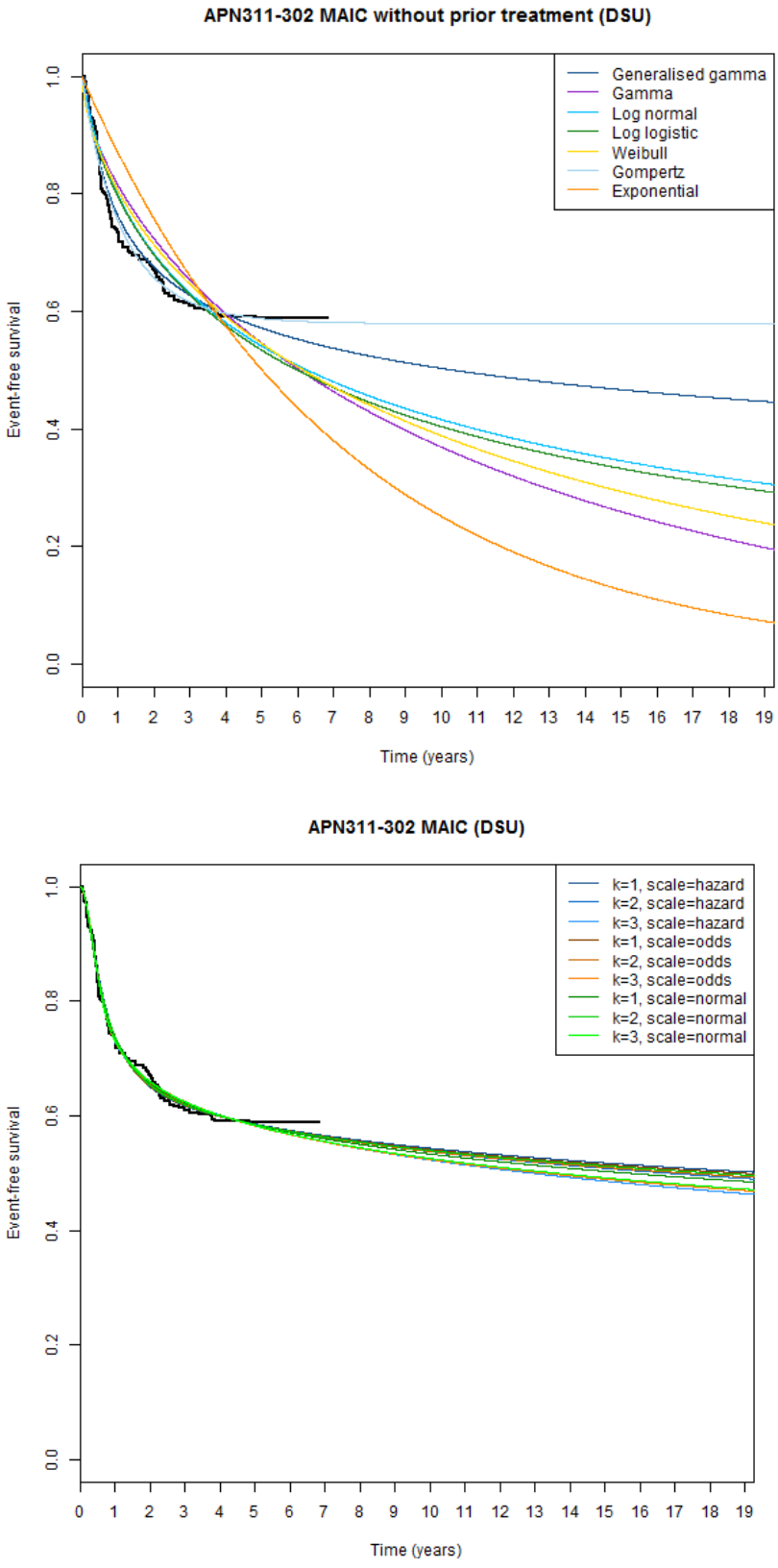
Table 11: Summary of goodness-of-fit of event-free survival

Model	**APN311-302 MAIC (DSU)**	
	AIC	**BIC**
Generalised gamma	**1649.50**	1660.99
Gamma	1697.14	1704.80
Log normal	1672.95	1680.62
Log logistic	1683.33	1690.99
Weibull	1692.32	1699.98
Gompertz	1655.62	1663.28
Exponential	1717.88	1721.71
k=1, scale=hazard	**1644.33**	**1655.83**
k=2, scale=hazard	**1646.02**	1661.35
k=3, scale=hazard	**1646.08**	1665.24
k=1, scale=odds	**1644.01**	**1655.50**
k=2, scale=odds	**1646.04**	1661.37
k=3, scale=odds	**1645.98**	1665.14
k=1, scale=normal	**1644.25**	**1655.74**
k=2, scale=normal	**1646.10**	1661.43
k=3, scale=normal	**1645.51**	1664.67

