NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

Pre-meeting briefing

Preview: Clinical effectiveness and treatment pathway issues

- CheckMate 238 compared nivolumab with ipilimumab, which is not used in the adjuvant setting. Recurrence free survival data is limited to 24 months follow up, overall survival data is very immature. What conclusions can be drawn about relapse free survival and the effect on overall survival?
- A key uncertainty is whether treatment with nivolumab mainly postpones disease recurrence or permanently cures the disease. What is the committee's view on this?
- To assess the effect of adjuvant nivolumab vs routine surveillance an indirect comparison was made using another trial CA184-029 (ipilimumab vs placebo). How reliable are the results for RFS compared with routine surveillance given the trial differences?
- Are the indirect comparison RFS results generalisable to the NHS given the change in classification of stages of melanoma since the trials?
- OS data are available from 029, what is the committee's view of these?

Advanced fully resected melanoma

- Cancer Research UK statistics from 2015 indicate melanoma is now 5th most common cancer in the UK
  - rates increased steadily since 1990s
  - incidence up by 45% in last decade
- Disease stage describes how deeply the tumour has grown into the skin, and whether it has spread.
  - Stage I and II: no evidence that melanoma cells have spread anywhere else in body (possibility of microscopic spread)
  - Stage III: melanoma cells have spread into skin, lymph vessels, or nearby lymph glands
  - Stage IV: melanoma cells have spread to other distant parts of the body
- In England, the majority of melanoma patients are diagnosed early (Stage I or II); ~ 8% (total N=1,100) patients diagnosed at Stage III or IV disease
- No UK-wide statistics available for melanoma survival by stage; data from former Anglia Cancer Network for men and women diagnosed between 2002-2006 indicates five-year survival approximately 50-55% for stage III disease and 8-24% for stage IV disease
- People who have had surgery to remove stage III or IV tumours are at high risk of relapse and death; for example, 5-year relapse-free survival is 28-44% for stage III melanoma

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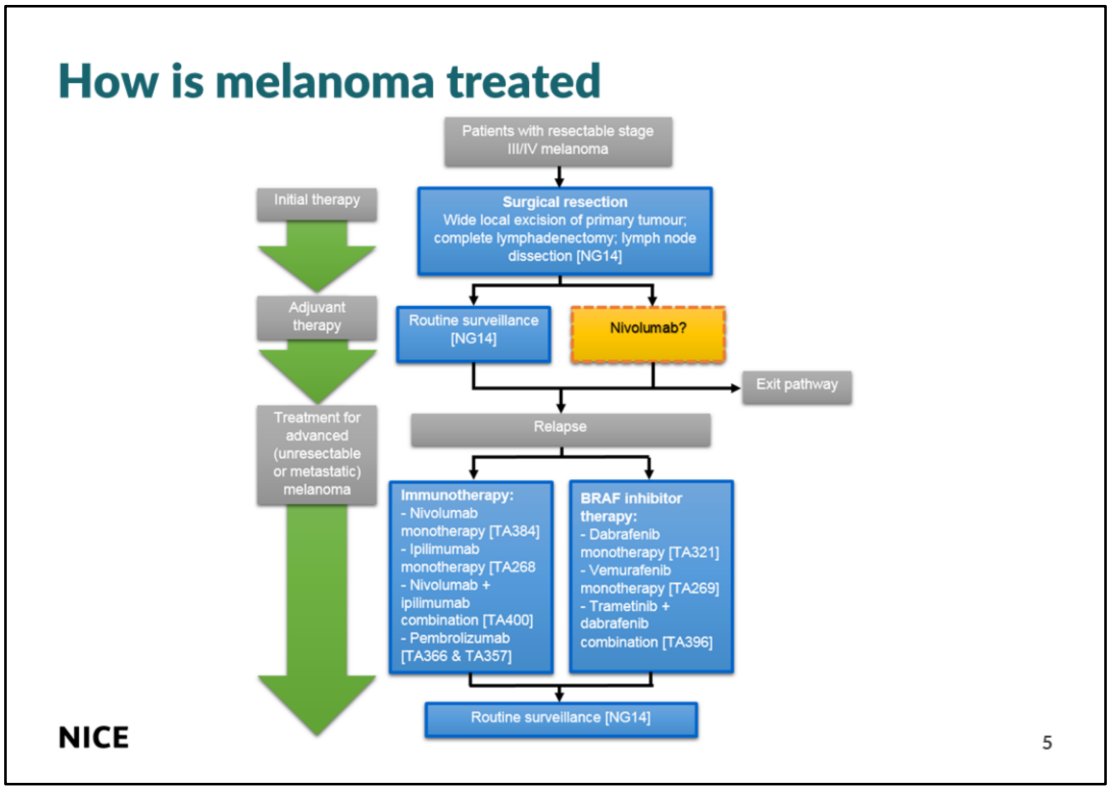
Source: NICE scope; Company submission: section B.1.3, pp10-13; Cancer research UK

Nivolumab

Mechanism of action	Nivolumab is a human immunoglobulin G4 monoclonal antibody that works by influencing how T-cells (a type of white blood cell) moderate the immune system's response to the cancer cells. Specifically, Nivolumab binds to PD-1 (a protein found on the surface of T-cells) blocking it from binding with its ligands PD-L1 and PD-L2 (proteins expressed on the surface of tumour cells or other cells in the tumour microenvironment). By interrupting this interaction nivolumab helps the body to recognise and destroy micrometastases or individual tumour cells
Anticipated marketing authorisation	As monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
Administration	Intravenous infusion
Dose	3mg/kg administered over 60 minutes every 2 weeks; maximum treatment duration 12 months
Cost (list price)	£439.00 per 4ml vial; £1,097.00 per 10ml vial. Average cost of a course of treatment £53,771
Patient access scheme	A patient access scheme has been approved and comprises a discount of [redacted] from the nivolumab list price Applying this PAS to the list price, the cost per nivolumab dose is [redacted] with an average cost per course of treatment of [redacted]

Source: Company submission: section B.1.2, table 2, pp9-10



Source: Company submission: section B.1.3, figure 1, p14; Melanoma NICE pathway; NICE guidelines NG14, TA384, TA268, TA400, TA366 & TA357

Routine surveillance [NICE guideline NG14]

All people who have had melanoma

Perform a full examination of the skin and regional lymph nodes at all follow-up appointments.

Consider personalised follow-up for people who are at increased risk of further primary melanomas (for example people with atypical mole syndrome, previous melanoma, or a history of melanoma in first-degree relatives or other relevant familial cancer syndromes).

Consider including the brain for people having imaging as part of follow-up after treatment for melanoma.

Consider imaging the brain if metastatic disease outside the central nervous system is suspected.

Consider CT rather than MRI of the brain for adults having imaging as part of follow-up or if metastatic disease is suspected.

Consider MRI rather than CT of the brain for children and young people (from birth to 24 years) having imaging as part of follow-up

or if metastatic disease is suspected.

Provide psychosocial support for the person with melanoma and their family or carers at all follow-up appointments.

All local follow-up policies should include reinforcing advice about self-examination, and health promotion for people with melanoma and their families, including sun awareness, avoiding vitamin D depletion, see sunlight exposure and vitamin D levels, and NICE's recommendations on stop smoking interventions and services.

Continue to manage drug treatment for other conditions in line with the recommendations on drug treatment for other conditions after treatment for melanoma.

Stage IIC melanoma with no sentinel lymph node biopsy or stage III melanoma

For people who have had stage IIC melanoma with no sentinel lymph node biopsy, or stage III melanoma, consider follow-up every 3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, and discharging them at the end of 5 years.

Consider surveillance imaging as part of follow-up for people who have had stage IIC melanoma with no sentinel lymph node biopsy or stage III melanoma and who would become eligible for systemic therapy as a result of early detection of metastatic disease if:

there is a clinical trial of the value of regular imaging **or**

the specialist skin cancer multidisciplinary team agrees to a local policy and specific funding for imaging 6-monthly for 3 years is identified.

Take into account the possible advantages and disadvantages of surveillance imaging and discuss these with the person.

Stage IV melanoma

Offer personalised follow-up to people who have had stage IV melanoma.

Ipilimumab

Previously treated advanced melanoma [NICE TA268]

Ipilimumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.

Nivolumab

Advanced melanoma [NICE TA384]

Nivolumab as monotherapy is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or

metastatic) melanoma in adults.

Nivolumab with ipilimumab

Advanced melanoma [NICE TA400]

Nivolumab in combination with ipilimumab is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults, only when the company provides ipilimumab with the discount agreed in the patient access scheme.

Pembrolizumab

Advanced melanoma not previously treated with ipilimumab [NICE TA366]

Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults, only when the company provides pembrolizumab in line with the commercial access agreement with NHS England.

Advanced melanoma after disease progression with ipilimumab [NICE TA357]

Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only:

- after the disease has progressed with ipilimumab and, for BRAF V600mutation-positive disease, a BRAF or MEK inhibitor and
- when the company provides pembrolizumab in line with the commercial access agreement with NHS England.

Decision problem – NICE vs. company

- Company's decision problem was in line with the NICE scope with the exception of the population
- Company explained difference in wording:
  - was to reflect the anticipated license
  - patients with Stage III and IV disease have involvement of lymph nodes or metastatic disease and therefore would be eligible for adjuvant nivolumab treatment
  - a patient population defined by lymph node involvement and metastatic disease accurately reflects the patient population of the pivotal trial (CheckMate 238)

NICE DP population	Company DP population
People with completely resected Stage III or IV melanoma	Adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection

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Source: Company submission: section B.1.1, table 1

Clinical effectiveness evidence

- Company submission, section B2

What evidence is available?

- Company conducted SLR to identify evidence relevant to decision problem
- **No head-to-head trials found for comparison of interest** (adjuvant nivolumab versus routine surveillance)
- In absence of direct evidence, indirect evidence was considered
- Two randomised controlled trials were identified; one provided evidence on adjuvant nivolumab and the other provided evidence for routine surveillance (placebo) in same setting.
- Comparator in both cases was **ipilumumab** (another biological therapy **not used in the adjuvant setting in clinical practice**) :
  - **Checkmate 238: Nivolumab vs. ipilimumab (Weber 2017)**
  - **CA184-029: Ipilimumab vs. placebo (Eggermont 2016)**
- Two trials were combined to provide indirect evidence for the effectiveness of nivolumab vs. routine surveillance

ERG comments on company SLR/included studies: searches adequate (although foreign language publications omitted); study inclusion and data extraction robust and in line with standard methods; Checkmate 238 trial of high methodological quality (no comment made on quality of CA184-092)

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Source: Company submission: appendix D, figure 2, p17

Checkmate 238 (nivolumab vs. ipilimumab; Weber 2017)

Design	Multinational, randomised, double-blind, Phase III trial (8 UK sites)
Population	N=906 patients (≥15 years of age) undergoing complete resection of stage IIIB, IIIC, or IV melanoma
Intervention	Nivolumab (IV, 3 mg per kilogram of body weight every 2 weeks for up to 1 year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent) (n=453)
Comparator	Ipilimumab (IV, 10 mg per kilogram every 3 weeks for four doses and then every 12 weeks for same duration as nivolumab) (n=453 patients)
Primary outcomes	Recurrence-free survival (RFS)
Secondary outcomes	Overall survival (OS); adverse events; recurrence-free survival according to tumor PD-L1 expression; health-related quality of life (HRQoL). Distant metastasis–free survival (DMFS) was an exploratory end point
Follow-up	Primary analysis 18 months (EMA requested analysis 24 months)
Stratification groups	Disease stage (stage IIIB or IIIC, stage IV M1a or M1b, or stage IV M1c); PD-L1 status (negative or intermediate vs. positive at 5% cutoff with PD-L1 staining only of tumor cells)

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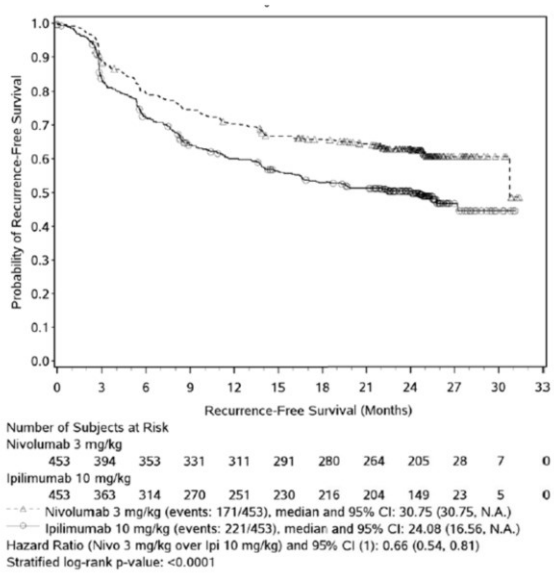
Source: company submission section B.2.3, table 3, p17; Weber 2017 (ref 4 in company submission)

Checkmate 238 (nivolumab vs. ipilimumab): RFS results

Intention-to-treat (ITT) 24-month follow-up (Data-cut: 19 December 2017)



Results of the pre-specified subgroup analyses were mostly consistent with the primary analysis.

Point estimates for following subgroups ≥1:

- mucosal melanoma
- stage IV M1c
- ulceration present plus microscopic lymph node involvement

Results for these groups all had wide CIs that encompassed 1.0

Point estimates for all other subgroups favoured nivolumab but not all results were statistically significant

P values for interaction NR in company submission

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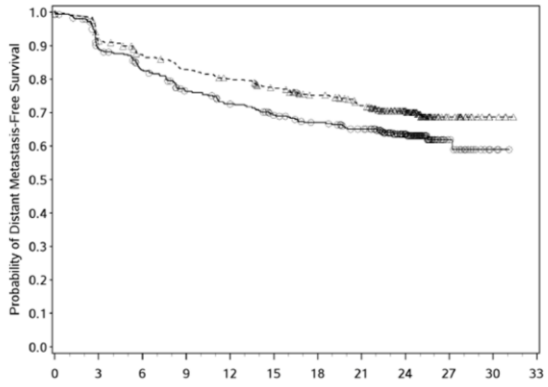
Source: Company submission, section B.2.6, figure 4, p28

Checkmate 238 (nivolumab vs. ipilimumab): DMFS results

ITT 24-month follow-up (Data-cut: 19 December 2017)



Number of Subjects at Risk

Nivolumab 3 mg/kg	370	334	312	295	283	269	249	231	175	24	4	0
Ipilimumab 10 mg/kg	366	313	286	254	239	223	210	197	141	22	3	0

Nivolumab 3 mg/kg (events: 107/370), median and 95% CI: N.A.

Ipilimumab 10 mg/kg (events: 126/366), median and 95% CI: N.A.

Hazard Ratio (Nivo 3 mg/kg over Ipi 10 mg/kg) and 95% CI (1): 0.76 (0.59, 0.98)

Stratified log-rank p-value: 0.0340

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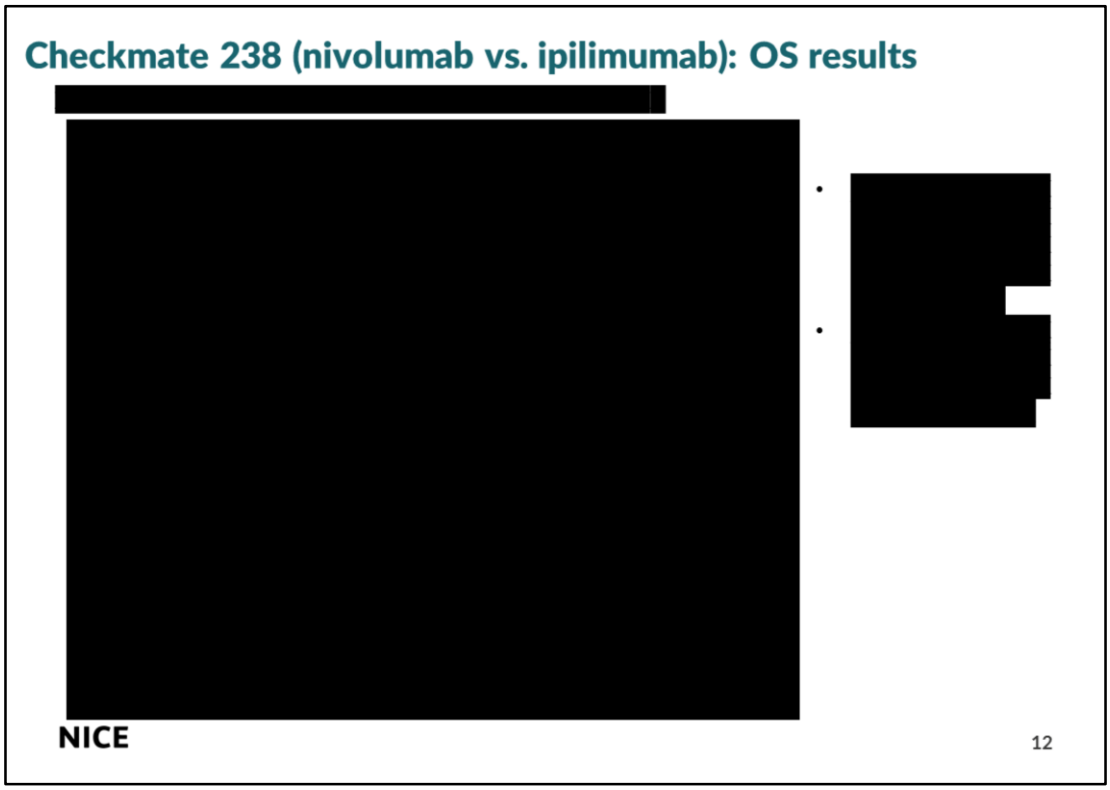
Source: company submission section B.2.6, figure 11, pp34-35



Source: company submission section B.2.9, p43; company response to clarification question A2

Checkmate 238 (nivolumab vs. ipilimumab): HRQoL results

ITT 18-month follow-up (Data-cut: 15 May 2017)

- HRQoL measured in the trial using various tools including EQ5D. Questionnaire completion rates reported in company submission but actual HRQoL scores are not reported
- Results are summarised narratively by company as follows:

  'HRQoL scores were maintained after treatment in both groups….. mean summary scale scores for all patients were comparable between treatment groups at baseline; no clinically meaningful deterioration or improvement was observed at any time point for either treatment group for any scale'

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Source: company submission, section B.2.6, pp36-37

Checkmate 238 (nivolumab vs. ipilimumab): Adverse events (AEs)

Safety population 18-month follow-up (Data-cut: 15 May 2017)

	Nivolumab (n=452)	Ipilimumab (n=453)
Any AE, n (%)	438 (96.9)	446 (98.5)
Grade 3–4	115 (25.4)	250 (55.2)
Any SAE, n (%)	79 (17.5)	183 (40.4)
Grade 3–4	[redacted]	[redacted]
Drug-related SAE, n (%)	[redacted]	[redacted]
Grade 3–4	[redacted]	[redacted]
Discontinuations due to drug-related AEs, n (%)	35 (7.7)	189 (41.7)
Grade 3–4	16 (3.5)	136 (30.0)
Treatment-related deaths, n (%)	0 (0)	2 (0.4)

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Source: Company submission section B.2.10, table 18, p82

Checkmate 238 (nivolumab vs. ipilimumab): ERG critique – RFS, DMFS & OS

- **RFS** Although median RFS has been reached, the data are still immature, with heavy censoring in the KM curve
  - Several of the subgroups failed to demonstrate a statistically significant benefit of nivolumab over ipilimumab in terms of RFS but small patient numbers and event rates in many of the subgroups and trial not powered to detect statistically significant differences in treatment effects
  - Key assumption in the company's base case model is that nivolumab is equally effective across all disease stages. Stage subgroup results show
    - Consistent trend favouring nivolumab using AJCC 7th edition staging across Stage IIIB, IIIC, and IV M1a and M1b subgroups but results only statistically significant in the Stage IIIC subgroup
    - Change in AJCC staging definitions means that a subset of the CheckMate 238 patients would be reclassified. RFS results for the n=[redacted] reclassified Stage IIIA patients demonstrated [redacted] between nivolumab and ipilimumab
- OS [redacted]
- **DMFS** Median DMFS [redacted] in either treatment group in latest data set (24 months' follow-up)
  - statistically significant difference between the treatment groups favouring nivolumab
  - DMFS rates were also consistently [redacted] in the nivolumab group than in the ipilimumab group at 12 months, 18 months and 24 months

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Source: ERG report section 4.3.1, p51 and section 4.3.5, pp55-56

Checkmate 238 (nivolumab vs. ipilimumab): ERG critique – HR-QoL and AEs

- ERG concluded there were no significant differences in HRQL with nivolumab compared to ipilimumab in CheckMate 238
- Safety data reported in company submission were from 18-month follow-up (Data-cut: 15 May 2017)
- 24-month CheckMate 238 AE data for immune-relate (any grade) AEs, diarrhoea (Grade ≥2) and any other Grade ≥3 AE included in model - demonstrated [redacted]
- Clinical experts -AE from CheckMate 238 are as expected and that they are consistent with

Trial level safety data relative risks CheckMate 238 - 24-month data (adapted from company clarification response Table 14)

	Immune-related (Any grade)	Diarrhoea (grade ≥2)	Other AEs (grade ≥3)
Nivolumab	[redacted]	[redacted]	[redacted]
Ipilimumab			
RR (95% CI)			

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Source: ERG report, section 4.3.4, p55 and section 4.3.6 pp61-64

CA184-029 (ipilimumab vs. placebo; Eggermont 2016)

Design	Multinational, randomised, double-blind, Phase III trial
Population	N=951 high-risk patients (≥18 years of age) with stage III cutaneous melanoma who had undergone a complete regional lymph node dissection
Intervention	Ipilimumab (IV, 10 mg/kg every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable level of toxic effects occurred) (n=475)
Comparator	Matched placebo (n=476)
Primary outcomes	RFS
Secondary outcomes	OS; DMFS; adverse events; HRQoL
Follow-up	5.3 years (median)
Stratification groups	Disease stage (stage IIIA vs. stage IIIB vs. stage IIIC with one, two, or three positive nodes vs. stage IIIC with four or more positive nodes); geographic region (North America, Europe, or Australia)

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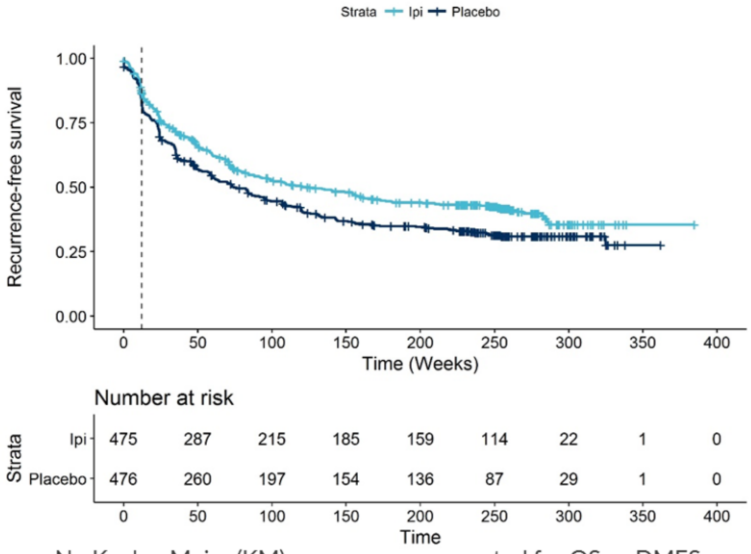
Source: company submission, section B.2.9, p40; Eggermont 2016 (ref 24 in company submission)

CA184-029 (ipilimumab vs. placebo): RFS

ITT population median follow-up of 5.3 years



Key: Ipi, ipilimumab; PBO, placebo.
Notes: Dashed line indicates time of first efficacy assessment (12 weeks).

No Kaplan Meier (KM) curves were presented for OS or DMFS result of CA184-029 trial

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Source: company submission, section B.2.9, figure 25, p59

CA184-029 (ipilimumab vs. placebo): RFS, OS, results

ITT population median follow-up of 5.3 years

	Ipilimumab (n=475)	Placebo (n=476)
RFS		
Events, n (%)	264 (55.6)	323 (67.9)
Median months (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)
5-year RFS rate (95% CI)	40.8 (36.0, 45.6)	30.3 (26.0, 34.6)
HR (95% CI)	0.76 (0.64, 0.89)	
p-value	<0.001	
OS		
Events, n (%)	162 (34.1)	214 (45.0)
Median months (95% CI)	Not reached	Not reached
5-year OS rate (95% CI)	65.4 (60.8, 69.6)	54.4 (49.7, 58.9)
HR (95% CI)	0.72 (0.58, 0.88)	
p-value	0.001	

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Source: Company submission section B.2.9, table 9, p42

CA184-029 (ipilimumab vs. placebo): ERG critique

The ERG did not provide a critique of the overall validity of CA184-029 but commented on aspects of the trial's design, methodology and results that related to the validity if the indirect treatment comparison. These issues are covered in the next section

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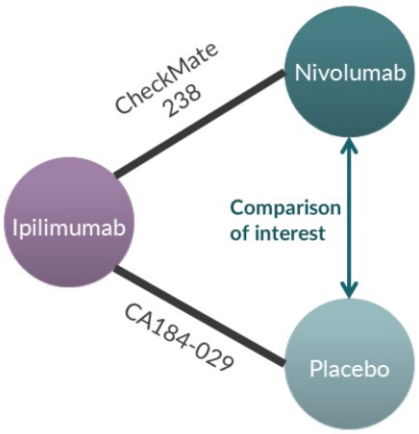
Source: Company submission, section B.2.9, table 10, p44, Appendix D, p20

Indirect treatment comparison (ITC) methods to compare nivolumab with routine surveillance

- Original company submission:
  - ITC only undertaken for RFS
  - Two different methodologies used to predict RFS: (1) individual patient data meta-regression; (2) Bucher method (both methods allow for treatment effect for comparison of interest to be estimated indirectly while preserving randomisation)
  - OS estimates were also required for economic modelling so company estimated these using data from CA182-029 trial and a surrogacy analysis
- [redacted]



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Source: Company submission, section B.2.9, Table 15, p77

ITC methods (cont.)