AIC: Akaike information criterion, BIC: Bayesian information criterion, DSU: decision support unit, MAIC: matching-adjusted indirect comparison

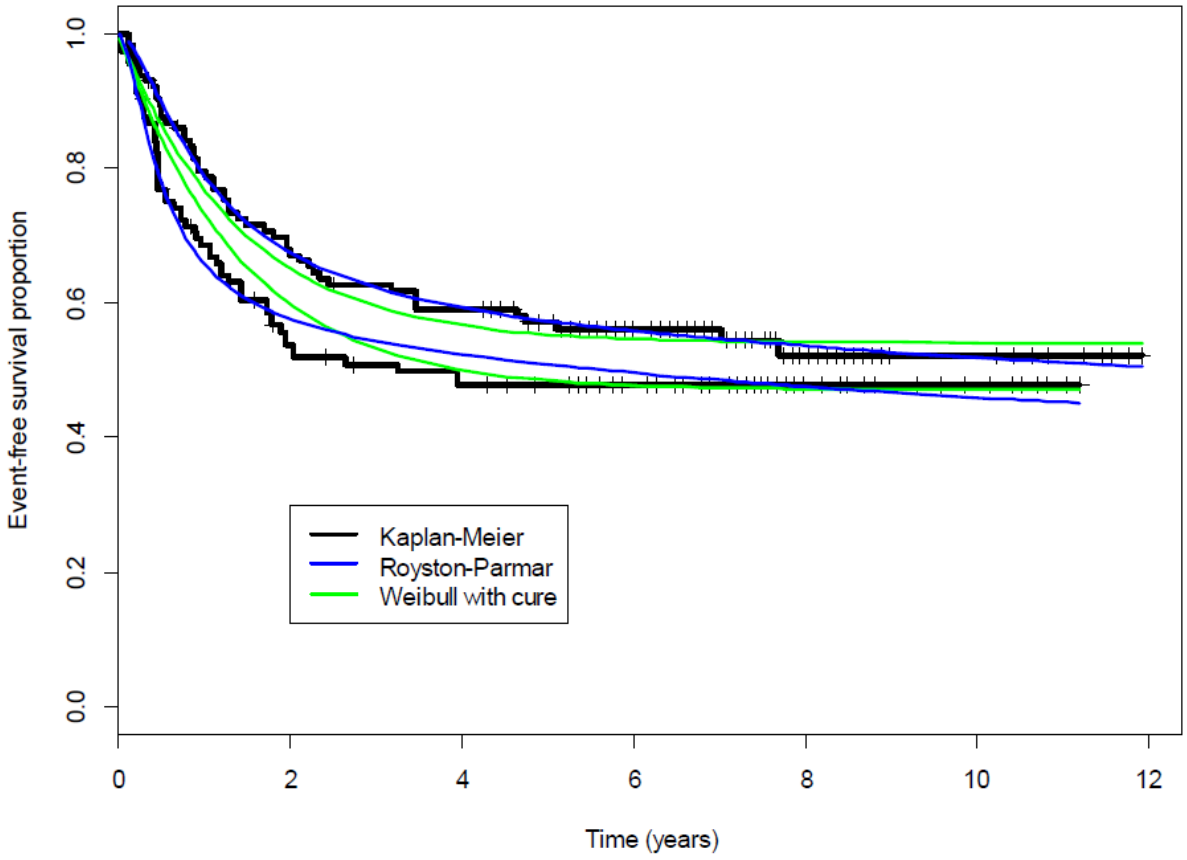
Bold: best fitting models determined using 5 points rule and visual inspection.

Figure 9: Event-free survival Kaplan-Meier curve vs. fitted models



DSU: decision support unit, MAIC: matching-adjusted indirect comparison

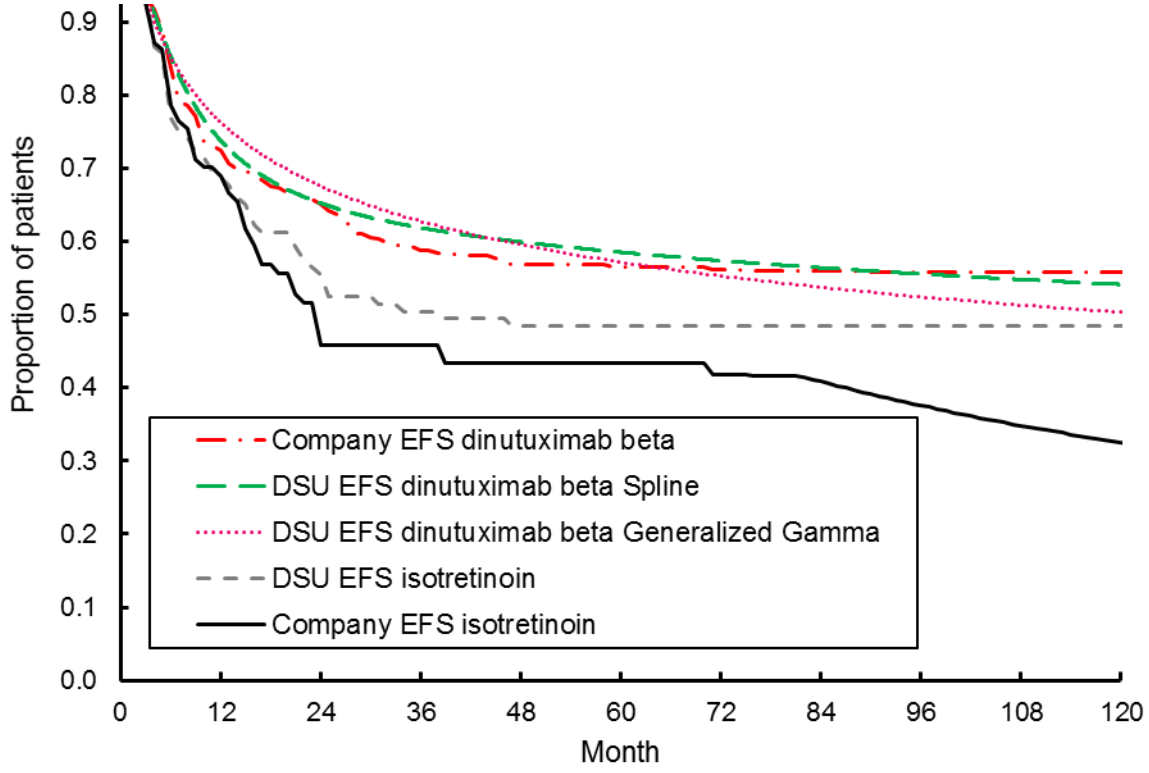
Figure 10: Event-free survival for dinutuximab alpha and isotretinoin (reproduced from ERG report)



ERG: evidence review group

Figure 11 compares the event-free survival for dinutuximab beta and isotretinion in the company's revised model and DSU's analyses. The DSU's spline lies slightly above the company's EFS curve until month 84, and then crosses the company's curve. The Generalised Gamma lies above the company's data until month 40, and then crosses it, and converges with the isotretinoin data at month 120. Results when the DSU's EFS data is used in combination with the DSU's other changes (corrected topotecan wastage, longer-term isotretinoin data, and the DSU's 3 different models for OS) are presented in Section 3.13.

Figure 11: Comparison of company and DSU event-free survival data



DSU: decision support unit, EFS: event-free survival

3.13. RESULTS FROM THE DSU'S REVISED ECONOMIC MODEL

3.13.1. Deterministic results

The DSU's revised model includes the adjustment for wastage of topotecan, incorporates the longer-term KM data for isotretinoin, incorporates uncertainty associated with the isotretinoin KM data and the curves fitted to the dinutuximab beta data, and uses the results from the DSU's revised MAIC and survival curve extrapolation for dinutuximab beta. All other settings are as in the company's revised model.

The results of the DSU's revised model using the spline model with k=1, scale=odds for EFS are presented in Table 12, using the cure point of 10 years. The DSU considers that these results present the most likely range of ICERs for the cost-effectiveness for dinutuximab beta versus isotretinoin. The results use the same model settings as those in Table 8, Table 9, Table 10 except that they use the DSU's spline model with k=1, scale=odds for EFS. The

ICER is lowest with the Gompertz because it has the highest probability of overall survival for dinutuximab beta over the 10 years.

Table 12: DSU results: EFS spline k=1, scale=odds

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: spline k=1, scale=odds							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£224,234	18.61	35.99	£163,775	2.16	4.40	£75,831
OS: spline k=1, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£224,192	17.96	34.07	£163,733	1.51	2.49	£108,301
OS: spline k=2, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£224,898	18.34	35.17	£164,439	1.89	3.59	£87,164

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years
*****LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.