IPD-meta-regression (only feasible for RFS, results used in all economic analyses)

- Same principle as simple regression: seeks to determine how an outcome variable (treatment effect) is predicted according to a unit change in one or more explanatory variable
- Analysis conducted at the individual patient level – not the study level
  - All data from both trials combined into a single data set, with each person having a treatment indicator and a trial indicator
  - These two variables are used to determine treatment effects and to account for differences across the two trials
- The meta-regression allows for the specification of an underlying survival function (e.g. Weibull) so it isn't restricted to estimating a proportional effect on the event hazard rate
  - No single measure of effect, instead, an effect on each of the parameters of the underlying function
  - Results of the meta-regression are parametric survival curves, based on each of the specified functional forms that have been adjusted for imbalances in key covariates across trials, as well as differences in treatment effects between the two trials

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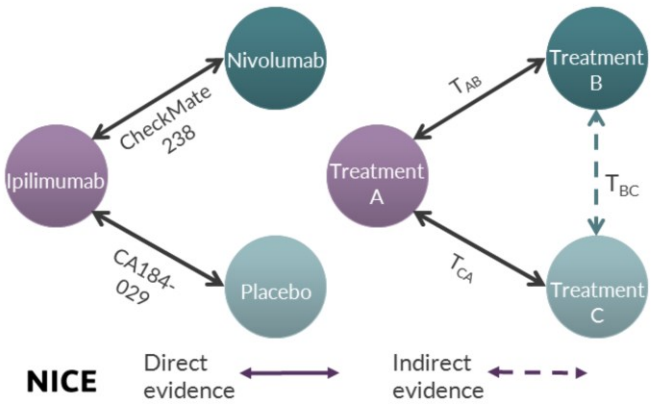
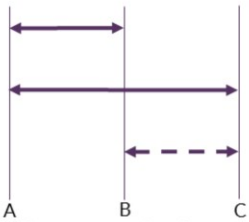
Source: Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [updated March 2011], section 9.6.4 Meta-regression; email correspondence with ERG

ITC methods (cont.)

Bucher method (results not used in any of the economic analyses, provided alternative estimates of treatment effect as 'sensitivity analysis' for main survival models)

- Simple form of anchored ITC
- Conducted when the interventions of interest are compared against a common (anchor) comparator but there is no direct evidence for the comparison of interest (no complete 'loops' in the evidence network [for an network meta-analysis {NMA} you would need both direct and indirect evidence])
- Calculated from summary measures of treatment effect, not IPD
- Hinges on similarity assumption





Similarity assumption in an indirect treatment comparison. AB trials and the AC trials are comparable on effect modifiers, and an unbiased indirect estimate for the relative effect of C versus B can be obtained from the estimates of the effect of B versus A and the effect of C versus A

Source: Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, Lee K, Boersma C, Annemans L, Cappelleri JC. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011 Jun;14(4):417-28

ITC methods (cont.)

Surrogacy analysis for OS

Due to the immaturity of the OS data for CheckMate 238, the company took the following approach to modelling OS up to 10 years:

- For routine surveillance: parametric survival models were fitted to the placebo arm of the CA182-029 trial (generalised gamma curve) and the curve was then adjusted to reflect the population of interest (patients with stage IIIA-IV NED) using the corrected group prognosis (CGP) method
- For nivolumab: surrogacy analysis was conducted

After 10 years OS was informed by AJCC version 8 OS registry data (background mortality using general population data used if extrapolations predict a lower mortality)

How was surrogacy analysis conducted?

1. An equation was used to predict a HR for OS treatment effect for comparison of nivolumab versus ipilimumab based on the observed RFS treatment effect (HR) from Checkmate238
2. predicted OS HR for nivolumab versus ipilimumab was then compared to the observed OS HR for ipilimumab vs placebo from the CA184-029 trial to produce the HR for nivolumab vs placebo
3. HR for nivolumab versus placebo was then applied to the routine surveillance curve estimated from the CA184-029 placebo OS data

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Source: ERG report section 4.4.7.2, pp85-88

Abbreviations: NED, no evidence of disease; HR, hazard ratio

Company identified differences between the trials (1)

Inclusion criteria relating to patients' disease stage

Trial	Eligible patients	Version of AJCC criteria
CheckMate 238	Stage IIIB, IIIC or IV melanoma	7th edition
CA184-029	Stage IIIA, IIIB, IIIC melanoma • patients with stage IIIA melanoma (patients with N1a cancer [i.e., only one node involved with micrometastasis]) had to have at least one metastasis measuring >1 mm in the greatest dimension) • patients with stage IIIB or IIIC melanoma with no in-transit metastases (i.e., growing >2 cm away from the primary tumour but before reaching the nearest lymph node)	6th edition

Permitted duration of ipilimumab treatment

Trial	Max treatment duration	Median no. doses	% patients who received treatment beyond 1 year
CheckMate 238	1 year	4 (range, 1 to 7)	0%
CA184-029	3 years	4 (IQR 3 to 8)	[redacted]

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Source: company submission, section B.2.9, pp79-80; Eggermont 2016; Weber, 2017

Company identified differences between the trials (2)

Primary definition of RFS (the studies have different primary reviewers and have different censoring rules for subsequent therapy)

Trial	Primary endpoint assessment (RFS)	Death	Subsequent therapy
CheckMate 238	Investigator	Event recorded at the time of death	Patient censored at time of last disease assessment prior to receipt of subsequent therapy
CA184-029	Independent	Event recorded at the time of death	Event recorded at time of recurrence or death, regardless of whether a patient received subsequent therapy

Stratification factors at randomization

Trial	Stratification factors at randomization
CheckMate 238	Patients stratified by PD-L1 expression classification
CA184-029	Patients stratified by disease stage (stage IIIA versus IIIB vs. IIIC with 1–3 positive nodes vs. IIIC with ≥4 positive nodes) and regions (North America, European countries and Australia)

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Source: company submission, section B.2.9, pp79-80; Eggermont 2016; Weber, 2017

ITC methods (cont.) Survival modelling

- Long-term RFS and OS estimates were produced for each treatment while controlling for differences within patient characteristics and trials through the use of the covariates and corrected group prognosis (CGP) method
- This calculates a survival curve for each unique combination of covariates with the proportion of patients in each group used to weight the individual survival curves, thus creating a weighted average curve for the entire population
- Does not account for all differences between the trials e.g. does not adjust for differences in RFS definition or duration of ipilimumab treatment across trials

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No.	Group
1	Trial = 238, Stage= IIIb, Sex= M, Age category = < 65
2	Trial = 238, Stage= IIIb, Sex= M, Age category = ≥ 65
3	Trial = 238, Stage= IIIb, Sex= F, Age category = < 65
4	Trial = 238, Stage= IIIb, Sex= F, Age category = ≥ 65
5	Trial = 238, Stage= IIIa, Sex= M, Age category = < 65
6	Trial = 238, Stage= IIIa, Sex= M, Age category = ≥ 65
7	Trial = 238, Stage= IIIa, Sex= F, Age category = < 65
8	Trial = 238, Stage= IIIa, Sex= F, Age category = ≥ 65
9	Trial = 238, Stage= IIIc, Sex= M, Age category = < 65
10	Trial = 238, Stage= IIIc, Sex= M, Age category = ≥ 65
11	Trial = 238, Stage= IIIc, Sex= F, Age category = < 65
12	Trial = 238, Stage= IIIc, Sex= F, Age category = ≥ 65
13	Trial = 238, Stage= IV, Sex= M, Age category = < 65
14	Trial = 238, Stage= IV, Sex= M, Age category = ≥ 65
15	Trial = 238, Stage= IV, Sex= F, Age category = < 65
16	Trial = 238, Stage= IV, Sex= F, Age category = ≥ 65
17	Trial = 029, Stage= IIIb, Sex= M, Age category = < 65
18	Trial = 029, Stage= IIIb, Sex= M, Age category = ≥ 65
19	Trial = 029, Stage= IIIb, Sex= F, Age category = < 65
20	Trial = 029, Stage= IIIb, Sex= F, Age category = ≥ 65
21	Trial = 029, Stage= IIIa, Sex= M, Age category = < 65
22	Trial = 029, Stage= IIIa, Sex= M, Age category = ≥ 65
23	Trial = 029, Stage= IIIa, Sex= F, Age category = < 65
24	Trial = 029, Stage= IIIa, Sex= F, Age category = ≥ 65
25	Trial = 029, Stage= IIIc, Sex= M, Age category = < 65
26	Trial = 029, Stage= IIIc, Sex= M, Age category = ≥ 65
27	Trial = 029, Stage= IIIc, Sex= F, Age category = < 65
28	Trial = 029, Stage= IIIc, Sex= F, Age category = ≥ 65
29	Trial = 029, Stage= IV, Sex= M, Age category = < 65
30	Trial = 029, Stage= IV, Sex= M, Age category = ≥ 65
31	Trial = 029, Stage= IV, Sex= F, Age category = < 65
32	Trial = 029, Stage= IV, Sex= F, Age category = ≥ 65

Source: company submission, section B.2.9, table 12, p64, ERG report p76

Patient level meta-regression ITC results – RFS

Adjusted long-term survival extrapolation from parametric survival curves rebased at Week 12 split by treatment

The following covariates were adjusted for in the regression analysis:

- sex (male or female)
- age (<65 or ≥65)
- stage (stage IIIa or stage IIIb or Stage IIIc or Stage IV). Of note, in the CheckMate 238 trial, [redacted] patients had unknown/other disease stage, so were excluded from analysis.
- trial (CA184-029 or CheckMate 238)

Based on data from CheckMate 238 (24 month follow-up) and CA184-029 (median follow-up 5.3 years)

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Source: Company response to clarification question A1, figure 7

Bucher ITC results (not used in economic analyses) – RFS

Covariate adjusted	Population	CheckMate 238 HR (95% CI) Nivo vs Ipi	CA184-029 HR (95% CI) PBO vs Ipi[b]	Bucher HR (95% CI) Nivo vs PBO
No	ITT	[redacted]	[redacted]	[redacted]
Yes[a]	ITT	[redacted]	[redacted]	[redacted]
No	Stage IIIb/c	[redacted]	[redacted]	[redacted]
Yes	Stage IIIb/c	[redacted]	[redacted]	[redacted]

[a]The following covariates were adjusted for in the analysis: sex (male or female); age (<65 or ≥65); stage (stage IIIa or stage IIIb or Stage IIIc or Stage IV). Of note, in the CheckMate 238 trial, [redacted] patients had unknown/other disease stage, so were excluded from analysis; [b] HRs presented are comparing placebo against ipilimumab, hence HR>1 means that ipilimumab performs better than placebo

Based on data from CheckMate 238 (24 month follow-up) and CA184-029 (median follow-up 5.3 years)

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Source: Company response to clarification question A1, table 3

Bucher ITC results (not used in economic analyses)– OS

- Patient level OS data was not available from CheckMate 238
- Therefore ITC using Bucher method was possible but ITC using IPD meta-regression was not
- [redacted]
- [redacted]

[a]HRs presented are comparing placebo against ipilimumab, hence HR>1 means that ipilimumab performs better than placebo

Based on data from [redacted] and CA184-029 (median follow-up 5.3 years)

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Source: Company response to clarification question A2, table 4

ITC – ERG critique: Trial heterogeneity

- **Different versions of AJCC criteria used to stage patients at trial entry:** no differences between the 6th and 7th editions of AJCC criteria (7th edition was used in the CheckMate 238 study) that would significantly affect the classification of Stage III patients in CA184-029 (ERG clinical expert)
- **Other population differences arising from trial selection criteria:** CA184-029 study also restricted to patients with cutaneous melanoma (approximately 15% of CheckMate 238 population had non-cutaneous). Company reported that melanoma subtype not found to be prognostic or a treatment effect modifier in CheckMate 238. ERG does not consider this sufficient justification to assume it has no effect on treatment outcomes as the subgroup was not adequately powered for this purpose

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Source: ERG report, section 4.4.1.1, p65

ITC – ERG critique: Trial heterogeneity (cont.)

- **Differences in permitted duration of ipilimumab treatment across trials:**
  - ERG considers that [redacted] of patients continuing treatment beyond one year in CA184-029 is a substantial proportion
  - Requested at the clarification stage that the company appropriately account for this in their analyses – company dealt with this in two different ways
    - provided a KM plot of RFS in CA184-029 for both the ITT population and the subgroup of patients who received up to 1 year's treatment split by treatment
    - provided analysis is which patients in CA184-029 who were still on ipilimumab treatment at one year were censored
      - ERG agreed this was most robust (although it was likely to be biased against ipilimumab)
      - this analysis indicates that the RFS treatment effect estimates from the ITC using the ITT population are potentially overestimated

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Source: ERG report, section 1.1.4.4, pp66 & 68; section 4.5, p90-91

ITC – ERG critique: Trial heterogeneity (cont.)

- **Differences in subsequent therapies across trials:**
  - subsequent therapies given in CheckMate 238 more consistent with UK clinical practice (ERG clinical expert)
  - differences likely to be related to advances in clinical practice since CA184-029
  - due to the outcome censoring selected for the ITC analyses, these differences in subsequent therapies will have the largest impact in the analysis of OS
  - ERG is unsure of the exact impact of these differences in subsequent therapies on the ITC results:
    - more effective subsequent treatments will minimise any difference in OS
    - less effective subsequent treatments will have less impact on subsequent OS
    - a larger proportion of patients are likely to receive more effective subsequent immunotherapies than in the CA184-029 trial, meaning that the overall survival is potentially underestimated

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Source: ERG report, section 1.1.4.4, pp66 & 68; section 4.5, p90-91; section 4.5.1, p93

ITC – ERG critique: Trial heterogeneity (cont.)

- **Differences in how RFS outcome was assessed across trials:**
  - ERG noted this as another source of heterogeneity but had no major concerns with the way the company had handled this issue in the ITC
  - Main difference unaccounted for in ITC analyses was how RFS was assessed (investigator in CheckMate vs. independently in CA184-029) - ERG noted this is likely to result in a conservative estimate of the efficacy of ipilimumab versus placebo
- **Differences in baseline characteristics of patients across trials:**
  - ERG's clinical experts considered the baseline characteristics broadly consistent across the trials (CA184-029 included a slightly lower risk population – lower stage, younger)
  - Company's choice of covariates was informed by the CheckMate 238 subgroup analysis which was underpowered to detect differences in treatment effect at the subgroup level so is not necessarily a reliable source of evidence for treatment effect modifiers
  - Although company had attempted to generate survival curves that reflected the entire population of interest (using covariate adjustment and CGP method), differences between the trial populations relating to disease stage could not been adequately adjusted for because some stages (Stage IIIA and Stage IV) lacked patients in at least one of the trials

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Source: ERG report section 4.5, pp90-91; section 4.4.3.1.1-2, pp75-76; section 5.4.5.4.1 p118

ITC – ERG critique: RFS results

- IPD meta-regression (survival model)
  - Results based on ITT population (used in company base case) represent 'best case' scenario due to differences between trials in terms of ipilimumab treatment duration (see previous slide)
    - Clarification stage analysis (where patients in CA184-029 who were still on ipilimumab treatment at one year were censored) represents 'worst case'
    - ERG prefer more conservative estimates and describe ITT-based results as 'overly optimistic'
  - Data for some disease stages was inadequate
  - ITC only informs survival model up to 10 years, after RFS estimated by applying a hazard ratio to AJCC version 8 OS registry data (HR was based on interferon trial [Argawala et al. 2017])
- Bucher analysis
  - Assumes proportional hazards
  - Results demonstrate
    - treatment effect is [redacted]
    - [redacted]

    When the ipilimumab censored at one-year data were used instead of full ITT ipilimumab dataset, [redacted]

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Source: ERG report section 3.3, p35; section 4.4.4, p79, section 4.5, p91

Bucher ITC OS results - ERG critique

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Source: ERG report section 4.4.7.1-2, pp84-88

Company's surrogacy analysis for OS – ERG critique

- Rationale for surrogacy analysis approach was informed by a study (Suciu et al. 2018) that concluded that RFS appears to be a valid surrogate endpoint for OS in Stage II–III melanoma adjuvant therapy. It used 13 interferon trials to derive a regression equation to estimate a HR for OS from a HR for RFS.
- Surrogacy analysis in the company submission (CS) differed from this original analysis
  - Approach used in CS based on ongoing, unpublished study funded by BMS, first part of which is complete and considered to be an update of the previous analysis by Suciu et al. 2018 et. al.
  - [redacted]
  - whereas Suciu et al. 2018 2018 used [redacted]
- ERG is unsure about reliability; unaware of any other publications in support of this method
- A publication supplied by the company considered this [redacted] - The ERG are concerned it is not robust
- It is unclear whether proportional hazards assumption holds for OS for nivolumab versus routine surveillance – if not then results for OS calculated using the surrogacy equation will be flawed
- Final estimates for both nivolumab and routine surveillance informed by CA184-029 placebo arm OS data – these data likely to underestimate OS because more effective subsequent treatments are now available

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Source: ERG report section 4.4.7.2, pp85-88

Validity of ITC results: impact of trial differences – ERG critique

- **Differences in subsequent therapies across trials is most important issue:**
  - subsequent therapies given in CheckMate 238 more consistent with UK clinical practice (ERG clinical expert)
  - differences likely to be related to advances in clinical practice since CA184-029
  - due to the outcome censoring selected for the ITC analyses, these differences in subsequent therapies will have the largest impact in the analysis of OS
  - ERG is unsure of the exact impact of these differences in subsequent therapies on the ITC results:
    - more effective subsequent treatments will minimise any difference in OS
    - less effective subsequent treatments will have less impact on subsequent OS
    - following routine surveillance, a larger proportion of patients are likely to receive more effective subsequent immunotherapies than in the CA184-029 trial, meaning that the OS estimate for nivolumab versus routine surveillance generated from the ITC is potentially underestimated

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Source: ERG report, section 1.1.4.4, pp66 & 68; section 4.5, p90-91; section 4.5.1, p93

ITC – ERG critique: other outcomes

No suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of

- DMFS
- HRQoL
- AEs

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Source: section 4.5, p89

Cost effectiveness evidence

- Company submission, section B3

Preview: Cost effectiveness issues 1

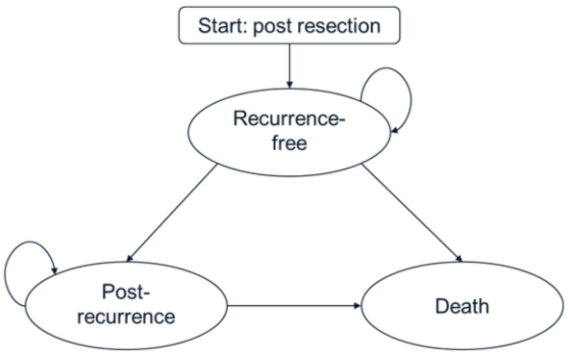
Staying in the recurrence free state for longer gives QALY gains from not dying of disseminated disease. The long term projections of RFS are therefore important:

- The company and the ERG models are reliant on OS predictions that are either known to be flawed or cannot be validated. Are these models robust enough for decision making?
- Given the immaturity of the OS data several methods were tried to predict OS; either relating OS to RFS via a surrogacy approach in a partitioned state mode, or using a post progression state in a Markov model. Which model is most appropriate?

Preview: Cost effectiveness issues 2

- In a Markov model the results are heavily influenced by treatments people received on progression, and whether these were likely to be different post adjuvant compared with post surveillance. What is the committee's view on this?
  - Avoidance of high cost treatments post progression offsets the adjuvant costs
  - highly effective treatments post progression after routine surveillance will reduce QALY gains from adjuvant therapy
  - ERG base case ICER is much higher than the company's because of different assumptions regarding subsequent treatments which increase the overall cost and reduce QALYs gained with adjuvant nivolumab treatment. Which assumptions (and resulting ICERs) most closely reflect of clinical practice?
  - Are the cost effectiveness analyses generalizable to the entire population of interest (CheckMate 238 excluded stage IIIA disease and CA184-029 excluded stage IV disease)?

Company's economic model structure



- Company chose partition survival model (PS) for base case
- 2 Markov models also provided
- All 3 models based on same 3 health state structure, 60 year time horizon & 28 day cycle length
- Patient characteristics in the model reflect CheckMate 238 and CA184-029 trials i.e. stage IIIA–IV NED patients with confirmed lymph node involvement

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Source: company submission, section B.3.2, figure 33, pp103-4

Company's justification for choosing three-health state partition survival model:

- Similar rate of the different types of recurrence between the 2 arms of CheckMate 238 ([redacted]% of recurrences were loco-regional, [redacted]% distant in the nivolumab arm compared to [redacted]% and [redacted]% on the ipilimumab arm)
- Published data used to validate treatment effect predictions (i.e. RFS for the routine surveillance arm from prior IFN trials and data on strength of RFS as a surrogate endpoint for OS) not split by recurrence type
- Costs assigned by the type of recurrence without tracking recurrence type in a time-dependent manner – this allows for sufficiently accurate costing of subsequent therapies
- Feedback on a prior more complex adjuvant submission was that extrapolating relapse in an overcomplicated manner lacked clinical validity and made the model difficult to critically appraise
- Feedback provided by clinical experts at the UK advisory board was that it was not necessary to split by recurrence type in order to maintain the clinical plausibility of the model and splitting by

recurrence type risked incorporating unnecessary complexity

- Incorporating time dependency would require a Markov structure, which would lead to artificially increased uncertainty due to the limited amount of data available to inform individual transitions
- Patients can experience more than one recurrence (e.g. local followed by distant); CheckMate 238 does not provide sufficient information to model this (and natural history data for a second recurrence are not available)

Company's key assumptions in their base case model

Assumption	Company's rationale
Nivolumab is equally effective across all disease stages	CheckMate 238 trial: No evidence of difference in effect across stages found; Bucher ITC: similar outcomes ITT and subgroup analysis
OS for Stage IV NED patients can be informed using data for Stage IIIC patients	No data are available on OS for Stage IV NED patients. CheckMate 238 trial: Stage IV NED RFS was found to be similar to Stage IIIC RFS; Clinical experts agreed that if resection is possible with Stage IV NED patients, then outcomes would be very similar to Stage IIIC patients
Stage IIIA patients' natural history RFS prognosis is not expected to have changed between the CA184-029 and CheckMate 238 trials	No rationale provided
The most relevant patient population to model is the CheckMate 238 population once stage and other covariates included are adjusted for	CheckMate 238 trial is our main trial of interest and is more recent

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Source: company submission, section B.3.3, p116-7 and section B.3.6, table 53, p165

Company's key assumptions in their base case (cont.)

Assumption	Company's rationale
Difference in duration of ipilimumab treatment across trials does not impact efficacy	Median number of doses in both trials was 4; outcomes were similar in stage IIIB and stage IIIC patients across the trials and only [redacted] doses of ipilimumab treatment in the CA184-029 trial
Routine surveillance 'other Grade 3+' AEs same as nivolumab	Comparison of AEs in both trials suggested placebo has more AEs than nivolumab - clinically implausible
Dosing and duration of treatments for local/regional recurrence = adjuvant dose and duration (unless data was unavailable in which case dose and duration assumed to be same as for distant recurrence)	No dosing information on subsequent treatments were available in the CheckMate 238 or CA184-029 trials; literature data were used to inform the dosing. Some subsequent treatments in the local/regional recurrence group are not indicated in the adjuvant setting and trial publications were not available; therefore, metastatic data were used.
Equal health-state utilities were assumed for all treatments	Utility regression equations did not show a large difference in utility, and data were not available to compare all treatments based upon treatment effects (mapped and literature data are used in sensitivity analysis)

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Source: company submission, section B.3.3, p116-7 and section B.3.6, table 53, p165

Abbreviations: NED, no evidence of disease

RFS – use of external long-term survival data in company base case

- ITC results only inform extrapolations up to 10 years in company base case
- After 10 years
  - a HR was calculated comparing RFS and OS
    - Pseudo PLD were created from digitised observation OS and RFS curves from the E1697 trial (phase III Randomized Study of 4 Weeks of High-Dose Interferon-a-2b in Stage T2bNO, T3a-bNO, T4a-bNO, and T1-4N1a-2a (microscopic) Melanoma, Agarwala 2017).
    - A Cox regression was used to estimate the HR, [redacted]
  - this HR is applied to the long-term OS curve (see next slide) to produce the long-term RFS curve

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Source: company submission, section B.3.3, pp125-127

OS – use of external long-term survival data in company base case

- Most clinically plausible extrapolated parametric survival curves produced from the trial data appeared to produce low estimates of survival compared to long-term sources available:
  - 10-year OS estimated from the CA184-029 placebo arm [redacted]%
  - AJCC registry data version 8: 70%
  - AJCC registry data version 7 (weighted stage III curve): 39%
  - E1697 (phase III trial comparing high-dose interferon to observation in stage T2bNO, T3a-bNO, T4a-bNO and T1-4N1a-2a melanoma patients): 75%
- In company base case, after 10 years no ongoing treatment effect is assumed and AJCC registry data (version 8) is applied to both arms. Company's rationale:
  - The availability of better treatments post-recurrence in the metastatic setting and more accurate staging (therefore better outcomes) means that the AJCC v8 is more reflective of current clinical practice.
  - 10-year time point selected because: (a) this is when long-term melanoma survival outcomes begin to plateau according to AJCC/E1697; (b) in line with view of clinicians at the UK advisory board (alternative time points of 5 years and 20 years are included in the scenario analysis)

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Source: company submission, section B.3.3, pp125-127

Overview of data sources for clinical parameters used in company base case

Input	Source
RFS	0-12 weeks • Routine surveillance: HR (derived by fitting a Cox proportional hazards (PHs) model to the ipilimumab groups of the CheckMate 238 and CA184-029 trials, with censoring applied at 12 weeks) applied to the KM data from the placebo group of CA184-029 trial • Nivolumab: KM data from checkmate 12 weeks to 10 years: • Both arms: Parametric survival models from the PLD meta-regression of CheckMate 238 and CA184-029 Year 10 onwards: • Both arms: HR applied to AJCC version 8 OS registry data (HR was based on interferon trial)
OS	Up to 10 years: • Routine surveillance: parametric survival models for CA184-029 trial data • Nivolumab: estimated from OS/RFS relationship using nivolumab vs. routine surveillance HR (HR was based on unpublished study) Year 10 onwards: • Both arms: AJCC version 8 OS registry data (background mortality using general population data used if extrapolations predict a lower mortality)

Source: company submission, section B.3.3, table 27, pp128-129; ERG report section 5.4.5.1, p103-104

Overview of data sources for other clinical parameters used in company base case

Input	Source
Time-on-treatment	Time on treatment for nivolumab was taken from the CheckMate 238 PLD, which recorded the proportion of patients receiving each dose up to the maximum duration of 1 year
Recurrences rates	Subsequent treatment costs and monitoring costs split by recurrence type and weighted by the proportion of patients who had a local/regional recurrence or a distant recurrence from CheckMate 238 Proportions experiencing each recurrence type similar across CheckMate 238 trial arms so pooled data were used in the model and applied to both nivolumab and routine surveillance
AEs	Immune-related AEs (any grade) and diarrhoea (Grade ≥2) • Nivolumab: CheckMate 238 PLD • Routine surveillance: rates calculated as relative difference in AEs between ipilimumab and placebo in CA184-029 and between ipilimumab and nivolumab in CheckMate 238 Other Grade ≥3 AEs • Both arms: CheckMate 238

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Source: company submission, section B.3.3, pp131-135

Summary of utility values used in company base case

State	Utility value: mean (SE)	95% CI	Justification
Utility values for health states defined by progression status			
Recurrence-free	[redacted]	Sampling using variance-covariance matrices assuming multivariate-normal distribution	Assumed equal across treatments. Based on statistical models fitted using EQ-5D data collected in CheckMate 238 trial and covariate for routine surveillance based on mapping from QLQ-C30 to EQ-5D using data collected in both CheckMate 238 and CA184-029 trials
Post-recurrence	[redacted]		
Utility decrements for adverse events			
Immune-related disorders	-0.11	-0.134, -0.09	Based on the Middleton et al. (2016) poster, which looks at disutilities due to AE in the adjuvant melanoma setting
Diarrhoea	-0.09	-0.108, -0.073	
Other AEs	-0.137	-0.165, -0.111	

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Source: company submission, section B.3.4, table 41

Routine surveillance utility was assumed at the same as placebo utility.