Results using the Generalised Gamma are presented in Table 13. The results use the same model settings as those in Table 12 except they use the DSU's Generalised Gamma model for EFS. The DSU considers that these ICERs are less realistic than those in Table 13 and these are presented as a scenario analysis. These ICERs are higher than those in Table 12 because the Generalised Gamma has lower probabilities of EFS than the spline model beyond month 40.

Table 13: DSU results: EFS Generalised gamma

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: Generalised gamma							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£220,255	18.24	35.71	£159,796	1.79	4.13	£89,351
OS: spline k=1, scale=hazards. EFS: Generalised gamma							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£220,213	17.59	33.80	£159,754	1.14	2.22	£140,073
OS: spline k=2, scale=hazards. EFS: Generalised gamma							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£220,919	17.97	34.90	£160,460	1.52	3.32	£105,899

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years
*****LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.

3.13.2. Probabilistic results

Probabilistic results for 10,000 simulations are summarised for OS using the Gompertz and spline with k=1, scale=hazards, and EFS using the spline with k=1, scale=odds and Generalised gamma in Table 14.

Table 14: Probabilistic results

	EFS: spline k=1, scale=odds		EFS: Generalised gamma	
	OS: Gompertz	**OS: spline k=1, scale=hazards**	**OS: Gompertz**	**OS: spline k=1, scale=hazards**
Deterministic ICER	£75,831	£108,301	£89,351	£140,073
Probabilistic mean ICER	£79,493	£121,563	£95,903	£158,708
Probability cost-effective at £20,000/QALY	1%	2%	1%	3%
Probability cost-effective at £30,000/QALY	1%	2%	1%	3%
Probability cost-effective at £50,000/QALY	3%	3%	3%	3%
Probability cost-effective at £100,000/QALY	7%	6%	6%	6%

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, OS: overall survival, QALY: quality adjusted life years

3.13.3. Scenario analysis varying the cure point

Results varying the cure point between 5 and 9 years are summarised for scenarios with OS using the Gompertz and spline with k=1, and EFS using the spline and Generalised Gamma in Table 15. The ICERs generally decrease when a lower cure point is used, as the economic model is then extrapolating data from where the difference between the effectiveness of dinutuximab beta and isotretinoin is greater.

Table 15: Scenario analysis varying the cure point

		Cure point (years)				
		5	**6**	**7**	**8**	**9**
EFS: spline k=1, scale=odds	***OS: Gompertz***	£60,824	£71,709	£68,100	£66,700	£71,564
	OS: spline k=1, scale=hazards	£61,222	£74,818	£74,701	£77,795	£91,432
EFS: Generalised gamma	***OS: Gompertz***	£62,329	£76,854	£74,553	£74,343	£82,090
	OS: spline k=1, scale=hazards	£62,747	£80,492	£82,715	£88,771	£110,224

EFS: event-free survival, OS: overall survival

3.13.4. Scenario analyses varying the proportion receiving concomitant IL-2

Scenario analyses varying the proportion of patients receiving concomitant IL-2 are presented in Table 16. The company conducted scenario analyses using the same assumptions, and similarly found these increased the ICERs. We note that clinical experts advised that patients would not receive concomitant IL-2 in clinical practice. Increasing the proportion of patients receiving concomitant IL-2 increases the ICERs as the cost of dinutuximab increases.

Table 16: Scenario analyses varying concomitant IL-2 usage

		Proportion receiving concomitant IL-2	
		41%	**51%**
EFS: spline k=1, scale=odds	***OS: Gompertz***	£86,215	£88,858
	OS: spline k=1, scale=hazards	£123,135	£126,911
EFS: Generalised gamma	***OS: Gompertz***	£101,888	£105,079
	OS: spline k=1, scale=hazards	£159,732	£164,735

EFS: event-free survival, OS: overall survival

3.13.5. Scenario analyses varying the duration of chemotherapy

Scenario analyses varying the duration of chemotherapy following failure are presented in Table 17. The company used a duration of one year, which experts advised the DSU seemed reasonable, but noted that some patients may receive multiple lines of chemotherapy.

Increasing the duration of chemotherapy decreases the ICERs as fewer patients on dinutuximab beta fail than on isotretinoin and so the incremental costs decrease when the cost of failing increases.