Immune-related disorders/other Aes: Toxicity-hospital and toxicity – outpatient disutility used weighted by % patients hospitalised.

95% CI for utility decrements for adverse events were not reported in the literature, SE assumed to be 10% mean.

Costs and resource used in company base case

Nivolumab vial options		
Concentration	10mg/ml	10mg/ml
Vial volume	4ml	10ml
Dose per vial	40mg	100mg
Price per vial (no PAS)	£439.00	£1097.00
Price per vial (with PAS) – base case	[redacted]	[redacted]
Source for prices without PAS	Monthly Index of Medical Specialities September 2017	

ERG note although CheckMate 238 and CA184-029 trials were conducted globally and the company's base case analysis uses the intention-to-treat (ITT) population to inform treatment effectiveness, estimation of nivolumab treatment costs, for which doses are determined by patient weight, data were taken only from the Western European population, which was considered to be more reflective of the UK than the global population. ERG agree with this approach

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Source: company submission, section B.3.5, table 42, p153, ERG report section 5.4.2.1, p100

Costs and resource used in company base case (cont.)

Resource	Cost (£)	Reference
Outpatient visits		
Oncologist/ Surgeon	107.00	PSSRU 2017
GP/PCP	28.00	
Dermatologist	106.00	
Nurse visits	37.00	
Imaging		
Chest x-ray	85.69	NHS reference costs
PET-CT (chest and abdomen)	334.28	16/17
CT (chest and abdomen)	112.33	
MRI (head)	139.30	
CT (head)	97.39	
Other	118.35	
Laboratory tests		
CBC	1.69	NHS reference costs
Comprehensive metabolic panel; LDH; Albumin; Calcium; C-reactive protein; Liver function test	1.13 each	16/17

Medical resource use was identified via a survey of six UK clinicians selected by the company

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Source: company submission, section B.3.5, table 43, p155-6

Abbreviations: CBC, complete blood count; CT, computed tomography; GP, general practitioner; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCP, primary care physician; PET, positron emission tomography; PSSRU, Personal Social Services Research Unit.

One clinician reported that the 'other' was a CT scan of the neck; the other clinicians did not specify. It is assumed that 'other' is a single scan of one area either by MRI or CT.

Costs and resource used in company base case (cont.)

Monitoring costs for patients split by timeframe and health state applied within the model

Health state	Year 1 cost (£)	Year 2 cost (£)	Year 3–5 cost (£)	Year 5+ cost (£)
Recurrence-free	[redacted]	[redacted]	[redacted]	[redacted]
Local/regional recurrence (unresectable)	[redacted]	[redacted]	[redacted]	[redacted]
Local/regional recurrence (resectable)	[redacted]	[redacted]	[redacted]	[redacted]
Distant recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Weighted average for post-recurrence monitoring costs*	[redacted]	[redacted]	[redacted]	[redacted]

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Source: company submission, section B.3.5, table 44, p156

Weighted average for post-recurrence monitoring costs based on post-recurrence patient proportions as reported in the CheckMate 238 patient-level data

Costs and resource used in company base case (cont.)

Summary of per patient AE costs in the economic model

	Nivolumab (£)	Routine surveillance (£)
Hospitalisation costs – immune-related disorders (any grade)	[redacted]	[redacted]
Hospitalisation costs – diarrhoea (Grade ≥2)	[redacted]	[redacted]
Hospitalisation costs – other AEs (Grade ≥3)	[redacted]	[redacted]
Hospitalisation costs – subtotal	[redacted]	[redacted]
Outpatient costs – immune-related disorders (any grade)	[redacted]	[redacted]
Outpatient costs – diarrhoea (Grade ≥2)	[redacted]	[redacted]
Outpatient costs – other AEs (Grade ≥3)	[redacted]	[redacted]
Outpatient costs – subtotal	[redacted]	[redacted]
Total cost (per trial patient)	[redacted]	[redacted]

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Source: company submission, section B.3.5, table 47, p158

Costs and resource used in company base case (cont.)

Subsequent treatment frequencies and costs were applied according to the recurrence type experienced and the initial adjuvant treatment received based on patients in CheckMate 238

	Local/regional recurrence		Distant recurrence	
	Nivolumab	RS*	Nivolumab	RS
Dacarbazine	[redacted]			
Temozolomide				
Interleukin				
Interferon				
Cisplatin				
Paclitaxel				
Ipilimumab				
Vemurafenib				
Dabrafenib + trametinib				
Dabrafenib				
Pembrolizumab				
Nivolumab				
Nivolumab + ipilimumab				
Talimogene laherparepvec				
Other palliative chemotherapy				
Other				

*Subsequent treatment data from ipi arm following recurrence

Source: company submission, section B.3.5, table 48, pp16-161

Costs and resource use in company base case (cont.)

Total subsequent treatment cost applied per recurrence in the model per adjuvant treatment

Recurrence type	Nivolumab	Routine surveillance
Local/regional	[redacted]	[redacted]
Distant		

End-of-life costs from Round et al. (2015)

Category	Breast	Colorectal	Lung	Prostate	Average
Health care	4,346	4,854	3,157	6,687	4,254
Social care	2,843	1,489	1,358	2,728	1,829
Informal care – indirect costs	4,868	2,850	2,420	4,814	3,265

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Source: company submission, section B.3.5, table 51, p163 and table 52, p164

A one-off, end-of-life cost, was applied to patients at the point of dying to reflect the cost of terminal care. The end-of-life cost in the base case was calculated based on a total cost derived from the Round et al. (2015) modelling study, which estimated the cost of caring for cancer during the final phases of life. Indirect costs are those costs arising from the illness but where a payment is not made, such as lost wages due to time off work. This has been valued using the human capital approach

Company base case results

Base case partitioned survival model results (provided at clarification stage, incorporating nivolumab PAS)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,882
ERG estimate incorporating subsequent treatment PASs	[redacted]						

Alternative Markov model results (provided at clarification stage, incorporating nivolumab PAS)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Markov option 1 – base case							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,567
Markov option 2 – base case							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,685
ERG estimate incorporating subsequent treatment PASs	[redacted]						

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Source: ERG report, section 5.5.1, table 50, p137, ERG report confidential appendix, tables 2-4, p3

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PS, partitioned survival; QALY, quality-adjusted life year

The company's base case analysis is based on the partitioned survival structure, which uses data from the ITC between the CheckMate 238 and CA184-029 trials for RFS, and the application of a surrogacy relationship to estimate OS from the RFS data.

Company analyses

How did the company's base case PS and Markov models differ?

PS model: uses overall survival (OS) and recurrence-free survival (RFS) data to directly inform the proportion of patients remaining in each of three health states at any given time

- OS data informs the proportion who are in the death state, RFS data informs the proportion who are in the RF state, difference between the two is the proportion in the PR state
- For this appraisal, RFS was informed by an indirect treatment comparison (ITC) between the CA184-029 trial; proportion of patients in the death state at any given cycle was informed by a surrogate relationship between RFS and OS

Source: ERG report, section 5.4.4.1, pp101-2, section 5.4.5, figures 25-26, pp110-111

Company analyses

How did the company's base case PS and Markov models differ? (cont.)

Markov 1 model: uses the same RFS modelling from the ITC as per the PS model but to estimate the probability of remaining in the PF state and the probability of transitioning to death from the PF state, the composite RFS measure needed to be "split" to separate out the rates of recurrence and the rates of death

- Post-recurrence survival (PRS) uses the same OS data as in the base case PS model
- PRS transition probabilities estimated from the OS data

Markov 2 model: RFS same approach as for base case PS and Markov 1 models but different approach for estimating PRS

- local/regional recurrence: survival curves were fitted to data from the CA184-029 trial
- distant recurrence: survival curves based on range of data sources, including data from drug trials for advanced and/or metastatic melanoma and registry data
- curves were then weighted to produce estimates expected to be reflective of the relevant population

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Source: ERG report, section 5.4.4.1, pp101-2, section 5.4.5, figures 25-26, pp110-111

Company analyses – ERG critique

General comments that apply to both company's PS model (base case) and alternative Markov models

- Largely in line with that proposed in the NICE final scope
- Model population appropriate and reflective of the expected population in the UK
- Use of the Western European population appropriate for the estimation of treatment costs, as differences in patient characteristics globally are not likely to be reflective of the UK population
- Contains relevant health states to capture the key changes in the natural history of the disease; namely, recurrence-free, disease recurrence and death
- Time horizon is long at 60 years but appropriate given that patients as young as 18 are included in the population
- Cycle length of 28 days to be appropriate and likely to capture the key changes in events and resource use with sufficient granularity

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ERG report sections 5.4.2.1, p100 and 5.4.4.3, p103

Company analyses – ERG critique

Clinical efficacy modelling

Partitioned survival model (base case)

- RFS
  - Issues highlighted in clinical evidence section above still remain relevant i.e.
    - Trial differences relating to disease stage not adequately adjusted for
    - reliability of the ITC results compromised by differences between trials in terms of duration of ipillimumab treatment
  - In addition
    - long term estimates of RFS potentially unreliable - calculated using a HR comparing RFS with OS data from Agarwala et al. 2017 (interferon study)
- OS
  - Relies on a surrogate relationship between RFS and OS; approach informed by unpublished study underpinned by data from predominantly interferon-based studies
  - Derived HR from the surrogacy relationship was applied to a baseline generalised gamma survival model; a model that does not support the use of proportional hazards
  - Subsequent treatments received by patients in the two trials are not reflective of current UK clinical practice, according to clinical expert advice sought by the ERG - OS estimates in the placebo group of the CA184-029 trial are likely to be underestimated and, therefore, the relative benefit of nivolumab over routine surveillance is likely to be overestimated
  - OS appears underestimated vs data from CA184-029 (already potentially underestimated because of the less effective subsequent treatments at time of trial)

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Source: ERG report section 5.4.5.4.1, pp117-120 and section 8, p156

Company analyses – ERG critique

Clinical efficacy modelling (cont.)

Markov model 1 (not used in company base case)

- Avoids need to use surrogacy analysis to predict OS
- However, in lieu of this, PRS transition probabilities informed by Agarwala *et al.* 2017 (interferon study)
- Regardless of the applicability of Agarwala *et al.* 2017 study, approach is based on an uncertain assumption of a constant relative effect on the OS hazard
- Does not resolve the issue of inappropriate subsequent therapies influencing OS outcomes

Markov model 2 (not used in company base case)

- Allows for the issues of inappropriate subsequent treatments to be explored
- But uses a range of potentially disparate sources of evidence to inform PRS, so it is unlikely that the estimates of PRS are robust/applicable to the population on which the ITC was formed
- Even if the analysis was considered reliable, the range of ICERs resulting from plausible scenarios demonstrates the potentially serious uncertainty that currently exists within the results

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Source: ERG report section 5.4.5.4., pp121-122 and section 8, p156

Company analyses – ERG critique

AEs, HR-QoL (comments relate to both PSM and Markov models)

AEs

- For the proportions of immune-related AEs and diarrhoea in the routine surveillance group, the risk of AEs from the placebo group of CA184-029 was adjusted for the difference in risks across the ipilimumab groups of the two trials
  - ERG considers approach methodologically incorrect; differences in AE risks between the ipilimumab groups in trials likely to be influenced by differences in treatment duration
  - However, the resulting AE risks for routine surveillance not implausible/not too dissimilar to the unadjusted data from the CA184-029 trial- impact of on ICER likely to be minimal

Utility estimation

- Company's approach to utility estimation generally sound
- ERG considers inclusion of AE decrements using an external source to be unnecessary but unlikely to affect the results of the cost-effectiveness analysis

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Source: ERG report section 5.4.6.1, p123 and section 5.4.7.4 p129

Company analyses – ERG critique

Resources and Costs

- Model inputs for resource use and costs generally suitable with only a few exceptions:
  - Most important is application of subsequent therapy costs - needs to be considered in parallel with the appropriateness of the treatment effectiveness measures and the impact of subsequent therapies on post-progression survival
  - proportion of patients receiving each subsequent therapy based on CheckMate 238 trial – ERG clinical expert suggests that these data are not reflective of UK clinical practice and there would be a greater use of more effective subsequent systemic therapies such as nivolumab following routine surveillance
  - company's scenario using the placebo group of the CA184-029 is even less reflective given the age of the trial, as it includes the use of therapies such as interferon and interleukin, which would not be used in UK clinical practice today
  - If more patients in nivolumab group received cost effective therapies, results may be biased against routine surveillance
- Other (more minor) issues:
  - ERG clinical expert opinion considers the assumptions regarding imaging resource use to be potentially excessive
  - End of life costs include social care costs which may not apply to all patients considered in the economic analysis. However, given the costs applied are equivalent in each treatment group, this is likely to have a negligible impact on the ICER

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Source: ERG report section 5.4.8.5, pp135-137

ERG base case – preferred model and assumptions

ERG preferred Markov model II because this allowed for exploration of alternative subsequent treatments but with the following adjustments:

- RFS based on the ITC analysis that used censoring for patients who received treatment beyond one year in the ipilimumab group of the CA184-029 trial
- nivolumab applied as subsequent therapy for patients with a distant recurrence after routine surveillance
- ipilimumab applied as subsequent therapy for patients with a distant recurrence after adjuvant nivolumab

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Source: ERG report, section 5.4.5.4.2-3, pp121-122

ERG base case results (with Nivolumab PAS)

	Results per patient	Nivolumab	Routine surveillance	Incremental value
Company's alternative model (Markov Option 2)	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs			
	LYs		14.08	
	ICER			£18,685
RFS using censoring at one-year of treatment continuation	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs			
	LYs		14.19	
	ICER (vs. company)			£18,960
	ICER (all changes)			**£18,960**
Nivolumab as subsequent therapy for distant recurrence after routine surveillance	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs			
	LYs		17.05	
	ICER (vs. company)			£96,443
	ICER (all changes)			**£107,787**
Ipilimumab as subsequent therapy for distant recurrence after adjuvant nivolumab	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs			
	LYs		17.05	
	ICER (vs. company)			£10,202
	ICER (all changes)			**£32,758**
Incorporating subsequent treatment PASs				[redacted]

Source: ERG report errata, section 6.3, table 67, pp152-3, ERG confidential appendix errata

ERG scenario analyses and overall conclusions

ERG also performed a variety of scenario analyses using the company's PS model, the company's Markov II model and their own preferred base case

- ICERs range for scenarios tested by ERG using company preferred base case PS model (with nivolumab and subsequent treatment PASs included) was £[redacted] to £[redacted] per QALY gained
- Most relevant scenario analysis for ERG (Markov 2 model) base case (in which 50% of patients with distant recurrence in each group receive dabrafenib + trametinib) produced an ICER of £[redacted]

ERG concluded

- ERG base case is still a very uncertain analysis and only partially mitigates the uncertainty in the company's analysis
- company's analyses no less certain than the ERG's scenario that resulted in an ICER greater than £300k per QALY, hence, emphasising the potential impact of the uncertainty

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Source: ERG confidential appendix errata tables 5 & 8, ERG report errata, p122

Equalities issues

- None identified

Innovation - Company comments

Nivolumab is the first checkpoint inhibitor agent licensed for use in the adjuvant setting for melanoma - represents a 'step-change' in the management

In contrast to routine surveillance, which cannot adequately capture metastases until they are large enough to be detected, nivolumab works by priming the immune system to respond to micrometastases in the first instance

As a treatment for advanced melanoma, nivolumab has made a significant difference in survival for metastatic patients

Anticipated that health-related benefits such as improved RFS and response benefits will be captured in QALY calculation but significance to patients should be viewed as innovative

- curative potential associated with immunotherapies such as nivolumab, and the possible return to normal living that this offers patients (in contrast to progression to advanced disease and the burden associated with this
- melanoma disproportionately affects a younger population, this has a significant impact on the working-age population, mainly a loss of economic productivity; such an effect is not captured in the QALY calculation
- nivolumab meets the need for an effective treatment to be offered to patients, removing the psychological burden and anxiety resulting from waiting for potential recurrence of disseminated disease

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Source: company submission section B.2.12

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

Document B

Company evidence submission

May 2018

File name	Version	Contains confidential information	Date
ID1316_Nivolumab Adjuvant Melanoma STA_DocB_REDACTED_13.07.18_v2.0_BMS_FINAL	**v2.0**	**Yes**	**13-July-2018**

Contents

Tables and figures

Abbreviations List	
AE	Adverse event
AJCC	American Joint Committee on Cancer
CGP	Corrected group prognosis
CI	Confidence interval
DMFS	Distant metastasis free survival
EMA	European Medicines Agency
EQ-5D-3L	EuroQol 5 dimension 3 level questionnaire
EPAR	European public assessment report
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan–Meier
LY	Life year
OR	Odds ratio
OS	Overall survival
PAS	Patient access scheme
PLD	Patient level data
PD-1	Programmed death receptor 1
PD-L1	Programmed death receptor ligand-1
PD-L2	Programmed death receptor ligand-2
PSA	Probabilistic sensitivity analysis
RCT	Randomised controlled trial
RFS	Relapse free survival
SAE	Serious adverse event
SmPC	Summary product characteristics
QALY	Quality adjusted life year
QLQ-C30	Quality of life questionnaire
WPAI-GH	Work Productivity and Activity Impairment questionnaire: General Health
WTP	Willingness to pay threshold

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

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem addressed within this submission is presented in Table 1.

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 completely resected Stage III or IV melanoma	Adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.	Wording changed to reflect the anticipated license.
Intervention	Nivolumab	Nivolumab	NA
Comparator(s)	Routine surveillance	Routine surveillance	NA
Outcomes	• Overall survival • Recurrence-free survival • Distant metastasis-free survival • Adverse effects of treatment • Health-related quality of life	• Overall survival • Recurrence-free survival • Distant metastasis-free survival • Adverse effects of treatment • Health-related quality of life	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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.	Adhering to the reference case, the cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year.	NA
	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.	Adhering to the reference case, a lifetime horizon is used.	NA
	Costs will be considered from an NHS and Personal Social Services perspective.	The reference case has been adhered to.	NA
	The availability of any PAS for the intervention or comparator technologies will be taken into account.	Adhering to the reference case, the PAS has been applied in all economic analysis for all BMS products.	Confidential PAS schemes that apply to relevant subsequent comparator therapies are not included in these analyses as BMS is not privy to such information.
Key: BMS, Bristol-Myers Squibb; NA, not applicable; NHS, National Health Service; PAS, patient access scheme.			

B.1.2. Description of the technology being appraised

A description of nivolumab is presented in Table 2. The draft summary of product characteristics (SmPC) is presented in Appendix C; the European Public Assessment Report (EPAR) will be available at a later date.

Table 2: Technology being appraised

UK approved name and brand name	Nivolumab (Opdivo®)
Mechanism of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to PD-1, an immune checkpoint receptor involved in T-cell differentiation and function, and blocks its interaction with its ligands, PD-L1 and PD-L2. Engagement of PD-1 with PD-L1 and PD-L2, which are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2. Malignant tumours may express PD-L1, making them susceptible to PD-1/PD-L1 therapeutic blockade. Within the adjuvant setting, nivolumab therefore acts by enhancing the ability of the patients own immune system to recognise and destroy micrometastases or individual tumour cells at an early stage and prevent further tumour growth and dissemination. This approach, enabling the body's own immune system to target cancer, is novel in resected Stage III or IV melanoma and is viewed by physicians and patient interest groups as a 'step-change' in its management.
Marketing authorisation/CE mark status	An application was filed on [redacted] to the EMA to allow nivolumab to be used in the adjuvant setting. CHMP opinion was received on June 2018, with marketing authorisation expected [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication of interest within this submission is: *"OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection"* Nivolumab is also indicated in the UK and Europe for the following indications: • As monotherapy or in combination with ipilimumab, for the treatment of advanced (unresectable or metastatic) melanoma in adults • As monotherapy, for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults • As monotherapy, for the treatment of advanced RCC after prior therapy in adults

	• As monotherapy, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin • As monotherapy, for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy • As monotherapy, for the treatment of locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy [redacted]
Method of administration and dosage	Intravenous infusion. The recommended dose of nivolumab for the treatment of adjuvant melanoma is weight based at 3mg/kg administered over 60 minutes every 2 weeks. Based on the pivotal CheckMate 238 trial, the maximum treatment duration is 12 months.[a]
Additional tests or investigations	No additional tests or investigations are needed.
List price and average cost of a course of treatment	£439.00 per 4ml vial; £1,097.00 per 10ml vial. Average cost of a course of treatment £53,771[b].
Patient access scheme (if applicable)	A patient access scheme has been approved and comprises a [redacted] from the nivolumab list price. Applying this PAS to the list price, the cost per nivolumab dose is [redacted] with an average cost per course of treatment of [redacted][c]
Key: ASCT, autologous stem cell transplant; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; IV, intravenous; NSCLC, non-small cell lung cancer; PD-1, programmed death receptor-1; PD-L1, programmed death receptor ligand-1; PD-L2, programmed death receptor ligand-2, RCC, renal cell carcinoma **Notes:** [a], some indications, not of interest to this submission, have a flat dose of 240mg every two weeks; [b], Average cost per dose = £2,739 x mean number of doses = [redacted]; [c], Mean number of doses = [redacted] **Source:** Nivolumab SmPC[5]	

B.1.3. Health condition and position of the technology in the treatment pathway

Melanoma is an aggressive type of skin cancer that refers to a malignant tumour of melanocytes, the melanin-producing cells found mostly in the skin.[6, 7] Rates of melanoma have been steadily increasing since the 1990s; in the last decade, incidence rates increased by almost half (45%), making it the fifth most common cancer in the UK.[8] This increasing incidence is widely attributed to changing lifestyle factors such as an increase in holidays taken in the sun and greater use of ultra-

violet (UV) sunbeds, both increasing people's exposure to UV light.[9, 10] In 2010, 89.8% of melanoma cases were thought to be caused by UV radiation.[9] Potentially as a reflection of lifestyle factors, melanoma occurs at a relatively young age. With approximately 50% of patients aged under 65 in the UK[11], this condition has a significant impact on the working age population.[12, 13]

As with other forms of cancer, melanoma is divided into stages describing the extent to which the cancer has spread. The staging system most commonly used for melanoma is the American Joint Committee on Cancer (AJCC) system based on Tumour (T), Node (N), and Metastasis (M) categories. This system has recently been updated to the 8th edition.[14] Key changes to the Stage III classification are presented in Appendix L and discussed further in Section B.2.5. Of note, the pivotal CheckMate 238 study (described in Section B.2.2) was based on the 7th edition of the AJCC system.[4] Importantly, patients with Stage III and IV disease have involvement of lymph nodes or metastatic disease and therefore would be eligible for adjuvant nivolumab treatment; as such, a patient population defined by lymph node involvement and metastatic disease accurately reflects the patient population of CheckMate 238, as accepted by the European Medicines Agency (EMA).[15] This is further discussed in Section B.2.13.

Melanoma can be asymptomatic at first, and often the first visible sign of disease is a mole that has changed in shape, colour, size or feel (cutaneous melanoma). Approximately 0.03% of the English population aged 18 or older were diagnosed with melanoma in 2014, resulting in an incidence of 13,744.[16, 17] In England, the majority of melanoma patients are diagnosed early (Stage I or II), with approximately 8% of patients diagnosed at Stage III or IV disease, a total of 1,100 patients.[18] These patients (Stage III or IV) are initially treated with surgery, which leads to completely resected disease in 80% of Stage III patients[19] and 8.6% of Stage IV patients.[20] In addition, of the 64% melanoma patients who are diagnosed as stage I, approximately 5% will recur to Stage III; similarly, for patients diagnosed as Stage II, approximately 15% will recur to resectable Stage III disease totalling 7.2% of Stage I and II patients who recur to Stage III, as per clinical input.

Therefore, a total of 1,481 patients in England are estimated to have melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection and thus be eligible for treatment with nivolumab in the adjuvant setting.

Following surgical resection, there is a clear lack of effective treatment options for completely resected melanoma patients with involvement of lymph nodes or metastatic disease. Currently, European Medicines Agency (EMA)-approved therapies for treatment of resected melanoma in the adjuvant setting are restricted to interferon alfa-2b (IFN-α).[21, 22] However, adjuvant therapy for melanoma is not common clinical practice in the UK due to the limited effectiveness and increased toxicities related to this treatment.[21, 23] Patients are instead managed through routine surveillance and receive no active adjuvant treatment. This has no clinical benefit, and patients may experience anxiety and stress due to the uncertainty of waiting for either a relapse and further treatment or to be declared to be in remission.[24]

The lack of adjuvant treatment results in melanoma patients with lymph node involvement or metastatic disease being at high risk for relapse and death following complete resection; ≥60% of patients will relapse[25], leading to extremely poor 5-year survival rates.[23] In a retrospective analyses of 340 evaluable patients with Stage III melanoma who presented to the Memorial Sloan Kettering Cancer Center (MSKCC), and who had completely resected disease but subsequently relapsed, the 5-year survival from time of first relapse ranged from 11% in Stage IIIC patients, to 20% in Stage IIIA and IIIB patients.[26] Following relapse, melanoma can invade and destroy nearby tissues[27], and patients may go on to develop advanced or metastatic disease, requiring long-term systemic treatment in the post-adjuvant setting. When this occurs, symptoms become more severe, and patients may typically experience pain and fatigue that affect their physical and mental well-being, weight loss, loss of appetite, nausea and shortness of breath.[27, 28] Alongside the physical symptoms of metastatic disease, approximately one-third of melanoma patients experience considerable levels of distress, mostly at the time of diagnosis and following treatment.[29, 30] Furthermore, as melanoma disproportionately affects younger people in their most productive economic years, an individual who dies from advanced melanoma loses 20.4 years of potential life on average, compared with 16.6 years for all malignant cancer types.[31] As a result, metastatic melanoma has the highest

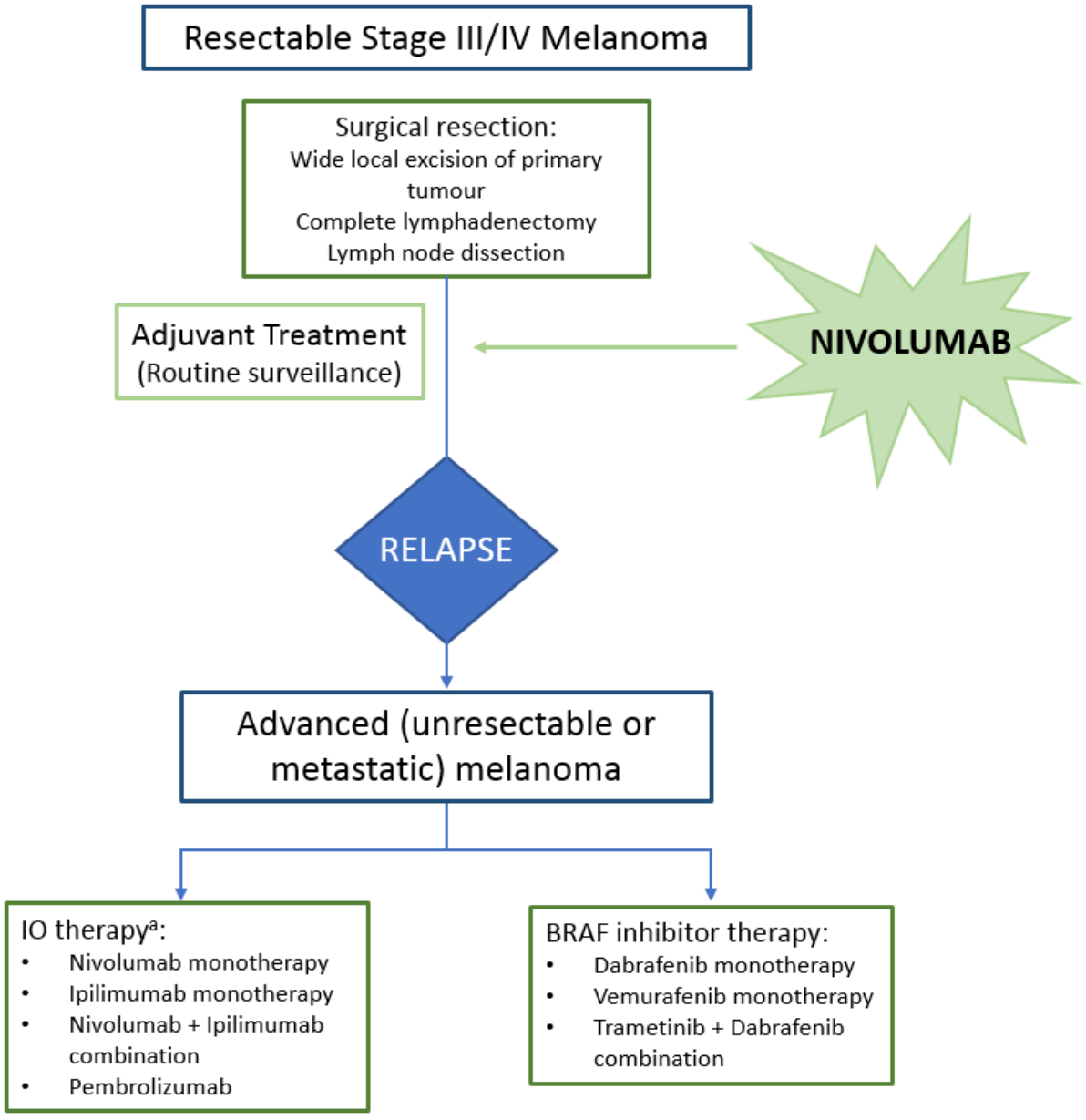
associated loss of economic productivity in Europe (estimated at €312,798 [approximately £272,316]/death in 2008) compared with other cancers, including brain cancer (€288,850 [approximately £251,468]/death).[32] Melanoma in the post-adjuvant setting is also associated with a greater economic burden, due to a greater symptom burden, more expensive systemic treatments and the monitoring and toxicity costs associated with advanced/unresectable disease.[33]

Where the primary tumour has been successfully removed and patients have been declared disease free, the aim of adjuvant treatment is to prevent recurrence of disease. Micrometastases and individual tumour cells may still be present following surgery or may arise *de novo* and will develop into larger tumours with the potential to disseminate to distant sites around the body resulting in advanced, unresectable melanoma. There is a clear unmet need for an active adjuvant treatment that can effectively prevent disease recurrence and progression to advanced (unresectable or metastatic) disease, which are associated with worse survival outcomes, reduced health-related quality of life (HRQL) and increased healthcare costs. Moreover, offering a clinically effective treatment to patients in the adjuvant setting would offer greater value compared to treatment in the post-adjuvant setting, at which stage the disease is considerably more difficult to treat and associated with significant costs. The availability of a treatment option in this setting will also alleviate some of the uncertainty patients feel with routine surveillance.

Nivolumab acts by enhancing the ability of the patients own immune system to recognise and destroy micrometastases or individual tumour cells at an early stage and prevent further tumour growth and dissemination. Nivolumab is the first checkpoint inhibitor agent and is the only active treatment option available for patients with resected melanoma patients with lymph node involvement or metastatic disease in the adjuvant setting that provides a proven clinical benefit (see Section B.2.6). Nivolumab will fit well into the existing treatment pathway (as shown in Figure 1), providing patients with a treatment option where none currently exists at this stage; nivolumab can therefore provide a ‘step-change’ in the management of malignant melanoma (see Section B.2.12). Furthermore, as an immunotherapy, nivolumab has the potential to offer long-term benefit to patients, reducing the risk of

advanced/metastatic disease progression, which is associated with increased health care costs and very poor survival benefit for patients.

Figure 1: Clinical pathway of care for malignant melanoma



Key: IO, immune-oncology.
Note: [a], regardless of BRAF status.
Source: Adapted from NICE melanoma pathway[34]

B.1.4. Equality considerations

No equality considerations have been identified or are anticipated.

B.2. Clinical effectiveness

Key Points

- CheckMate 238, a Phase III study investigating as adjuvant treatment for resected melanoma patients with involvement of lymph nodes or metastatic disease (Stage III or IV), compared nivolumab to ipilimumab, an active comparator, which has previously demonstrated improved clinical benefit versus placebo.
- As such, the magnitude of clinical benefit of nivolumab is expected to be even greater compared to placebo (i.e. routine surveillance, the key comparator of interest).
- The primary outcome was recurrence-free survival (RFS), as the most clinically relevant endpoint in the adjuvant setting since the aim of adjuvant treatment is to prevent disease progression following surgical resection.
  - As RFS has previously been positively correlated with overall survival (OS), nivolumab is expected to extend OS benefit in patients with resected melanoma (clinical experts have confirmed extended RFS results in improved OS).[1]
- After a minimum follow-up of 24 months, nivolumab treatment was associated with a 34% reduction in the risk of recurrence or death compared to ipilimumab (hazard ratio [HR]: 0.66 [95% confidence interval (CI): 0.54, 0.81]; p<0.0001).[2]
  - Median RFS was 30.8 months (95% CI: 30.8, not applicable [NA]) with nivolumab compared to 24.1 months (95% CI: 16.6, NA) with ipilimumab.
  - 24-month RFS rates were 62.6% (95% CI: 57.9, 67.0) and 50.2% (95% CI: 45.3, 54.8).
- Median distant metastasis-free survival (DMFS) was not reached in either treatment group, although nivolumab was associated with improved DMFS compared to ipilimumab (HR: 0.76 [95% CI: 0.59, 0.98]).[2]
- The Phase III CA184-029 study of ipilimumab versus placebo in high-risk patients (Stage III) with cutaneous melanoma following complete resection was used to create an indirect treatment comparison (ITC) between nivolumab and placebo (i.e. routine surveillance).
  - A Bucher ITC demonstrated a significantly [redacted] after treatment with nivolumab compared to placebo, in both the unadjusted ITT population (HR: [redacted]) and after adjustment for patient characteristics (HR: [redacted]).
- Nivolumab was well-tolerated, with a safety profile generally comparable to placebo (i.e. routine surveillance).
  - Most adverse events (AEs) in the CheckMate 238 study were due to the immunotherapeutic mode of action, with most immune-mediated AEs (IMAEs) Grade 1-2, medically manageable and resolved through corticosteroid administration.[3]
- Health-related quality of life (HRQL) scores, with respect to the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) were maintained after treatment with nivolumab, with mean summary scores comparable between the two groups.[4]
- HRQL scores were also maintained after treatment with respect to the European Organisation for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire (QLQ-C30) and the EuroQoL 5-Dimension (EQ-5D).[4]
  - Compared to routine surveillance, which has no clinical benefit, the use of an effective and tolerable treatment that extends the disease-free period can be expected to positively impact patients' HRQL.

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2. List of relevant clinical effectiveness evidence

The systematic literature review (SLR) identified one randomised controlled trial (RCT) that provided evidence on the clinical benefits of nivolumab in patients with resected melanoma with lymph node involvement or metastatic disease. This was the pivotal registrational CheckMate 238 study[4], a manufacturer-sponsored, multinational, randomised, double-blind, Phase III trial that investigated nivolumab compared to ipilimumab after complete resection of Stage III and IV melanoma. This is the only trial providing data specific to the intervention of interest within the target (i.e. licensed) population. Results are presented in Section B.2.6, and a summary is provided in Table 3.

An additional study, CA184-029, was also identified, which investigated ipilimumab compared to placebo (i.e. routine surveillance) in patients with completely resected Stage III melanoma.[35] This trial provides a link for comparison to placebo through an indirect treatment comparison (ITC) and is discussed in Section B.2.9.

Table 3: Clinical effectiveness evidence

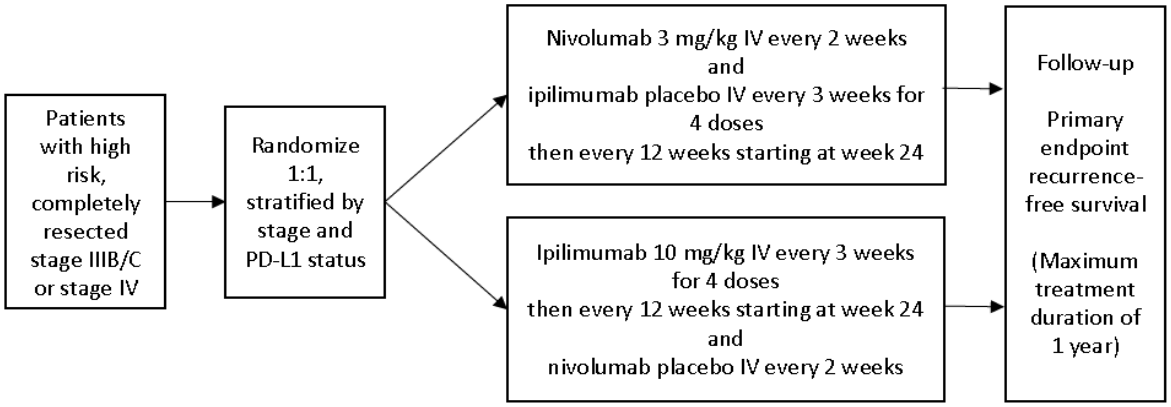
<table>
<tr><td>Study</td><td colspan="5">CheckMate 238 (Weber et al., 2017)[4]</td></tr>
<tr><td>Study design</td><td colspan="5">A manufacturer-sponsored, multinational, randomised, double-blind, active-controlled Phase III trial.</td></tr>
<tr><td>Population</td><td colspan="5">Patients aged ≥15 years of age who were undergoing complete resection of Stage IIIB, IIIC or IV melanoma[a]</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Nivolumab 3mg/kg Q2W[b]</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Ipilimumab 10mg/kg Q3W for four doses, then Q12W [b,c]</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>X</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>X</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">Pivotal trial supporting this indication.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• RFS
• DMFS
• Adverse effects of treatment
• Health-related quality of life using the EQ-5D, QLQ-C30 and WPAI:GH</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• RFS by PD-L1
• RFS and DMFS by BRAF mutation status</td></tr>
<tr><td colspan="6">Key: DMFS, distant metastases-free survival; PD-L1, programmed death receptor ligand-1; Q12W, every 12 weeks; Q2W, every 2 weeks; Q3W, every 3 weeks; QLQ-C30, quality of life questionnaire; RFS, recurrence-free survival; WPAI-GH, Work Productivity and Activity Impairment questionnaire: General Health.
Notes: [a], All enrolled patients were ≥18 years old; [b], 1 year maximum treatment duration; [c], this differs from the licensed dose of ipilimumab currently used in advanced or metastatic melanoma although this is the dose approved and licensed in the US for the treatment of adjuvant melanoma; Bold text represents outcomes that were incorporated into the model.</td></tr>
</table>

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Study design

CheckMate 238 is a randomised, double-blind, Phase III study that evaluates nivolumab compared to ipilimumab in patients with completely resected Stage IIIB, IIIC or IV melanoma.[4] CheckMate 238 is the pivotal trial for this indication and was the key trial used in the regulatory submission. The trial was conducted at 130 centres in 25 countries, including 9 sites in England and Wales. Patients were randomised in a 1:1 ratio to receive nivolumab or ipilimumab, with randomisation stratified according to disease stage and PD-L1 status. A study design schematic diagram is presented in Figure 2.

Figure 2: Study design schematic, CheckMate 238



Key: IV, intravenous; PD-L1, programmed death receptor ligand-1.
Source: Weber *et al.*, 2017[4]

To be eligible for inclusion into the study, patients had to be 15 years of age or older and have Stage IIIB, IIIC or IV melanoma, according to the 2009 classification of the American Joint Committee on Cancer (AJCC) 7th edition.[4] Despite this inclusion criteria, only patients aged 18 or over were enrolled into the trial, a reflection of the difficulties in paediatric trial recruitment; this is further discussed in Section B.2.13. Of note, the AJCC classification has recently been updated to the 8th edition[14]; a summary of changes is discussed in Section B.1.3, and both criteria are outlined in Appendix L.

The primary endpoint of the study is recurrence-free survival (RFS) assessed by investigator, defined as the time from randomisation until the date of the first recurrence (local, regional or distant metastasis), new primary melanoma, or death from any cause.[4] RFS is deemed the most relevant endpoint in the adjuvant setting, as the aim of treatment is to prevent progression of disease to the systemic setting. Furthermore, assessment by investigator is more clinically relevant and more closely resembles real world practice compared to independent assessment. Although overall survival (OS) is clinically meaningful, this endpoint requires extended follow-up and is confounded by subsequent treatments. As such, RFS was chosen as the primary endpoint for CheckMate 238 given the established correlation of RFS and OS with immunotherapy in adjuvant melanoma.[36] This is further discussed in Section B.2.13. Secondary endpoints included safety, RFS according to tumour PD-L1

expression, and HRQL. OS is a secondary endpoint, although this is not presented due to immaturity of follow-up at the time of database lock. Distant metastasis-free survival (DMFS) is an exploratory endpoint. All patients were to be assessed for recurrence every 12 weeks for the first 2 years after randomisation and every 6 months thereafter until 5 years had elapsed.

A summary of methodology is presented in Table 4.

Table 4: Summary of methodology, CheckMate 238

Trial name	**CheckMate 238**
Location	130 centres in 25 countries including Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Finland, France, Greece, Hungary, Ireland, Italy, Japan, Korea, the Netherlands, Norway, Poland, Romania, South Africa, Spain, Sweden, Switzerland, Taiwan, the UK and the US.
Trial design	A multinational, randomised, double-blind, active-controlled, Phase III trial. Patients were randomised in a 1:1 ratio through an IVRS using a permuted block design, with stratification by PD-L1 status (positive vs negative/indeterminate) and AJCC stage at screening (Stage IIIB/C vs Stage IV M1a-M1b vs Stage IV M1c).
Eligibility criteria for participants	Men and women aged ≥15 years were included if they met the following criteria: • Stage IIIB, IIIC or IV melanoma as per AJCC 7th edition (as detailed in Appendix L) • Histologically confirmed melanoma with metastases to regional lymph nodes or distant metastases that had been surgically resected • ECOG score of 0 or 1 • Complete regional lymphadenectomy or resection required within 12 weeks before randomisation • Disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomisation with complete set of radiographic images available before randomisation • PD-L1 expression classification • Prior CNS metastases must be without evidence of recurrence for at least 4 weeks after treatment. Patients must be off immunosuppressive doses of systemic steroids for at least 14 days prior and must have returned to neurological baseline post-operatively. • Prior surgery that requires general anaesthesia must be completed at least 4 weeks before study drug administration. • WBCs ≥2,000/µl, neutrophils ≥1,500/µl, platelets ≥100x10^3/µl, haemoglobin ≥9.0g/dl, serum creatinine ≤1.5xULN or creatinine

	clearance >40ml/minute, AST and ALT ≤3xULN, total bilirubin ≤1.5xULN • Negative pregnancy test in women of childbearing potential and women must not be breastfeeding • Agreement to follow instructions for methods of contraception • Signed written informed consent Patients were excluded from the study if they met any of the following criteria: • Ocular or uveal melanoma • Carcinomatosis meningitis • History of autoimmune disease • Previous non-melanoma cancer without complete remission for more than 3 years • Systemic use of glucocorticoids • Previous systemic therapy for melanoma • Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the patient to receive protocol therapy • Any positive test for hepatitis B or C virus • Known history of testing positive for HIV or AIDS • History of Grade ≥3 allergy to human monoclonal antibodies
Settings and locations where the data were collected	An independent DMC was set up to provide independent oversight of safety, efficacy and study conduct. The DMC reviewed RFS data at the planned interim analyses. Data were collected locally by fully trained investigators. Site monitoring and pre-specified data validation checks were regularly conducted to ensure data quality.
Trial drugs	Nivolumab 3mg/kg Q2W. Ipilimumab 10mg/kg Q3W for four doses then Q12W. Treatment was administered for 1 year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent.
Permitted and disallowed concomitant medication	The following medications were prohibited during the treatment and follow-up phases: • Immunosuppressive agents • Immunosuppressive doses of systemic corticosteroids • Any concurrent systemic anti-neoplastic therapy for the treatment of melanoma or a new malignancy Patients were permitted the use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). Physiological replacement doses of systemic corticosteroids were permitted even if >10mg daily prednisone. A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions was permitted. Intravitreal injections of VEGF inhibitors were permitted if used according to the approved ocular indication, such as macular degeneration.

Primary outcomes (including scoring methods and timings of assessments)	• RFS, defined as the time from randomisation until the date of the first recurrence (local, regional or distant metastasis), new primary melanoma, or death from any cause (whichever occurred first). Patients were assessed for recurrence every 12 weeks for the first 2 years after randomisation, and every 6 months thereafter until 5 years had elapsed. Assessments included a physical examination, CT and MRI scan.
Other outcomes used in the economic model/specified in the scope	• DMFS, determined based on the first date of distant metastasis provided by the investigator and was defined as the time between the date of randomisation and the date of first distant metastasis or death, whatever the cause.[a] • AEs according to the CTCAE v4.0. Immune-mediated AEs were determined on the basis of a prespecified list of terms from the MedDRA. • HRQL according to the EORTC QLQ-C30 and the EQ-5D. HRQL was assessed at baseline, Weeks 5, 7, 11, 17, 25, 37 and 49, and then at two follow-up visits.
Pre-planned subgroups	RFS and safety were analysed according to PD-L1 status (5% cut-off selected based on previously verified PD-L1 assay).

Key: AE, adverse event; AJCC, American Joint Committee on Cancer; ALT, alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; DMC, data monitoring committee; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; HRQL, health-related quality of life; IVRS, interactive voice response system; MedDRA, Medical Dictionary for Regulatory Activities; PD-L1, programmed death receptor ligand-1; Q12W, every 12 weeks; Q2W, every 2 weeks; Q3W, every 3 weeks; QLQ, quality of life questionnaire; RFS, recurrence-free survival; ULN, upper limit of normal; VEGF, vascular endothelial growth factor; WBC, white blood cell.
Notes: [a], In Stage III patients only.
Source: Weber *et al.*, 2017[4]; CheckMate 238 CSR[3]

Baseline characteristics

Baseline characteristics are presented in Table 5. Overall, demographic and disease characteristics were well balanced between the two treatment groups.[4] Patients had a median age of 55 years, and the majority of patients were white (95%) and male (58%). Most patients (47%) had Stage IIIC disease, while 34% of patients were diagnosed with Stage IIIB disease and 19% with Stage IV disease.[4] PD-L1 expression <5% was reported in 62% of patients, and 45% of patients were BRAF-wildtype.

Table 5: Baseline characteristics, all randomised patients, CheckMate 238

	Nivolumab (n=453)	Ipilimumab (n=453)
Male, n (%)	258 (57.0)	269 (59.4)
Median age (range):	56 (19-83)	54 (18-86)
Disease stage, n (%):		
IIIB	163 (36.0)	148 (32.7)
IIIC	204 (45.0)	218 (48.1)
IV	82 (18.1)	87 (19.2)
Other or NR	4 (1.0)	0
Type of lymph node involvement in Stage III, n (%):		
Microscopic	125/369 (33.9)	134/366 (36.6)
Macroscopic	219/369 (59.3)	214/366 (58.5)
NR	25/369 (6.8)	18/336 (4.9)
Tumour ulceration in Stage III, n (%):		
Yes	153/369 (41.5)	135/366 (36.9)
No	201/369 (54.5)	216/366 (59.0)
NR	15/369 (4.1)	15/366 (4.1)
Metastasis in Stage IV, n (%):		
M1a	50/82 (61.0)	51/87 (58.6)
M1b	12/82 (14.6)	15/87 (17.2)
M1c with brain metastases	[redacted]	[redacted]
M1c without brain metastases	[redacted]	[redacted]
PD-L1 expression, n (%):		
<5%	275 (60.7)	286 (63.1)
≥5%	152 (33.6)	154 (34.0)
NR	26 (5.7)	13 (2.9)
BRAF status, n (%):		
Mutation	187 (41.3)	194 (42.8)
No mutation	197 (43.5)	214 (47.2)
NR	69 (15.2)	45 (9.9)

Key: NR, not reported; PD-L1, programmed death receptor ligand-1.
Source: Weber *et al.*, 2017[4]; CheckMate 238 CSR[3]

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

The hypothesis and associated statistical analysis methods adopted in CheckMate 238 are presented in Table 6.

Statistical analysis plans (SAPs) were developed and approved prior to study initiation. The primary efficacy analyses were conducted on the intention-to-treat (ITT) population, defined as all randomised patients.[4] Safety analyses were conducted on all treated patients, which included all randomised patients who received at least one dose of study drug. Results presented within this submission are based on a clinical data cut-off of 15 May 2017 with a median follow-up of 19.5 months and a minimum follow-up of 18 months.[4] As requested by the European Medicines Agency (EMA), an updated database lock of 19 December 2017 was conducted, with a minimum follow-up of 24 months[15]; additional results for RFS and DMFS are presented based on this analysis. These data were provided after model development and are therefore not utilised in the economic analysis or indirect treatment comparison (ITC).