Table 17: Scenario analyses varying the duration of chemotherapy

		Duration of chemotherapy	
		2 years	**3 years**
EFS: spline k=1, scale=odds	***OS: Gompertz***	£69,657	£61,330
	OS: spline k=1, scale=hazards	£99,162	£86,806
EFS: Generalised gamma	***OS: Gompertz***	£80,554	£68,720
	OS: spline k=1, scale=hazards	£125,855	£106,689

EFS: event-free survival, OS: overall survival

4. CONCLUSIONS

The company has correctly implemented many of the changes requested by the Committee, and the DSU has made minor corrections to others. However, the DSU has identified errors in the company's MAIC, and considered that the company's extrapolation of overall and event-free survival is not appropriate.

The DSU has conducted an MAIC correcting the errors, used the longer-term KM data for isotretinoin and undertaken new survival analysis to extrapolate dinutuximab beta data beyond the trial period. Using a 10-year cure point, the ICERs in the DSU's analysis generally lie in the range of £76,000 - £108,000/QALY, unless pessimistic assumptions are made about the overall survival modelling, in which case the range increases to £89,000 – £140,000/QALY. Considering a shorter cure point, the ICERs decrease to a range of £61,000 - £91,000/QALY, or £62,000 - £131,000/QALY using pessimistic assumptions about overall survival modelling.

5. REFERENCES

1. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med* 2010; **363**(14): 1324-34.
2. Saramango P SM, Biswas M, Wright K, Woolacott N, Rothery C. Dinutuximab for treating high-risk neuroblastoma: A Single Technology Appraisal.: CRD and CHE Technology Assessment Group., 2015.
3. NJ. PDAADSPSAKW. NICE DSU TSD 18: Methods for population-adjusted indirect comparisons in submissions to NICE. . 2016 2016. http://nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf (accessed 26 March 2018).
4. Ladenstein R, Pötschger U, Pearson ADJ, et al. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. *The Lancet Oncology* 2017; **18**(4): 500-14.
5. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010; **13**(5): 509-18.
6. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 2002; **21**(15): 2175-97.
7. NJ GPAAOMW. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Medical Research Methodology* 2012; **12**(9): 1-13.
8. Latimer N. NICE DSU TSD 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013. http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf (accessed March 22 2018).
9. Jackson C. flexsurv: A Platform for Parametric Survival Modeling inR. *Journal of Statistical Software* 2016; **70**(8).

6. APPENDIX – CHANGES TO THE ECONOMIC MODEL

This appendix describes the changes that the DSU has made in the economic model. The changes refer to the model "20180326 dinutuximab DSU model".

6.1. ADJUSTMENT FOR COST OF TOPOTECAN

The DSU has added column AD to the LifetimeFL sheet to use the corrected costs. This column is then used instead of column AC in column AH. Similarly, the DSU has added column K to the 5y10yFL sheet, which is then used in column O.

6.2. ADDITION OF NEW DATA

The DSU has added dropdowns to the Results sheet to select whether the DSU or company data are used for isotretinoin ('select_data_iso'), dinutuximab OS ('select_data_OS') and dinutuximab EFS ('select_data_EFS'). These feed into columns T, AA, AF and AM in the sheet 5y10yFL.

6.2.1. Isotretinoin data

The company has added the isotretinoin 2014 data to the sheet Iso_IPD. This is then used in the sheet 'NewSurvival' columns E and F. The sheet Iso_IPD contains deterministic and probabilistic data for isotretinoin IPD.

6.2.2. DSU MAIC

The DSU has fitted parametric and spline models to their MAIC in the sheet NewSurvival. Survival probabilities for the different models are provided and selected in columns B and C depending on the options selected using the dropdown menus 'maic_select_os', 'maic_select_efs', 'adj_efs_select' and 'adj_os_select'.

6.3. CHANGES TO THE PROBABILISTIC SENSITIVITY ANALYSIS

The DSU has changed the macro PSA to run more quickly and to incorporate the additional parameters.

The DSU has added rows 88 to 97 to model the distribution of patients amongst the BSA categories.

The sheets PSA_EFS_spline, PSA_OS_spline and PSA_EFS_GenGam contain 10,000 sampled monthly survival probabilities outputted from R. In the PSA, columns from the appropriate sheet are randomly sampled in the columns B and C in the sheet NewSurvival. If

the Gompertz is selected for EFS, the survival probabilities are randomly sampled from the multinormal distribution using the parameters in the sheet PSA_OS_Gompertz.
The sheet prob_det compares mean probabilistic and deterministic survival probabilities and is not used in model calculations.