From 30 March to 30 November 2015, 1,264 patients were enrolled at 130 centres in 25 countries.[4] Of these, 358 patients were not randomised, most commonly due to no longer meeting study criteria (24.4%) and withdrawing consent (2.9%).[3] A total of 906 patients underwent randomisation with 453 patients in each arm.[4] In the nivolumab arm, 177 patients discontinued treatment; this was due to disease recurrence in 121 patients and study drug toxicity in 41 patients. In the ipilimumab arm, 331 patients discontinued treatment; this was due to disease recurrence in 101 patients and study drug toxicity in 208 patients.[4] Participant flow is presented as a Consolidated Standards Of Reporting Trials (CONSORT) flow diagram in Appendix D; further information on disease recurrence and adverse events (AEs) is presented in Sections B.2.6 and B.2.10, respectively.

Table 6: Summary of statistical analyses, CheckMate 238

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Treatment with nivolumab will improve RFS compared to ipilimumab in patients with Stage IIIB, IIIC or IV melanoma.	A stopping boundary was derived on the basis of the interim analysis with the use of a Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. The critical HR was 0.78 with an adjusted alpha level of 0.0244 (two-sided). Time-to-event distributions were estimated using KM techniques for RFS and DMFS. Median survival times along with 95% CIs were constructed based on a log-log transformed CI for the survivor function. Comparison between treatment groups was performed using a log-rank test stratified by disease stage and PD-L1 status at randomisation, at a two-sided alpha level of 0.0244 as indicated in the main text. Using a Cox proportional hazards model stratified by disease stage and PD-L1 status at randomisation, the HR for having an RFS event in the nivolumab group compared with the ipilimumab group and corresponding 97.56% CIs were computed.	A sample of 800 patients was planned for a final analysis of RFS that was time-driven (rather than event-driven) at a minimum of 36 months of follow-up for all patients. 507 events of RFS were initially anticipated, although this was revised to 450 for the final analysis. 450 events would provide 85% power to detect a HR for disease recurrence or death of 0.75 (under the 0.83 cut-off for significance) with an overall two-sided type I error rate of 0.05. An interim analysis took place at 18 months, where 360 (80%) events had taken place.	Where recurrence or distant metastases do not occur, RFS and DMFS will be censored on the date of last evaluable disease assessment. Patients who receive subsequent anti-cancer therapy or report second non-melanoma primary cancer without prior recurrence will be censored on the date of last evaluable disease assessment. Where no post-randomisation disease assessment is recorded, RFS was censored on the day of randomisation.

Key: CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; KM, Kaplan–Meier; RFS, recurrence-free survival.
Source: Weber *et al.*, 2017[4]; CheckMate 238 CSR.[3]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

A summary of quality assessment for CheckMate 238 is presented in Table 7, with full details in Appendix D.

The study is of high quality as it was conducted in accordance with Good Clinical Practice (GCP) guidelines by qualified investigators using a single protocol to promote consistency across sites and with measures taken to minimise bias. Baseline demographics and disease characteristics between treatment arms were well balanced, with no key differences between groups. The most common reason for study withdrawal was disease progression in the nivolumab arm, which is accounted for within the efficacy assessments, and toxicity within the ipilimumab arm; patient withdrawals for other reasons were accounted for with standard censoring methods.

Disease evaluation and safety evaluation methods are consistent with other studies of melanoma therapy, and outcome assessments were all conducted in accordance with trial-validated methodology. It should be noted that, although clinically meaningful, OS requires extended follow-up and is confounded by subsequent lines of treatment; therefore, OS was not a specified primary outcome in the trial. However, RFS is a well-accepted efficacy measure and surrogate endpoint in adjuvant therapy.[37] This is further discussed in Section B.2.13. In addition, alongside clinical efficacy and safety outcomes, HRQL outcomes were also measured, as requested by reimbursement agencies.

Patients with Stage IIIB, IIIC and IV melanoma were eligible for inclusion in the study, a population of direct relevance to the decision problem and capturing most patients with involvement of lymph nodes or metastatic disease. Although the trial population did not include Stage IIIA patients who also have involvement of lymph nodes, results are expected to be generalisable to these patients, due to similarities in the underlying biology of the disease. Furthermore, changes to the latest, 8th edition of the AJCC criteria mean that some patients previously classified as Stage IIIA would now be classified as Stage IIIB or IIIC; similarly, some patients classified

as Stage IIIB as per the 7th edition, would now be reclassified as Stage IIIA in the 8th edition. In addition, although the comparator arm of the trial was not routine surveillance, the superior results of nivolumab versus ipilimumab can reasonably be expected to be of an even greater magnitude when compared to the current standard of care. Discussions of generalisability of the trial are presented in Section B.2.13.

Table 7: Quality assessment of CheckMate 238

CheckMate 238	
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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
Source: Weber *et al.*, 2017[4]	

B.2.6. Clinical effectiveness results of the relevant trials

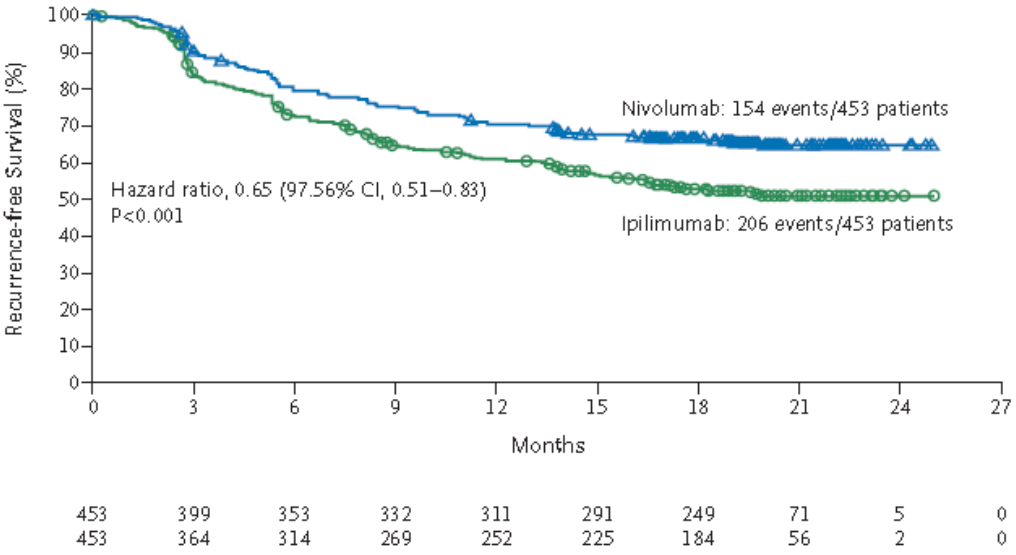
Recurrence-free survival (primary outcome)

18-month follow-up (Data-cut: 15 May 2017)

After 18-months follow-up, nivolumab demonstrated a statistically significant and clinically relevant improvement in RFS compared to ipilimumab, as presented in Figure 3, resulting in a hazard ratio (HR) of 0.65 (97.56% confidence interval [CI]: 0.51, 0.83; p<0.001) in patients with completely resected Stage IIIB, IIIC or Stage IV melanoma.[4]

Median RFS was not reached in either treatment group.[4] At 12 months, the RFS rate was 70.5% (95% CI: 66.1, 74.5) in the nivolumab group and 60.8% (95% CI: 56.0, 65.2) in the ipilimumab group; at 18 months, the corresponding rates were 66.4% (95% CI: 61.8, 70.6) and 52.7% (95% CI: 47.8, 57.4), respectively.

Figure 3: KM curve for RFS, ITT population, CheckMate 238, 18-month follow-up



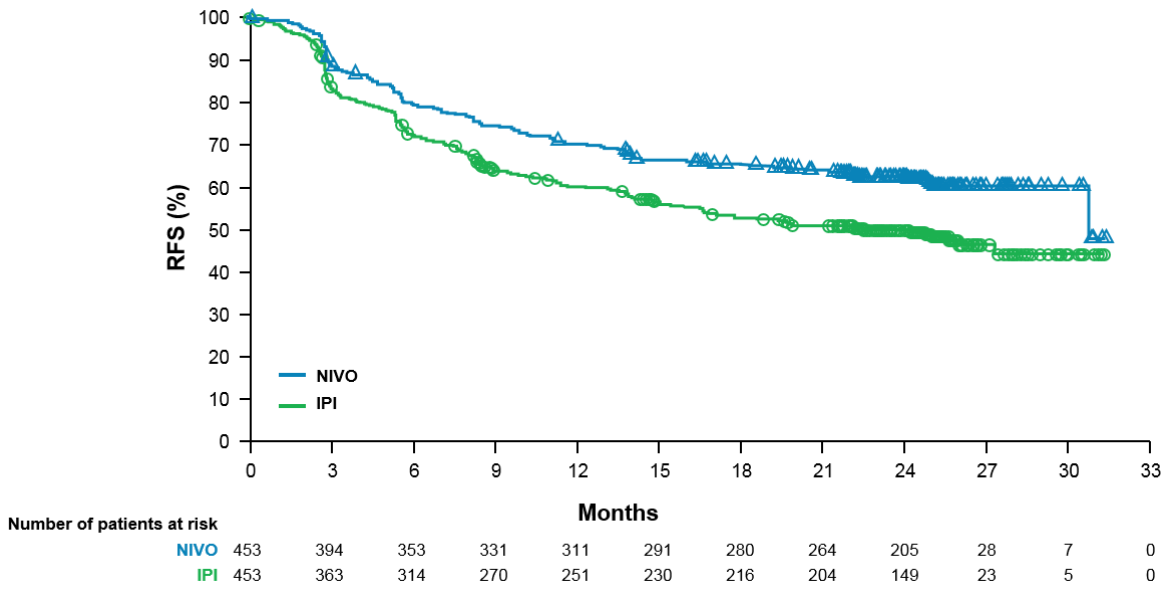
Key: CI, confidence interval; ITT, intention-to-treat; KM, Kaplan–Meier; RFS, recurrence-free survival.
Source: Weber *et al.*, 2017.[4]

24-month follow-up (Data-cut: 19 December 2017)

Consistent with the earlier data-cut, at 24 months, nivolumab demonstrated a statistically significant and clinically relevant improvement in RFS compared to ipilimumab, as presented in Figure 4, resulting in a HR of 0.66 (95% CI: 0.54, 0.81; p<0.0001) in patients with completely resected Stage IIIB, IIIC or Stage IV melanoma.[2] Recurrence or death was reported by investigators in 171 (37.7%) and 221 (48.8%) of patients treated with nivolumab and ipilimumab, respectively.

Median RFS was 30.8 months (95% CI: 30.8, NA) in the nivolumab arm, and 24.1 months (95% CI: 16.6, NA) in the ipilimumab arm.[2] Although median RFS has now been reached, it should be noted that the data are still immature, with heavy censoring present, hence the drop in the tail of the nivolumab curve (seen in Figure 4). The 12-, 18- and 24-month RFS rate for the nivolumab group was 70.4% (95% [redacted] 65.8% (95% CI: [redacted] 62.6% (95% CI: [redacted], respectively.[2, 15] For ipilimumab, the respective rates were 60.0% (95% CI [redacted] 53.0% (95% CI: [redacted] 50.2% (95% CI: [redacted].[2, 15]

Figure 4: KM curve for RFS, ITT population, CheckMate 238, 24-month follow-up



Key: ITT, intention-to-treat; KM, Kaplan–Meier; RFS, recurrence-free survival.
Source: Weber *et al.,* 2018[2]

It should be acknowledged that these results for both data-cuts were seen versus an active comparator (i.e. ipilimumab at the increased dose of 10mg/kg); therefore, the magnitude of clinical benefit is expected to be even greater when compared to placebo (i.e. routine surveillance, the comparator of interest to this submission). In addition, the two curves do not converge at the point that treatment finishes (12 months) demonstrating that no reduction in treatment effect is seen after this point.

Subgroup analyses of RFS is presented in B.2.7.

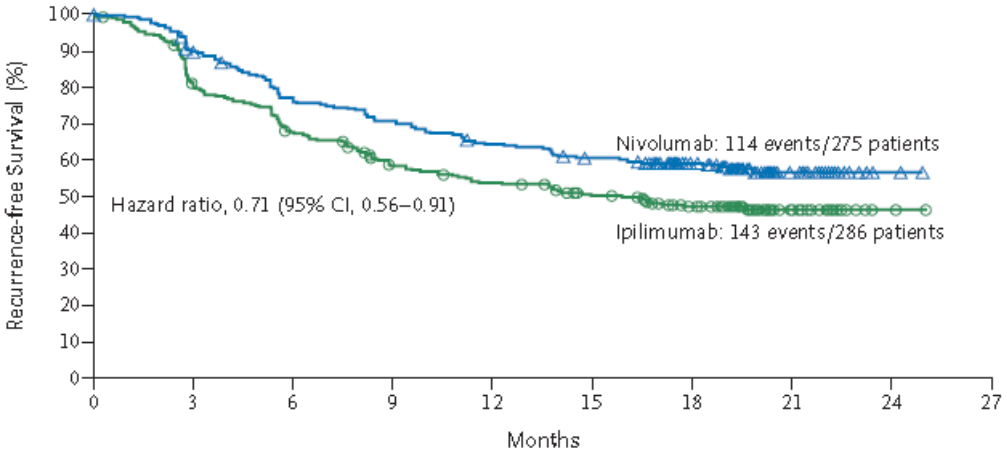
RFS by PD-L1 expression level (secondary outcome)

Subgroup analyses of RFS according to tumour PD-L1 expression was a pre-specified secondary endpoint. Consistent with the primary analysis, HRs favoured nivolumab compared to ipilimumab, showing that benefit with nivolumab is observed irrespective of PD-L1 status.

18-month follow-up (Data-cut: 15 May 2017)

At 18-months, among the patients with <5% PD-L1 expression, the 12-month RFS rate was 64.3% (95% CI: 58.3, 69.7) in the nivolumab group and 53.7% (95% CI: 47.6. 59.4) in the ipilimumab group, as presented in Figure 5.[4] In patients with ≥5% PD-L1 expression, the 12-month RFS rate was 81.9% (95% CI: 74.7, 87.2) in the nivolumab group and 73.8% (95% CI: 65.9, 80.1) in the ipilimumab group, as presented in Figure 6.

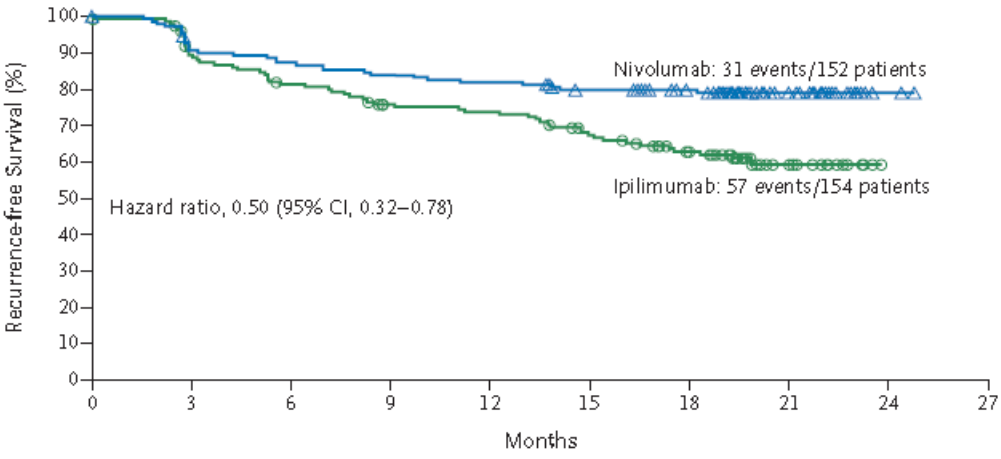
Figure 5: KM curve for RFS, <5% PD-L1 expression, CheckMate 238, 18-month follow-up



No. at Risk										
Nivolumab	275	242	204	189	171	159	129	41	3	0
Ipilimumab	286	219	184	153	139	124	100	31	2	0

Key: CI, confidence interval; KM, Kaplan–Meier; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: Weber *et al.*, 2017.[4]

Figure 6: KM curve for RFS, ≥5% PD-L1 expression, CheckMate 238, 18-month follow-up



No. at Risk										
Nivolumab	152	135	130	125	122	114	105	26	2	0
Ipilimumab	154	133	120	108	105	93	78	21	0	0

Key: CI, confidence interval; KM, Kaplan–Meier; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: Weber *et al.*, 2017.[4]

At [redacted] pre-defined expression [redacted] ≥5% and [redacted], baseline PD-L1 expression was associated with a [redacted] nivolumab compared to ipilimumab, as presented in Figure 7. As such, nivolumab demonstrates an [redacted].

Figure 7: Forest plot of RFS by PD-L1 expression level, CheckMate 238, 18-month follow-up

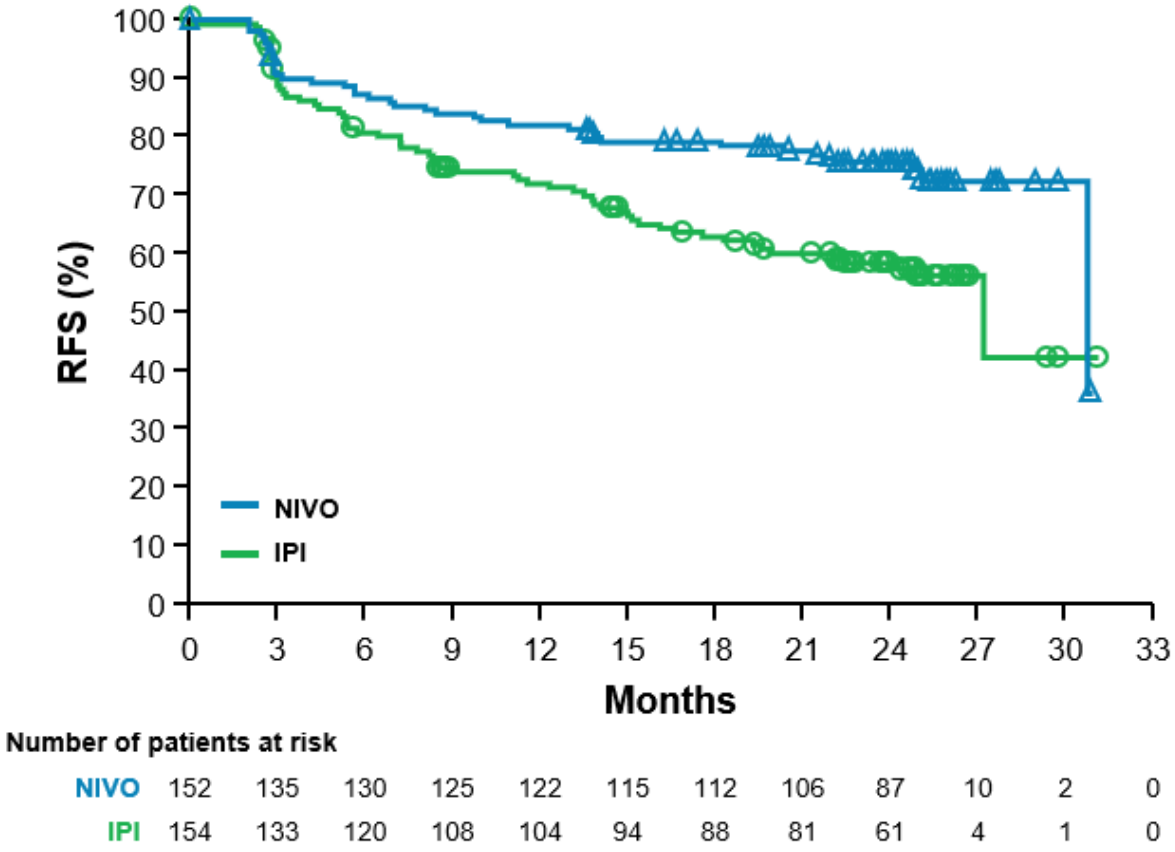
Key: CI, confidence interval; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: BMS Data on File, 2017[36]

24-month follow-up (Data-cut: 19 December 2017)

After a minimum of 24 months follow-up among the patients with ≥5% PD-L1 expression, median RFS was 30.8 months (95% CI: 30.8, NA) in the nivolumab arm and 27.2 months (95% CI: 22.4, NA) in the ipilimumab arm, resulting in a HR of 0.54 (95% CI: 0.36, 0.81), as presented in Figure 8.[2] As previously noted, despite median RFS being reached, these data are still immature, with heavy censoring present, resulting in the drop in the tail of the nivolumab curve.

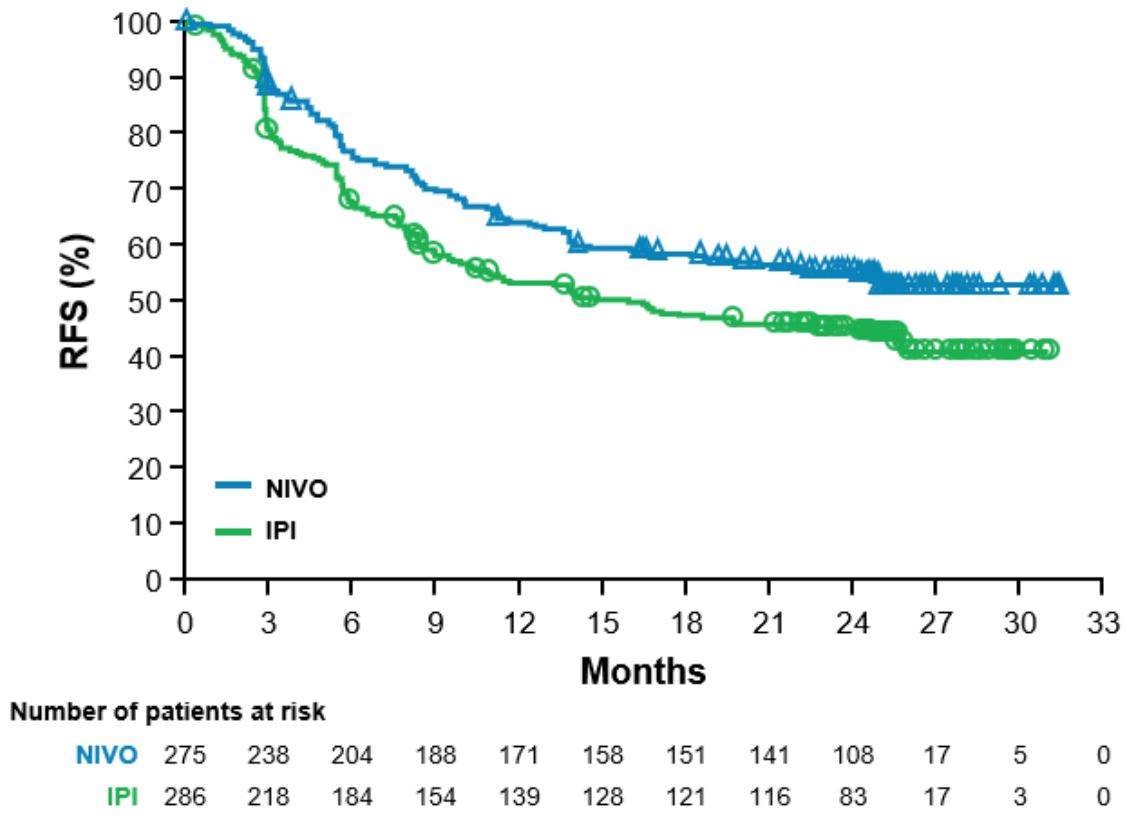
In patients with <5% PD-L1 expression, the median RFS was not reached (95% CI: 21.7, NA) in the nivolumab arm but was 15.9 months (95% CI: 10.3, 25.5) in the ipilimumab arm, resulting in a HR of 0.73 (95% CI: 0.57, 0.92), as presented in Figure 9.[2]

Figure 8: KM curve for RFS, ≥5% PD-L1 expression, CheckMate 238, 24-month follow-up



Key: KM, Kaplan–Meier; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: Weber *et al.,* 2018[2]

Figure 9: KM curve for RFS, <5% PD-L1 expression, CheckMate 238, 24-month follow-up



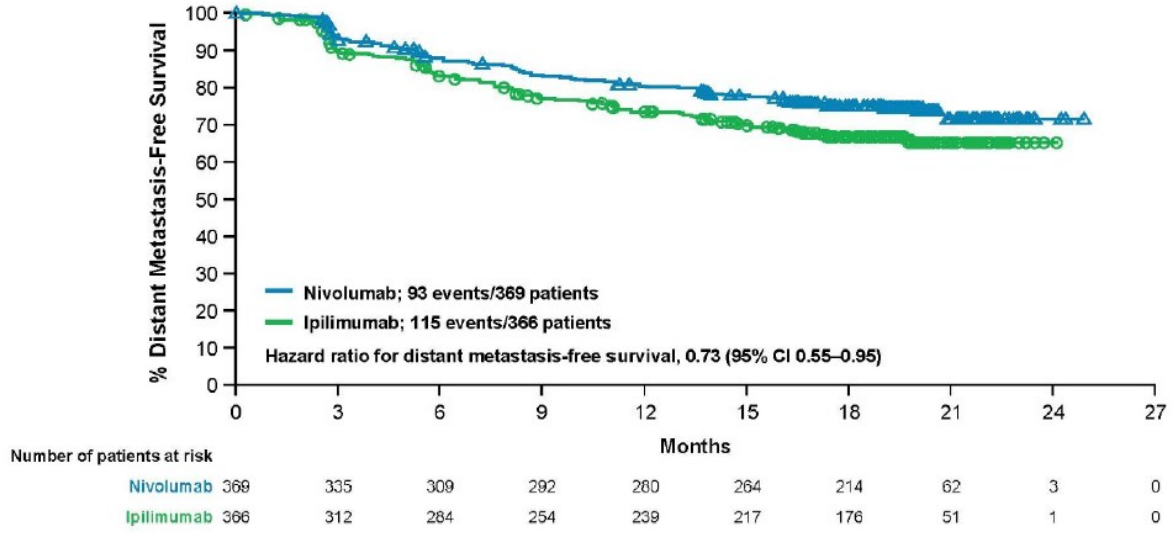
Key: KM, Kaplan–Meier; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: Weber *et al.,* 2018[2]

Distant metastasis-free survival (exploratory outcome)

18-month follow-up (Data-cut: 15 May 2017)

The median DMFS was not reached in either treatment group, although longer DMFS was observed in the nivolumab group than the ipilimumab group (HR: 0.73; 95% CI: 0.55, 0.95), as presented in Figure 10.[4] DMFS rates were [redacted] in the nivolumab group than in the ipilimumab group at 6 months ([redacted]), 12 months ([redacted]) and 18 months ([redacted]).[3]

Figure 10: KM curve for DMFS, ITT population, CheckMate 238, 18-month follow-up

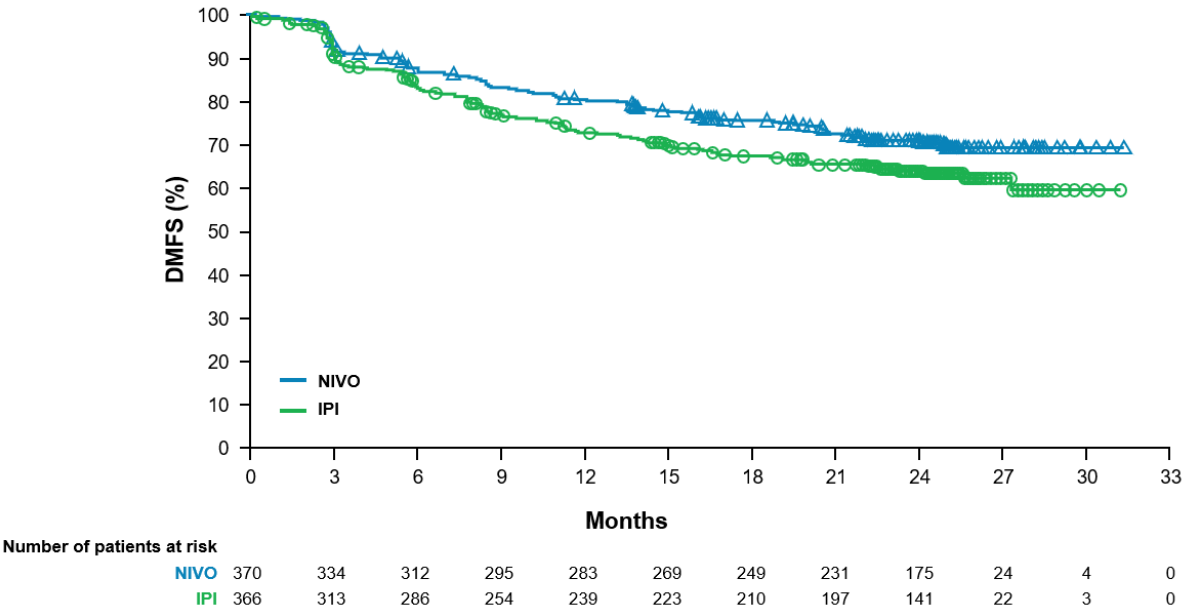


Key: CI, confidence interval; DMFS, distant metastasis-free survival; ITT, intention-to-treat; KM, Kaplan–Meier.
Source: Weber *et al.*, 2017.[4]

24-month follow-up (Data-cut: 19 December 2017)

After a minimum of 24 months follow-up, the median DMFS was not reached in either treatment group, although longer DMFS was observed in the nivolumab group than the ipilimumab group (HR: 0.76; 95% CI: 0.59, 0.98), as presented in Figure 11.[2] DMFS rates were higher in the nivolumab group than in the ipilimumab group at 12 months (80.1% versus 72.7%, respectively), 18 months (75.2% versus 67.1%, respectively) and 24 months (70.5% versus 63.7%, respectively).

Figure 11: KM curve for DMFS, ITT population, CheckMate 238, 24-month follow-up



Key: DMFS, distant metastasis-free survival; ITT, intent-to-treat; KM, Kaplan–Meier.
Source: Weber *et al.,* 2018[2]

Health-related quality of life (secondary outcome)

A summary of the HRQL tools used in the CheckMate 238 study is presented in Appendix M. HRQL results are reported with 18-months follow-up (data-cut: 15 May 2017).

Questionnaire completion rates for the disease specific European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) were [redacted]% and [redacted]% at baseline in the nivolumab and ipilimumab groups, respectively.[3] At all assessments through Week 49, completion rates met or exceeded [redacted]% and [redacted]%, respectively (when calculated as a percentage of patients on study or in follow-up). Completion rates for Follow-up Visits 1 (30 days after last dose) and 2 (approximately 84 days after 1st follow up) for the nivolumab and ipilimumab groups met or exceeded [redacted]% and [redacted]%, respectively.

Similarly, in the general health status questionnaire, EQ-5D®, baseline completion rates were [redacted]% and [redacted]% in the nivolumab and ipilimumab groups, respectively.[3] At all assessments through Week 49, completion rates met or exceeded [redacted]% and

[redacted]%, respectively. Finally, completion rates for the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) at baseline were [redacted]% and [redacted]% in the nivolumab and ipilimumab groups, respectively. Through 49 weeks, completion rates met or exceeded [redacted]% and [redacted]% in each group, respectively; at Follow-up Visits 1 and 2, completion rates met or exceeded [redacted]% and [redacted]%, respectively.

HRQL scores were maintained after treatment in both groups with respect to the score on the EORTC QLQ-C30 Global Health Status or on any of the individual scales, as well as to scores on the EQ-5D utility index and the EQ-5D visual analogue scale (VAS).[4] With respect to the WPAI:GH, mean summary scale scores for all patients were comparable between treatment groups at baseline; no clinically meaningful deterioration or improvement was observed at any time point for either treatment group for any scale.

It should be noted that prior to treatment patients are otherwise clinically well and disease-free; therefore, maintenance of quality of life (QoL) after receiving active treatment should be viewed positively. Furthermore, these data should be viewed in the context of an active comparator arm. Compared to routine surveillance, which has no clinical benefit, the use of an effective treatment that extends the disease-free period and is tolerable can be expected to positively impact patients' HRQL.

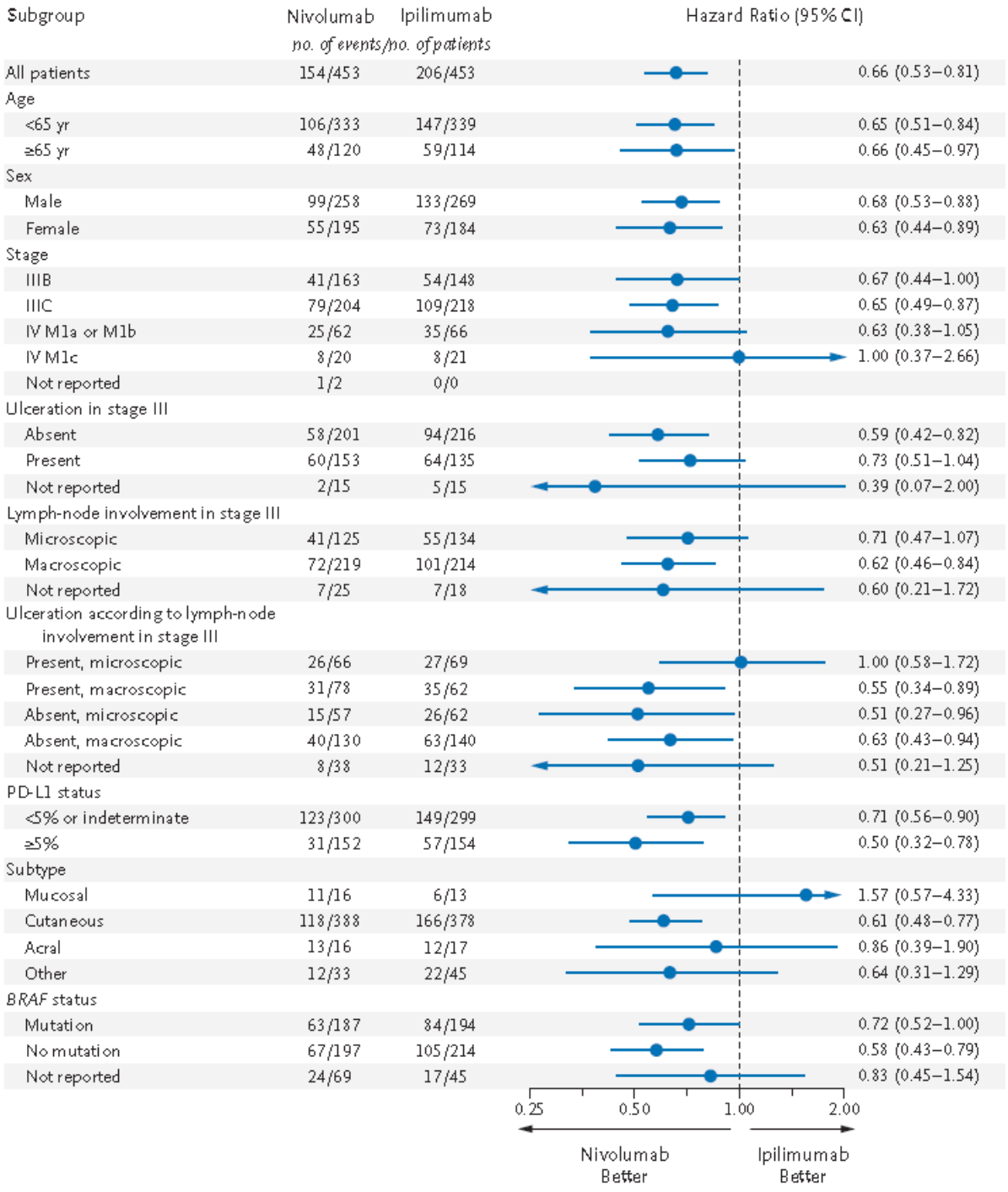
B.2.7. Subgroup analysis

Results of RFS by PD-L1 status (a secondary outcome in the CheckMate 238 study) have previously been presented in Section B.2.6 for both the 18- and 24-month follow-up.

Additional pre-specified subgroup analyses of RFS, conducted after a minimum of 18-months follow-up (data-cut: 15 May 2017), were consistent with the primary analysis. Nivolumab was superior to ipilimumab suggesting a consistent clinical benefit for nivolumab-treated patients in all pre-defined subgroups, with the exception of patients with mucosal melanoma, Stage IV M1c and ulceration present plus microscopic lymph node involvement. All had a wide CI that encompassed 1.0, however, it should be noted that his could be due to the small population sizes

informing these analyses.[4] A forest plot of subgroup analyses is presented in Figure 12.

Figure 12: Forest plot of RFS subgroup analyses, ITT population, CheckMate 238, 18-month follow-up



Key: CI, confidence interval; ITT, intention-to-treat; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: Weber *et al.*, 2017[4]

Subgroup analyses of DMFS were also consistent with the primary analysis. After 18-months follow-up, the unstratified HRs for DMFS favoured nivolumab over ipilimumab in pre-defined subgroups among all randomised patients with Stage III disease, with the exception of patients with mucosal melanoma [redacted] and patients from Eastern Europe [redacted].[3] In addition, the analyses of subgroups for ulceration present plus microscopic lymph node involvement [redacted].

After [redacted] follow-up, Asian patients [redacted] patients with ulceration present plus microscopic lymph node involvement [redacted] patients with mucosal melanoma [redacted] patients with acral melanoma [redacted] patients from Eastern Europe [redacted] and patients from Asia [redacted].[15] [redacted].

B.2.8. Meta-analysis

Meta-analysis has not been performed because a single RCT provides evidence supporting the use of nivolumab for the adjuvant treatment of patients with completely resected, Stage III and IV melanoma.

B.2.9. Indirect and mixed treatment comparisons

No studies were identified through the SLR (described in Appendix D) that investigated nivolumab in comparison to routine surveillance in patients with completely resected Stage III and IV melanoma (see Section B.2.2). Therefore, the CA184-029 study has been used to create an indirect treatment comparison (ITC)

between nivolumab, from the CheckMate 238 study, and routine surveillance for completely resected Stage III and IV melanoma both by using patient-level data (PLD) to create regression models and the Bucher method.

The CheckMate 238 study has been described in detail in Section B.2.3. The CA184-029 study methodology and results are summarised below, with further details provided in Table 5 of Appendix D.

For the statistical analysis of the 238 and 029 trials, analyses were performed on the 18-month follow-up data (data cut-off 15th May 2017) for CheckMate 238 and using the 13th May 2016 cut-off for CA184-029.

CA184-029

CA184-029 is a multinational, randomised, double-blind, Phase III study of adjuvant ipilimumab in high-risk patients with Stage III cutaneous melanoma who have undergone a complete regional lymph node dissection.[25] Eligible patients were at least 18 years of age and had histologically confirmed melanoma metastatic to lymph nodes only. Patients had to have either Stage IIIA, IIIB or IIIC melanoma, according to the AJCC 6th edition, with no in-transit metastasis. Of note, there were no differences between the 6th and 7th editions (as used in the CheckMate 238 study); this is discussed in further detail in the 'Covariate adjustment' section (Page 61). The size of metastases within nodes was not available in the trial data, and therefore, no staging adjustments were made between the two trials.

Patients were randomly assigned to receive either ipilimumab 10mg/kg or placebo every 3 weeks for four doses (Q3W), then every 3 months up to a maximum of 3 years or until disease recurrence, unacceptable toxicity, major protocol violation or treatment refusal.[25] Randomisation was stratified by disease stage (Stage IIIA versus IIIB versus IIIC with 1–3 positive nodes versus IIIC with ≥4 positive nodes) and regions (North America, European countries and Australia). The primary endpoint was RFS, defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis) or death from any cause, whichever occurred first, with assessments conducted by an independent review committee. Secondary endpoints included DMFS, OS, safety and HRQL. Results are presented after a median follow-up of 5.3 years.

Between 10 July 2008 and 1 August 2011, 951 patients were randomly assigned: 475 in the ipilimumab group and 476 in the placebo group.[25] Patient and disease characteristics are presented in Table 8. Overall, 186 (20%) patients had Stage IIIA, 420 (44%) had Stage IIIB, and 345 (36%) had Stage IIIC disease; 400 (42%) patients had an ulcerated primary, and 548 (58%) had macroscopic lymph node involvement.

Table 8: Baseline characteristics, CA184-029

	Ipilimumab (n=475)	Placebo (n=476)
Male, n (%)	296 (62)	293 (62)
Age, median (range):	51 (20–84)	52 (18–78)
Disease stage[a], n (%):		
Stage IIIA	98 (21)	98 (21)
Stage IIIB	182 (38)	182 (38)
Stage IIIC (1–3 LN+)	122 (26)	121 (25)
Stage IIIC (≥4 LN+)	73 (15)	75 (16)
AJCC 2002[b], n (%):		
Stage IIIA	98 (21)	88 (18)
Stage IIIB	213 (45)	207 (43)
Stage IIIC (1-3 LN+)	69 (15)	83 (17)
Stage IIIC (≥4 LN+)	95 (20)	98 (21)
Lymph node involvement, n (%):		
Microscopic	210 (44)	193 (41)
Macroscopic	265 (56)	283 (59)
Number of positive lymph nodes, n (%):		
1	217 (46)	220 (46)
2–3	163 (34)	158 (33)
≥4	95 (20)	98 (21)
Ulceration, n (%)		
No	257 (54)	244 (51)
Yes	197 (41)	203 (43)
Unknown	21 (4)	29 (6)

Key: AJCC, American Joint Committee on Cancer; EORTC, European Organisation for Research and Treatment of Cancer; LN, lymph node.
Notes: [a], As provided at randomisation; [b], As indicated on case report forms.
Source: Eggermont *et al.*, 2015.[25]

Patient characteristics between the CA184-029 and CheckMate 238 studies were well balanced, although there are some differences between trials, most notably, between the staging of patients. Covariate adjustments were therefore considered in

later analyses for all characteristics that influenced the relative treatment effect (effect modifiers) or absolute survival (prognostic factors).

In addition, the primary definition of RFS differed between the two studies, and thus, the pre-existing RFS definition, which most closely matched CheckMate 238, was chosen for analysis (this is discussed further in the parametric survival modelling section).

Finally, the permitted duration of ipilimumab treatment between the two studies differs, although in actuality, the number of doses received is similar (discussed further on Page 45. Handling of these differences is discussed in further detail within the methods of the parametric survival modelling ITC.

A summary table of results is presented in Table 9.

Table 9: Summary of efficacy results, ITT population, CA184-029

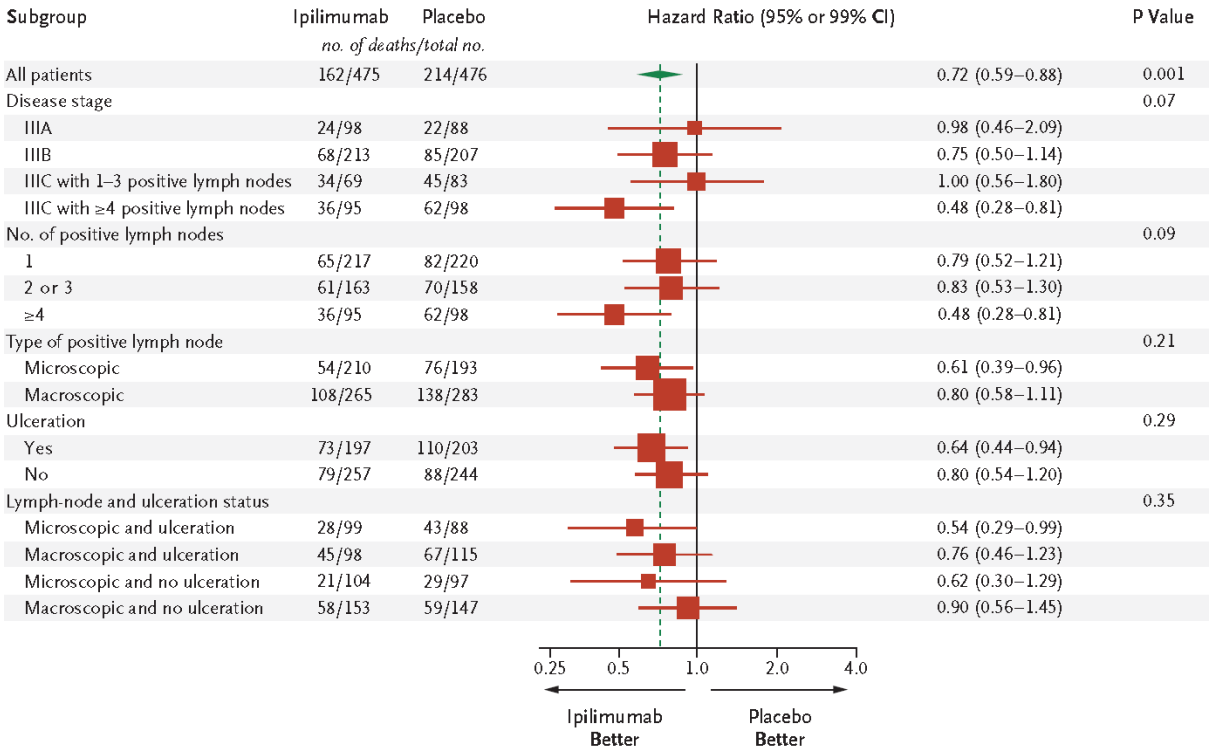
	Ipilimumab (n=475)	Placebo (n=476)
RFS		
Events, n (%)	264 (55.6)	323 (67.9)
Median months (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)
5-year RFS rate (95% CI)	40.8 (36.0, 45.6)	30.3 (26.0, 34.6)
HR (95% CI)	0.76 (0.64, 0.89)	
p-value	<0.001	
OS		
Events, n (%)	162 (34.1)	214 (45.0)
Median months (95% CI)	Not reached	Not reached
5-year OS rate (95% CI)	65.4 (60.8, 69.6)	54.4 (49.7, 58.9)
HR (95% CI)	0.72 (0.58, 0.88)	
p-value	0.001	
DMFS		
Events, n (%)	227 (47.8)	279 (58.6)
Median months (95% CI)	48.3 (35.5, 71.6)	27.5 (21.9, 34.8)
5-year DMFS rate (95% CI)	48.3 (43.4, 53.0)	38.9 (34.3, 43.5)
HR (95% CI)	0.76 (0.64, 0.92)	
p-value	0.001	

Key: CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; RFS, recurrence-free survival.
Source: Eggermont *et al.*, 2016.[35]

After a median follow-up of 5.3 years, the rate of RFS was 41% in the ipilimumab group compared with 30% in the placebo group (HR: 0.76; 95% CI: 0.64, 0.89; p<0.001).[35] OS after disease recurrence was similar in the two trial groups (HR for ipilimumab versus placebo: 0.89), which suggests that the difference in RFS would persist in terms of OS.

Median OS was not reached in either treatment group, although the 5-year OS rate was 65% in the ipilimumab group compared with 54% in the placebo group, resulting in a HR of 0.72 (95% CI: 0.58, 0.88; p=0.001).[35] The improved OS with ipilimumab compared to the placebo group was consistent across subgroups, as presented in Figure 13. Finally, DMFS was 48 months in the ipilimumab group compared to 28 months in the placebo group, with a HR of 0.76 (95% CI: 0.64, 0.92; p=0.002).

Figure 13: Forest plot of OS in subgroups, CA184-029



Key: CI, confidence interval; OS, overall survival.
Source: Eggermont et al. 2016[35]

Compliance to HRQL assessments was good, with 94% of patients completing the questionnaires at baseline.[38] Compliance rates slowly decreased over time with the lowest reported at Week 108 (55% and 47% for the placebo and ipilimumab groups,

respectively), and tended to be higher in the placebo arm throughout. Global health scale scores differed most at Week 7 (77 versus 72) and Week 10 (77 versus 70), with lower scores in the ipilimumab arm. Differences between treatment arms in diarrhoea (8 versus 18) and insomnia (15 versus 26) were beyond 10 points at Week 10. Patient mean global health scores during and after induction were statistically ($p<0.001$) but not clinically relevant between arms.

A summary of AEs is presented in Table 10.

Table 10: Summary of adverse events, safety population, CA184-029

	Ipilimumab (n=471)	Placebo (n=474)
Any AE, n (%)	465 (98.7)	432 (91.1)
Grade 3–4	255 (54.1)	124 (26.2)
Any SAE, n (%)	[redacted]	[redacted]
Grade 3–4	[redacted]	[redacted]
Drug-related AE, n (%)	[redacted]	[redacted]
Grade 3–4	[redacted]	[redacted]
Drug-related SAE, n (%)	[redacted]	[redacted]
Grade 3–4	[redacted]	[redacted]
Discontinuations due to AEs, n (%)	251 (53.3)	22 (4.6)
Grade 3–4[a]	[redacted]	[redacted]
Discontinuations due to drug-related AEs, n (%)	240 (51.0)	[redacted]
Grade 3–4[a]	[redacted]	[redacted]
Treatment-related deaths, n (%)	5 (1.1)	0

Key: AE, adverse event; SAE, serious adverse event.
Notes: [a], On-study.
Source: Eggermont et al. 2016[35]; CA184-029 CSR[39]

Further discussion of safety outcomes is presented in Appendix D.

In the ipilimumab group, a median of four doses were received by patients (range: 3–8), and a median of eight doses were received by patients in the placebo arm (range: 4–16).[35]

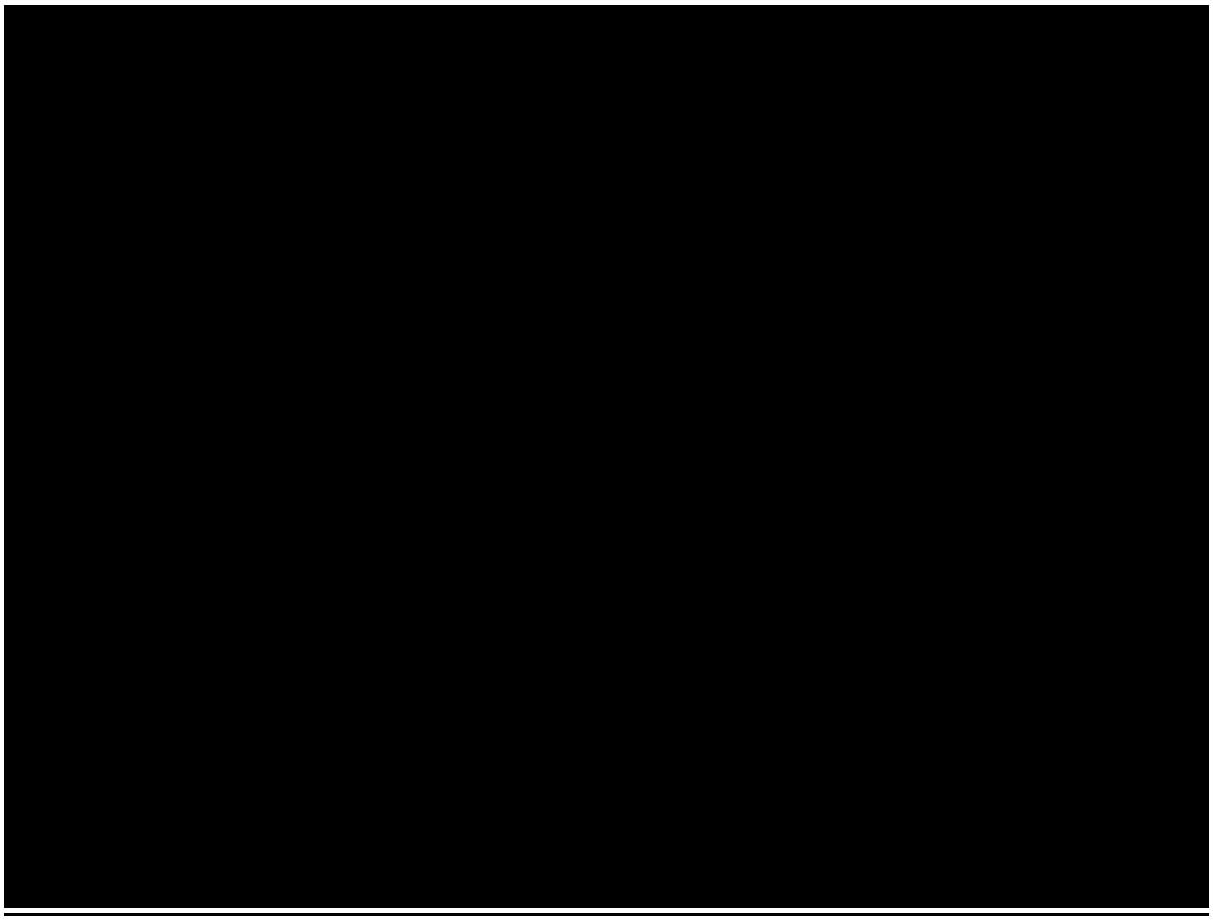
The ipilimumab arms between both trials had the same median doses, and only a small proportion of patients ([redacted]%) in the CA184-029 trial had ipilimumab treatment

beyond 1 year. Additionally, Figure 14 and Figure 15 show the comparison of Stage IIIB and IIIC, respectively, between ipilimumab arms in both trials. This indicates that RFS between patients who received ipilimumab within the trials is similar (95% confidence intervals overlap throughout) with no obvious change in the difference between the trials at the point where treatment is stopped in the CheckMate 238 trial (12 weeks), therefore, it is appropriate to consider ipilimumab as a common comparator between both trials for the ITC.

Figure 14: Recurrence-free survival in Stage IIIB patients who received ipilimumab by trial

Key: Ipi, ipilimumab.

Figure 15: Recurrence-free survival in Stage IIIC patients who received ipilimumab by trial



Key: Ipi, ipilimumab.

Indirect treatment comparison – RFS

RFS is the only survival outcome reported across both studies with which it is possible to inform an ITC between nivolumab and placebo to inform the economic model. To form the ITC between nivolumab, two approaches were used:

- PLD meta-regression using parametric survival models (this was possible as BMS led both studies)
- Bucher adjusted indirect comparison

The PLD meta-regression was performed as it utilises PLD from both studies to provide the "gold standard" in population adjustment between studies. This method represents the most robust estimate of the ITC between nivolumab and placebo.[40]

The Bucher indirect comparison was performed to validate the more robust PLD analysis and to provide more easily communicated results in the form of HRs.
A scenario is also included in the model which uses parametric curves fit directly to the CheckMate 238 trial (Appendix D) and uses the Bucher ITC HR to estimate the RFS for routine surveillance.

Patient level indirect treatment comparison and extrapolation

Endpoints included in the analysis

At the present time, OS data in CheckMate 238 was not available and therefore, RFS was the only survival endpoint required for the economic model where an ITC could be formed. However, given that OS data with extensive follow up were available for CA184-029, it was possible to use OS and post-local/regional recurrence survival data from CA184-029 to support the economic model.

To extrapolate RFS within the ITC and OS and post-local/regional recurrence survival within CA184-029, parametric survival models were used. The procedure used for curve fitting and selection and covariates used for adjustment were consistent across all endpoints, and followed NICE Decision Support Unit (DSU) technical support document (TSD) 14.[41] Note, results for post-local/regional recurrence survival are presented in Appendix D.

Types of curves fitted

Parametric survival modelling was performed in R using the 'survival' and 'flexsurv' packages. Survival models for the following parametric distributions were estimated (the assumption for non-stratified models for each distribution is presented in brackets), as per NICE DSU TSD 14[41]:

- Exponential (assumes proportional hazards [PH])
- Weibull (assumes PH)
- Log-normal (assumes accelerated failure time [AFT])
- Log-logistic (assumes AFT)
- Gompertz (assumes PH)
- Generalised gamma (assumes AFT)

Decision regarding model stratification for RFS

For non-stratified models, the data is pooled and the treatment effect is only applied to one parameter for each of the given distributions; as a result, non-stratified models assume either PH or AFT. PH assumes that for non-stratified models, the treatment effect multiplies the hazard by a constant value, whereas AFT assumes that for non-stratified models the treatment effect multiplies the survival of the reference treatment by a constant value. To determine whether it is appropriate to fit non-stratified models, the AFT and PH assumptions were checked.

The PH assumption in each trial was checked using a log-cumulative hazard plot where parallel lines indicate that the PH assumption is reasonable. Figure 16 and Figure 17 display the log cumulative hazard plot for RFS for the 238 and 029 trials, respectively. In each plot, it is observed that the log cumulative hazard plots do not cross and appear to be reasonably parallel. It should be noted in both plots that the curves converge before separating at 12 weeks, which is due to the timing of the first RFS assessment date. The pronounced ‘kink’ at 12 weeks is most likely protocol driven given that the first planned scan was at 12 weeks, and therefore, the PH assumption does not seem unreasonable. It is likely that if RFS assessments were more frequent, the ‘kink’ at Week 12 would not be observed.

The AFT assumption was checked using quantile-quantile (QQ)-plots, where a straight line indicates the AFT assumption is reasonable, as shown in Figure 18 and Figure 19 for the 238 and 029 trials, respectively.

Figure 16: 238 Recurrence-free survival log-cumulative hazard plot

Key: Ipi, ipilimumab; Nivo, nivolumab.
Notes: Dashed line indicates first assessment time (12 weeks).

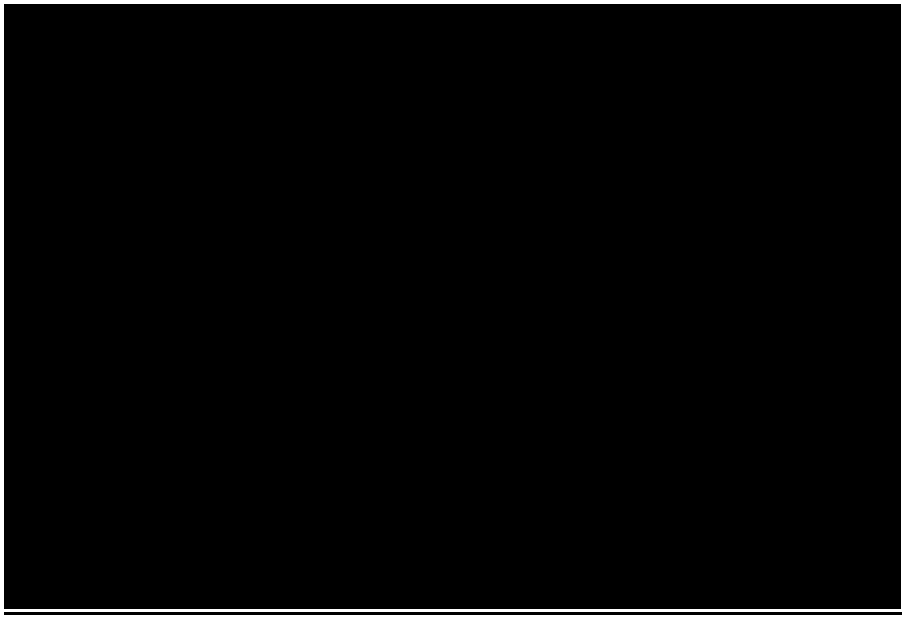
Figure 17: 029 Recurrence-free survival log-cumulative hazard plot

Key: Ipi, ipilimumab; PBO, placebo.
Notes: Dashed line indicates first assessment time (12 weeks).

Figure 18: 238 Recurrence-free survival QQ-plot

Key: Ipi, ipilimumab; Nivo, nivolumab.

Figure 19: 029 Recurrence-free survival QQ-plot



Key: Ipi, ipilimumab; PBO, placebo.

As the plots indicate that the PH and AFT assumptions are reasonable in both trials, non-stratified models may be used. However, it should also be noted that as PLD is available, stratified models may be preferred. In effect, stratified models split data by

treatment and a separate curve is fitted to each treatment placing the treatment effect on two model parameters (e.g. shape and scale for Weibull), removing the PH and AFT assumptions. As stated within NICE TSD DSU 14: "Generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach".[41] Stratified models were therefore used within this analysis.

Criteria used to select the most plausible curve fit

In line with NICE Decision Support Unit guidance[41], the following criteria were used to assess the model fit/plausibility to aid selection of base case survival curves:

- Goodness of fit measures, the Akaike information criterion (AIC) and the Bayesian information criterion (BIC)
  - The lower the AIC or BIC, the better the model fit to the observed data. Of note, a nominal difference of at least 5 in AIC and/or BIC is considered to imply a meaningful difference in the fit of the parametric survival models to the observed data.
- Visual inspection
  - The fitted survival curves have been overlaid on KM data to assess how closely the curves match the observed data.
- Clinical validation
  - Key opinion leaders were asked for their clinical opinion on what the expected outcomes would be based on clinical practice. Emphasis was placed on the clinical plausibility of the extrapolation of the data and expectations in the long term.
- Long-term data
  - Long-term melanoma data were also used to validate longer-term outcomes.
  - The model OS outcomes were overlaid on digitised KM data to assess how closely they match the external data sources or if the differences are clinically plausible given the lack of relevant long-term data.

Use of external long-term survival data

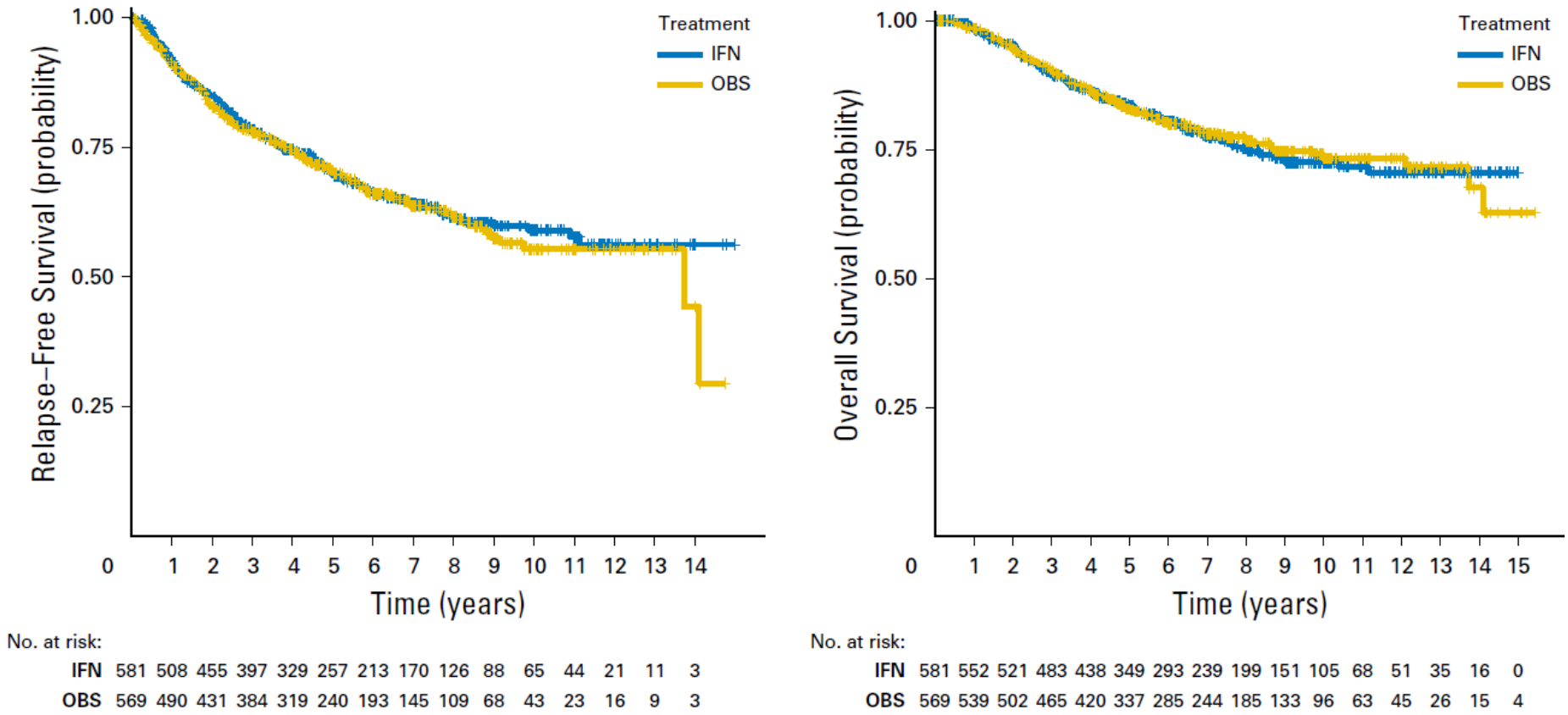
One of the key issues surrounding the long-term extrapolation of outcomes within adjuvant melanoma is the conflict between the long-term nature of a dataset and its generalisability to current practice. As noted in Section B.2.13, there have been changes in recent surgical practice. Additionally, a large number of active subsequent therapies have recently become available in the metastatic setting including nivolumab. Clinical experts at the recent advisory board suggested a rule of thumb that datasets older than 5 years would likely have issues with respect to their generalisability to current practice.[1] While this limits the applicability of long-term datasets to our current decision problem, it is still important to use the information we have to inform extrapolation. However, when doing so, we need to carefully consider these datasets' likely direction of bias; when comparing on a like-for-like basis across stages, older datasets are likely to under-predict current survival.

The long-term data available in the adjuvant melanoma setting are restricted to registry data and interferon studies.

Interferon studies

The majority of the available interferon studies are over 10 years old and include Stage II patients within the survival projections. The longest data set, which included OS and RFS outcomes in the adjuvant setting, was the E1697 study, which was a Phase III trial comparing high-dose interferon to observation in Stage T2bNO, T3a-bNO, T4a-bNO and T1-4N1a-2a melanoma patients.[42] These data show OS and RFS outcomes up to 15 years for observation patients (Figure 20).

Figure 20: OS and RFS KM data from the E1697 study – Agarwala et al., 2017



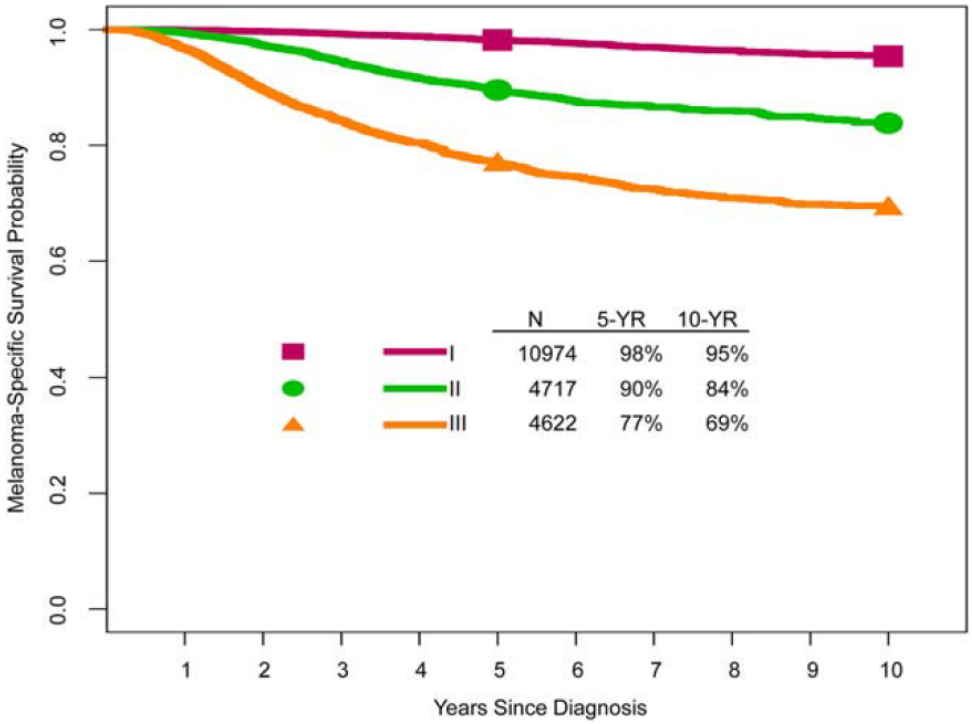
Key: IFN, interferon; KM, Kaplan–Meier; OBS, observation; OS, overall survival; RFS, relapse-free survival.

In this study, only 19% of patients were lymph node positive in the observation arm and therefore not fully reflective of our patient population. Additionally, this study started in 1998 and finished in 2010. As a consequence, this study is not clinically reflective of post-recurrence treatment options, which are now available and therefore not reflective of survival estimates experienced by patients currently. Nevertheless, these data provide long-term RFS estimates from the adjuvant melanoma setting, and although our population is at higher risk of recurrence, the outcomes reported by Agarwala et al. can provide an upper bound for where our estimates should be around 15 years for the routine surveillance arm and a general idea of the likely distribution of the long-term hazard function. Unfortunately, long-term data are not available in patients more similar to those in the CheckMate 238 trial.

Registry data

The recently published 8th edition AJCC database[14] shows up to 10 years survival outcomes for patients in different stages from centres in Australia, Europe and North America. As these data use a new definition of Stage IIIA, B and C compared to the 7th edition used in the CheckMate 238 trial, the overall Stage III curve is the most relevant as the overall Stage III definition did not change across AJCC editions. It should be noted that AJCC registry data may include a small proportion of patients with Stage III melanoma who are not treated surgically and it is unclear whether the distribution of stages is reflective of our patient population; however, it does represent the most up to date long-term data source on survival outcomes for this patient population.

Figure 21: OS for Stage III patients from AJCC 8th edition database – Gershenwald et al., 2017

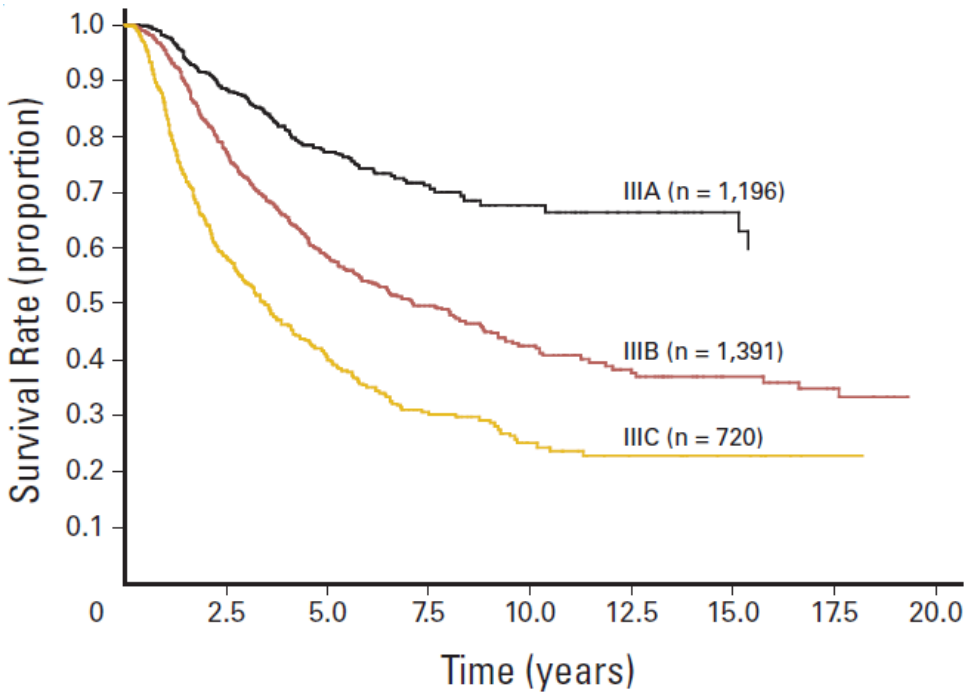


These data suggest that at 10 years, the survival rate is 69% for Stage III patients, the previous AJCC 7th edition data show that the 10-year survival rate is approximately 68%, 43% and 25% for Stage IIIA, IIIB and IIIC patients, respectively. The higher survival rates in the 8th edition could be due to changes in clinical practice for melanoma patients since the published 7th edition data. Clinical opinion suggests that the higher survival rates are due to better definition and more accurate staging of disease, improved care within the melanoma setting, and improvement in early detection of disease.

The 7th edition database has survival outcomes up to 20 years split by disease stage; Stage IIIA, IIIB and IIIC.[43] These data were published in 2009 and are therefore less likely to be reflective of current clinical practice for unresectable tumours. However, these data provide long-term outcomes for patients by disease stage subtype. To provide an estimate for a comparable population to our decision problem population, the stage subtype curves from Balch 2009 were weighted to create one overall Stage III curve based on the proportion of patients in our

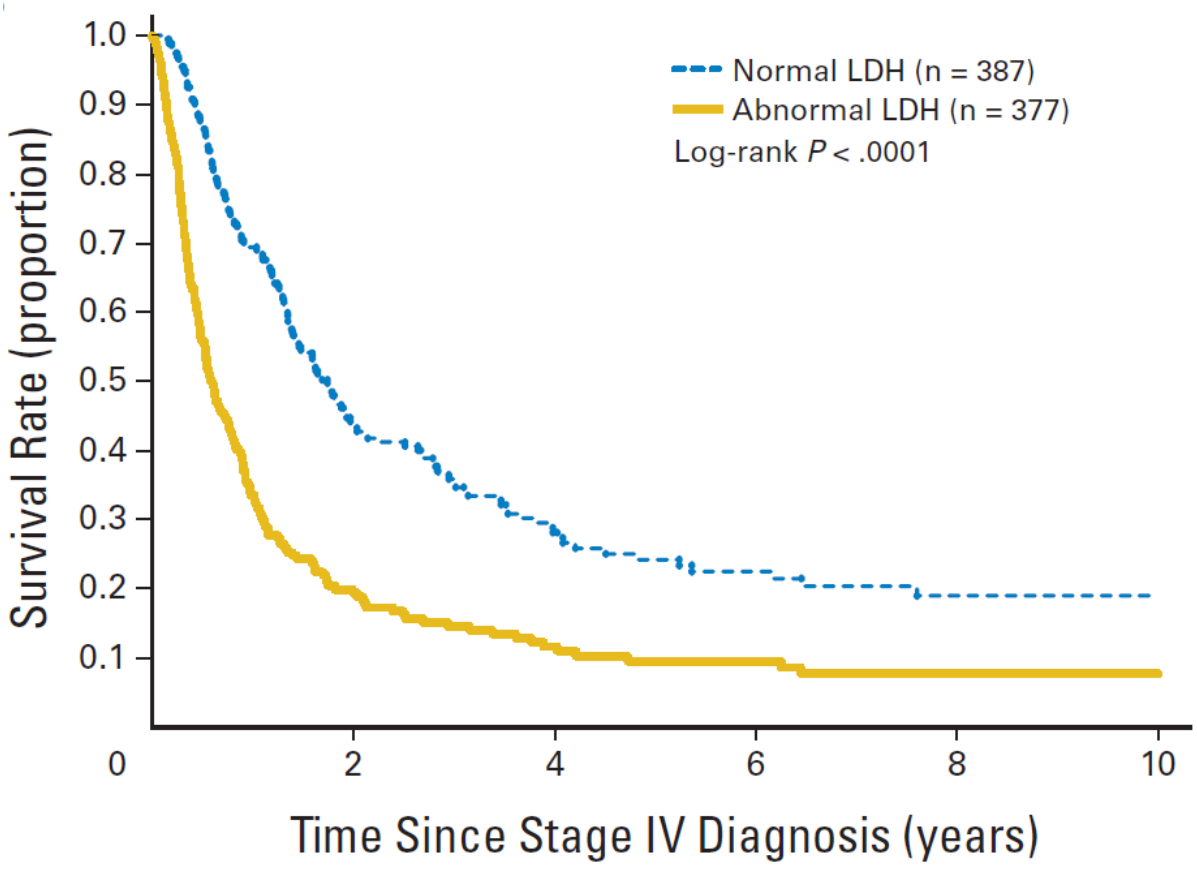
population who were Stage IIIA, B and C (Stage IV NED patients were grouped with Stage IIIC based on earlier assumption – see Section B.3.3).

Figure 22: OS for Stage III patients from AJCC 7th edition database – Balch et al., 2009



There are no long-term data available for the Stage IV NED patients within either version of the AJCC registry or elsewhere; therefore an assumption is made, similar to the assumption made for RFS, that Stage IV NED patients have similar outcomes to Stage IIIC patients, which is a reasonable approximation based on feedback received by clincians.[44] The Stage IV curve, which represents both resectable and unresectable patients (majority expected to be unresectable), reported in AJCC 7th edition with 10-year follow-up can be used as a lower bound estimate and used to validate projections to ensure that the survival estimates do not go below these (Figure 23).

Figure 23: OS for Stage IV patients from AJCC 7th edition database – Balch et al., 2009



Key: LDH, serum lactose dehydrogenase.

RFS definition

A limitation of the ITC was the difference in primary definition of RFS, as presented in Table 11.

Table 11: Primary RFS trial definitions

Trial	Primary endpoint assessment (RFS)	Death	Subsequent therapy
CheckMate 238	Investigator	Event recorded at the time of death	Patient censored at time of last disease assessment prior to receipt of subsequent therapy
CA184-029	Independent	Event recorded at the time of death	Event recorded at time of recurrence or death, regardless of whether a patient received subsequent therapy
Key: RFS, recurrence-free survival.			

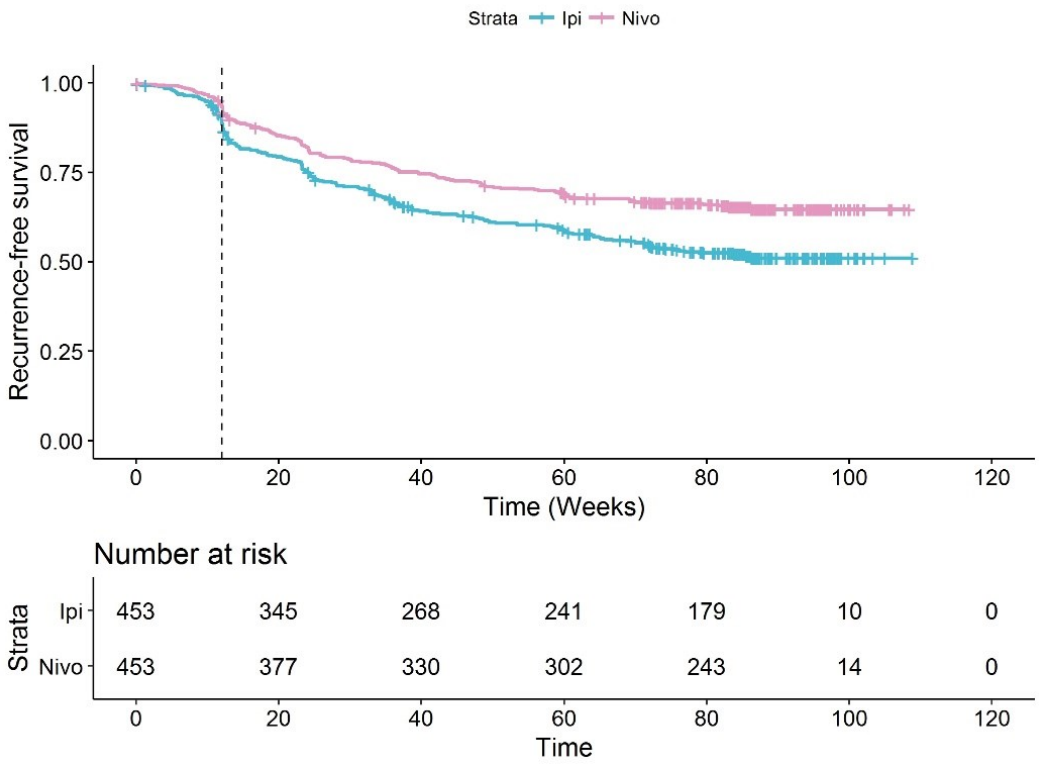
The definition of RFS differs between the two studies in two ways: the studies have different primary reviewers and have different censoring rules for subsequent therapy. The primary definition will be used for the CheckMate 238 study. For the CA184-029 study, a number of pre-specified sensitivity analyses were conducted; however, none matched the primary definition used in the CheckMate 238 study. Therefore, a number of possible options for the CA184-029 RFS definition were considered (as detailed in Appendix D), including matching on subsequent therapy definition, matching on reviewer or using the primary analysis. Although each of the three options showed similar results (as presented in Figure 3 of Appendix D) and a consistent treatment effect is observed between ipilimumab and placebo (as presented in Table 6 of Appendix D), ultimately a sensitivity analysis with matching on subsequent therapy definition (thus differing from CheckMate 238 with regards to the reviewer) was chosen as the outcome definition was deemed most similar between studies in order to stick to a pre-defined analysis within the CA184-029 trial.

Use of RFS data after 12 weeks

Figure 24 and Figure 25 display the KM curves for RFS split by treatment using the proposed definitions for CheckMate 238 and CA184-029, respectively. The CheckMate 238 trial KM data are observed to be immature, i.e. median RFS is not reached for either treatment. For CA184-029, median RFS is reached at 125.3 weeks for the ipilimumab arm and at 74.1 weeks for the placebo arm. In both trials, the rate of events is observed to slow over time, and heavy censoring is observed at the end of each KM as they begin to plateau. In the CheckMate 238 trial, nivolumab

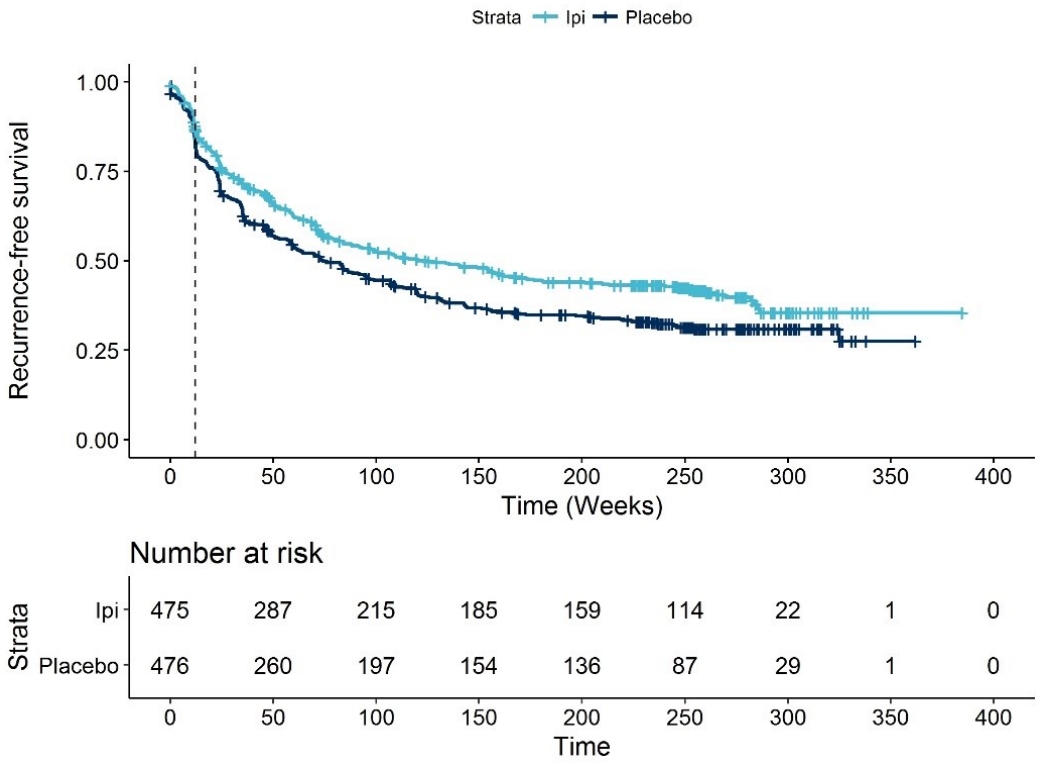
appears to perform consistently better than ipilimumab after the initial 12 weeks, while in the CA184-029 trial, ipilimumab appears to perform consistently better than placebo after the first 12 weeks. The first assessment date is not until 12 weeks in both trials, so little separation is observed within the KM curves before a large change in hazard at this time point (this is also observed at subsequent assessments, although the separation of curves is less pronounced). Due to the change in hazard at 12 weeks, it was likely that any parametric survival models fit to the full KM data would provide a poor fit to the observed data, and it was therefore appropriate to identify a relevant timepoint to rebase the RFS data.

Figure 24: Recurrence-free survival 238 Kaplan–Meier split by treatment



Key: Ipi, ipilimumab, Nivo, nivolumab.
Notes: Dashed line indicates time of first efficacy assessment (12 weeks).

Figure 25: Recurrence-free survival 029 Kaplan–Meier split by treatment



Key: Ipi, ipilimumab; PBO, placebo.
Notes: Dashed line indicates time of first efficacy assessment (12 weeks).

As the overlap in the KM curves corresponds to the time of the first assessment date, which is 12 weeks (±1 week) for CheckMate 238 and 12 weeks (±2 weeks) in CA184-029. For each trial, cut-offs could be selected either at the time of first assessment (12 weeks), prior to the first assessment (11 weeks for 238 and 10 weeks for 029) or post first assessment (13 weeks for 238 and 14 weeks for 029). KM curves rebased at 11, 12 and 13 weeks are presented in Figures 4, 5 and 6 in Appendix D.

The KMs rebased at 11 weeks show an initial drop prior to the separation of the curves. In comparison, the initial drop is reduced when the curves are rebased at 12 weeks, although there is less separation of the KM curves. Finally, when the curves are rebased at 13 weeks, the initial drop observed when the KMs are rebased at 11 and 12 weeks is not present; however, there is almost complete overlap in the KMs until the time of the next assessment. Similar results are also observed in the CA184-029 data and are presented in Figures 7, 8 and 9 in Appendix D. Therefore,

the RFS analysis would be performed from baseline and rebased at 12 weeks. For the analysis rebased at 12 weeks, the KM data were used to inform survival for the initial 12-week period as it is still appropriate to capture change in survival prior to the first assessment. Therefore, the KM data were used directly to inform survival for survival estimates for the period prior to the first assessment. From the above assessment, it is unlikely that the choice of rebase point will have a major impact on the outcomes of this analysis.

Covariate adjustment

Patient characteristics between the two studies had some differences, notably the staging of patients. As per study inclusion criteria, the CheckMate 238 study does not include patients with Stage IIIa disease, while the CA184-029 study does not include patients with Stage IV NED disease. Of note, CA184-029 defines disease stage by AJCC 6th edition, while CheckMate 238 uses the 7th edition. However, there were no alterations within these editions that would affect the patient population staging, except for the 7th edition not including a lower threshold for the size of tumours to qualify as a metastatic node.[43] To elaborate, within the 6th edition, an implied lower threshold of 0.2mm was used to class a metastatic node, but this lower threshold was not included in the 7th edition. The size of metastases within nodes was not available in the study data, and therefore, no staging adjustments were made between the two studies. Melanoma subtype was the only other main difference between the trials; the CA184-029 study consists entirely of patients with cutaneous disease, whereas in CheckMate 238 approximately 15% of patients have non-cutaneous cancer. Melanoma subtype was not, however, found to be prognostic or a treatment effect modifier in CheckMate 238.

To explore impact of differences in patient characteristics between the CheckMate 238 and CA184-029 studies, covariate adjustment was considered for both characteristics that influenced the relative treatment effect (effect modifiers) or absolute survival (prognostic factors). The list of covariates chosen was validated by clinical key opinion leaders.[1] Adjusting for effect modifiers allows the indirect treatment effect to be estimated more accurately across trials, whereas adjusting for prognostic factors allows the economic model to estimate outcomes for different patient populations.

Assessment of covariates that would impact the treatment effect was considered for RFS only, while assessment of covariates that would impact absolute prognosis (prognostic factors) were considered for RFS and OS.

In CheckMate 238, the RFS treatment effect was consistent in all pre-defined subgroups with the exception of patients with Stage IV M1c melanoma, ulceration present plus microscopic lymph node involvement, and mucosal melanoma (as reported in Figure 12). Due to the small patient numbers in these subgroups, and large uncertainty observed in the relative treatment effect estimate (confidence intervals overlap), it is unclear whether the relative treatment effect within these subgroups is different. Therefore, there do not appear to be any clear treatment effect modifiers within the CheckMate 238 study.

Similarly, in the CA184-029 study, treatment effect was consistent in each of the pre-defined subgroups with the exception of patients with unknown ulceration status (21 ipilimumab patients and 29 placebo patients), as presented in Figure 13. Again, due to the low patient numbers in these subgroups, there do not appear to be any clear treatment effect modifiers. However, it should be noted that in both trials the subgroup analyses are not powered to detect differences in the populations, and in reality, treatment effect modifiers may exist.

For the economic model, it is important that the model can predict survival in the full decision problem population; therefore, covariate adjustment for prognostic factors was considered.

A multivariate unstratified Cox regression analysis of the CheckMate 238 study reports that [redacted] were significant prognostic variables for RFS; in the CA184-029 study, [redacted] were reported as key prognostic variables (Table S5.5 in the CSR). As a patient's disease stage is highly correlated with lymph node involvement and ulceration status (disease stage is partially defined by these two factors; Stage IIIa by definition must have microscopic lymph node involvement and no ulceration), it is not advisable to perform regression analysis with covariates for disease stage with either or both ulceration status or lymph node involvement. Disease stage was included instead of lymph node involvement in the base case model as disease

stage is a better predictor than ulceration status or lymph node involvement for RFS in CheckMate 238, and the long-term data used to validate model extrapolations are also presented by disease stage, therefore adjusting by stage allows for easier comparisons. The impact of using lymph node involvement within the covariate adjustment is shown as a sensitivity analysis within the Bucher ITC, there is very little change to results.

[redacted], clinical opinion at the global advisory board suggested that due to the changing nature of PD-L1 expression and challenges associated with measuring and assessing PD-L1, it would not be informative to present outcomes by PD-L1 status. Indeed, a recent retrospective chart review of UK practice has shown that [redacted].[45] Additionally, these data were not available in CA184-029.[44] [45]B-RAF status was not included due to the high level of missing data in CA184-029 after post-hoc data collection: 88.2% in the ipilimumab arm and 86.6% in the placebo arm.

In addition to the covariates that were identified as prognostic for RFS across the two trials, patient age (<65 or ≥65) and trial were also included as covariates for the ITC PLD meta-regression analysis. [redacted]. However, the inclusion of a trial covariate is analogous to performing a traditional ITC on summary data using ipilimumab as a common comparator because the trial effect will account for all unobserved differences between trials, thus maintaining randomisation.

In summary, the following covariates were included within each analysis.

- Sex (Male or female)
- Age (<65 or ≥65)
- Stage (Stage IIIa or Stage IIIb or Stage IIIc or Stage IV). Of note, in the CheckMate 238 trial, [redacted] patients had unknown/other disease stage, so were excluded from analysis.
- Trial (CA184-029 or CheckMate 238; trial was included as a covariate in the RFS ITC PLD meta-regression analysis only)

Group prognosis

The corrected group prognosis (CGP) method was used to calculate the parametric survival curves used in the economic model. This calculates a survival curve for each unique combination of covariates with the proportion of patients in each group used to weight the individual survival curves, thus creating a weighted average curve for the entire population. The possible groupings for CGP are presented in Table 22.

Table 12: Groups used for corrected group prognosis

Number	Group
1	Trial = 238, Stage= IIIb, Sex= M, Age category = < 65
2	Trial = 238, Stage= IIIb, Sex= M, Age category = ≥ 65
3	Trial = 238, Stage= IIIb, Sex= F, Age category = < 65
4	Trial = 238, Stage= IIIb, Sex= F, Age category = ≥ 65
5	Trial = 238, Stage= IIIa, Sex= M, Age category = < 65
6	Trial = 238, Stage= IIIa, Sex= M, Age category = ≥ 65
7	Trial = 238, Stage= IIIa, Sex= F, Age category = < 65
8	Trial = 238, Stage= IIIa, Sex= F, Age category = ≥ 65
9	Trial = 238, Stage= IIIc, Sex= M, Age category = < 65
10	Trial = 238, Stage= IIIc, Sex= M, Age category = ≥ 65
11	Trial = 238, Stage= IIIc, Sex= F, Age category = < 65
12	Trial = 238, Stage= IIIc, Sex= F, Age category = ≥ 65
13	Trial = 238, Stage= IV, Sex= M, Age category = < 65
14	Trial = 238, Stage= IV, Sex= M, Age category = ≥ 65
15	Trial = 238, Stage= IV, Sex= F, Age category = < 65
16	Trial = 238, Stage= IV, Sex= F, Age category = ≥ 65
17	Trial = 029, Stage= IIIb, Sex= M, Age category = < 65
18	Trial = 029, Stage= IIIb, Sex= M, Age category = ≥ 65
19	Trial = 029, Stage= IIIb, Sex= F, Age category = < 65
20	Trial = 029, Stage= IIIb, Sex= F, Age category = ≥ 65
21	Trial = 029, Stage= IIIa, Sex= M, Age category = < 65
22	Trial = 029, Stage= IIIa, Sex= M, Age category = ≥ 65
23	Trial = 029, Stage= IIIa, Sex= F, Age category = < 65
24	Trial = 029, Stage= IIIa, Sex= F, Age category = ≥ 65
25	Trial = 029, Stage= IIIc, Sex= M, Age category = < 65
26	Trial = 029, Stage= IIIc, Sex= M, Age category = ≥ 65
27	Trial = 029, Stage= IIIc, Sex= F, Age category = < 65
28	Trial = 029, Stage= IIIc, Sex= F, Age category = ≥ 65
29	Trial = 029, Stage= IV, Sex= M, Age category = < 65
30	Trial = 029, Stage= IV, Sex= M, Age category = ≥ 65

Number	Group
31	Trial = 029, Stage= IV, Sex= F, Age category = < 65
32	Trial = 029, Stage= IV, Sex= F, Age category = ≥ 65

For the within trial analysis, the proportion of patients within each group was matched to that observed in the trial. This allows for the weighted curve produced to be compared with the KM, making it possible to assess goodness of fit and determine the most appropriate distribution to use as a base case within the economic model.

The use of the CGP method also allows the model to predict survival curves for the total population of interest (Stages III–IV) despite the only partial overlapping populations between the two trials. Within the ITC PLD meta-regression analysis, as the disease stage coefficients are estimated irrespective of treatment, it was assumed that the Stage IIIa coefficient value and the Stage IV coefficient value could be applied to the nivolumab and placebo arms, respectively, without modification of the treatment effects. To form the ITC, the proportion of patients within each group were held constant between treatment groups regardless of trial to give a simulated treatment comparison. This allows for long-term survival estimates to be produced for each treatment while controlling for differences within patient characteristics and trials.

Results – survival analysis

Overall survival CA184-029

Figure 18 and Figure 19 in Appendix D displays the long-term survival extrapolations estimated using parametric survival models fit to the CA184-029 OS data from baseline for ipilimumab and placebo; respectively. The model fit statistics are presented in Table 13. The coefficients used to estimate the curves are presented in Table 14 in Appendix D. The exponential, Weibull and Gompertz curves each fit the KM poorly throughout. The log-logistic and log-normal curves fit the initial part of the KM well but overestimate survival in the middle section of the KM. The generalised gamma is the only curve that appears to give a good fit to the KM. This is reflected in the model fit statistics; the generalised gamma model has the lowest AIC and BIC

scores, while the Weibull and exponential models have the highest AIC scores. Similar to RFS within CheckMate 238, each of the curves fan out after the end of the KM, suggesting large uncertainty within the extrapolated period. For the placebo curve, the parametric survival curves appear to be pessimistic compared to the long-term survival data from AJCC 7th edition database given that all curves other than the generalised gamma and the Gompertz model produce estimates similar to those for the Stage IIIC patients. The generalised gamma and the Gompertz curves appear more optimistic, and the rate of events is observed to slow over time, and they therefore provide a better estimate for OS in 029. Additionally, each curve was assessed for validity (Table 13) looking at:

- whether the predicted curves for ipilimumab and observation cross during trial follow-up (indicates poor fit as the KMs don't cross)
- the time at which the OS and RFS curves meet in the model for the routine surveillance arm
- validation comparing the survival curve against long-term data.

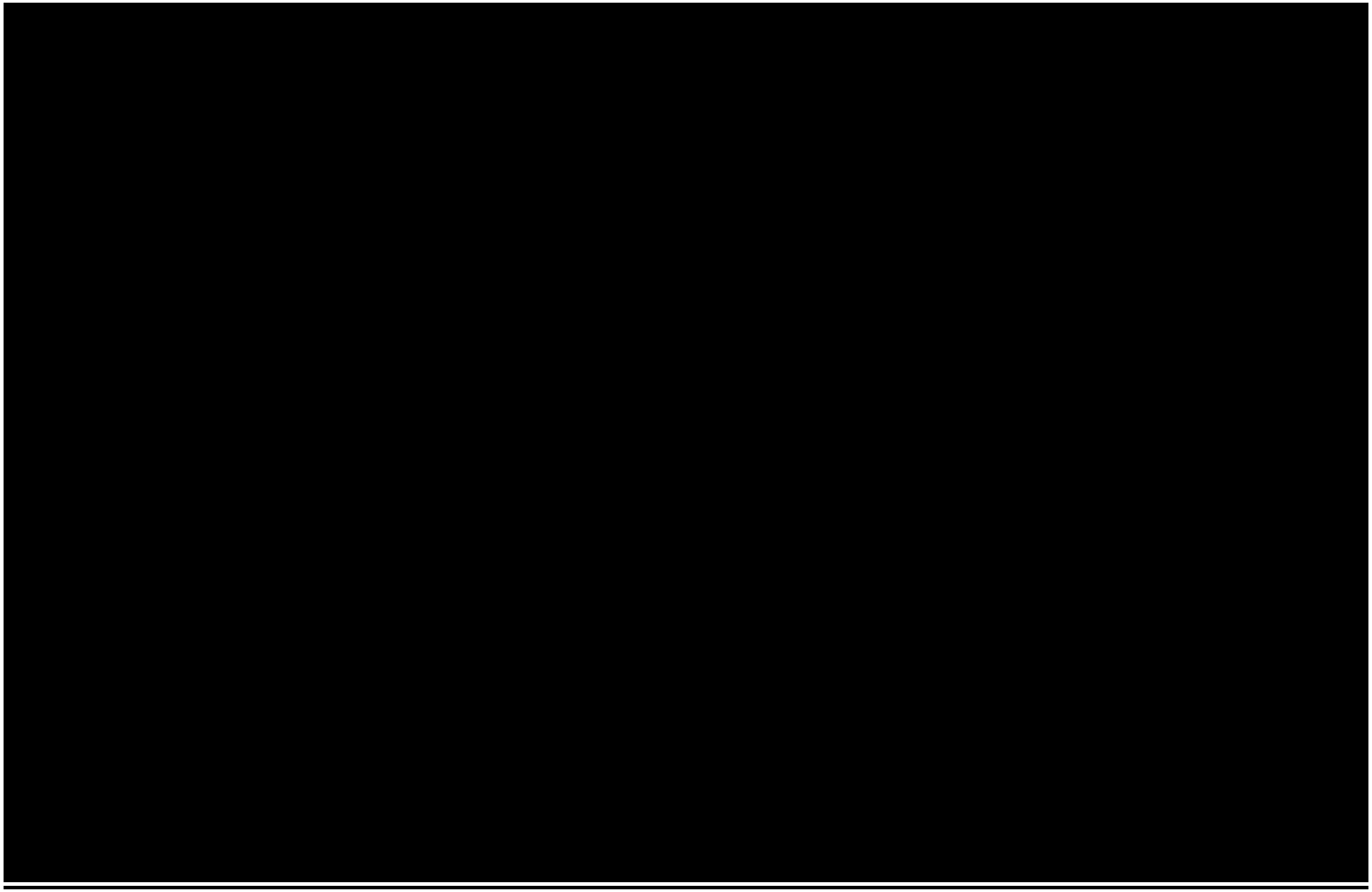
As the generalised gamma has improved model fit over the Gompertz distribution, the generalised gamma was selected as the base case for OS within the economic model. Figure 26 presents the long-term OS extrapolations estimated using the generalised gamma distribution for both ipilimumab and placebo in CA184-029.

Table 13: 029 overall survival – model fit statistics

Model	AIC	AIC rank	BIC	BIC rank	Arms cross within CA-029 trial FU	Time RFS meets OS (years)*	Validation vs AJCC v8**	Validation vs Balch 2009 (Stage III)***	Validation vs Balch 2009 (Stage IV)****
Exponential	6867.52	5	6896.67	4	×	6	✓	×	×
Generalised gamma	**6797.38**	**1**	**6841.10**	**1**	×	**39**	✓	✓	✓
Gompertz	6862.01	4	6900.87	5	×	38	✓	✓	✓
Log-logistic	6842.18	3	6881.04	3	×	34	✓	×	✓
Log-normal	6816.42	2	6855.28	2	×	35	✓	×	✓
Weibull	6870.87	6	6909.73	6	×	9	✓	×	×

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Notes: Bold distribution represent the base case selection.
*Post 20 years a patient who remains recurrence-free should be more or less similar to general population mortality.
**029 survival projections are expected to be lower than the AJCC v8 data
***Using within 10% range of the weighted Stage III curve. A tick refers to a curve within this range.
****This is used as a lower bound, the survival curve would not be expected to be lower than patients in the metastatic setting.

Figure 26: CA184-029 overall survival – generalised gamma survival extrapolations split by treatment



Key: Ipi, ipilimumab; KM, Kaplan–Meier; PBO, placebo.

Parametric survival modelling indirect treatment comparison

Results - RFS

Parametric survival models fit to the KM rebased at 12 weeks provide an improved model fit in comparison with the baseline models; therefore, for the parametric survival model ITC, only models rebased at 12 weeks are presented here. Figure 20 – Figure 23 in Appendix D present separately, the long-term survival extrapolations for each treatment in CheckMate 238 and CA184-029, respectively. The model fit statistics are presented in Table 14. The coefficients used to estimate the curves are presented in Table 15 in Appendix D.

For RFS, the ITC PLD meta-regression model produces good fit to the KM data for both treatments in the CheckMate 238 trial for all models, with the exception of the exponential curve. It is likely that the exponential provides a poor fit to the KM data as the exponential distribution assumes that the hazard rate is constant over time, whereas it is observed in the RFS KM for CheckMate 238 that the rate of events and thus the hazard decrease over time. For the CA184-029 trial, the exponential curve provides a poor fit to both treatment arms, and the Weibull distribution fits poorly to the placebo arm. Each of the remaining models provide a reasonable fit to the KM curves; the log-logistic and generalised gamma provide the best fitting models to the CA184-029 ipilimumab arm, while the log-normal and Gompertz models are visually the best fitting models for the placebo arms.

Overall, the model statistics indicate that the log-logistic model provides the best statistical fit to the data, particularly for the CheckMate 238 trial, after the end of the KM each of the curves fan out, suggesting large uncertainty within the extrapolated period. Notably, the Gompertz model appears to almost plateau completely, shortly after the end of the KM for each of the four treatment arms, and as a result is unsuitable for use within the economic model. It was noted at the UK advisory board that the placebo and nivolumab parametric survival curves looked pessimistic compared to what clinicians would expect in practice.[1] Excluding the Gompertz curve, the log-logistic, log-normal and generalised gamma curves produce the most optimistic estimates for the placebo data as well as for nivolumab and ipilimumab. Out of the log-logistic, log-normal and generalised gamma curves, the log-logistic

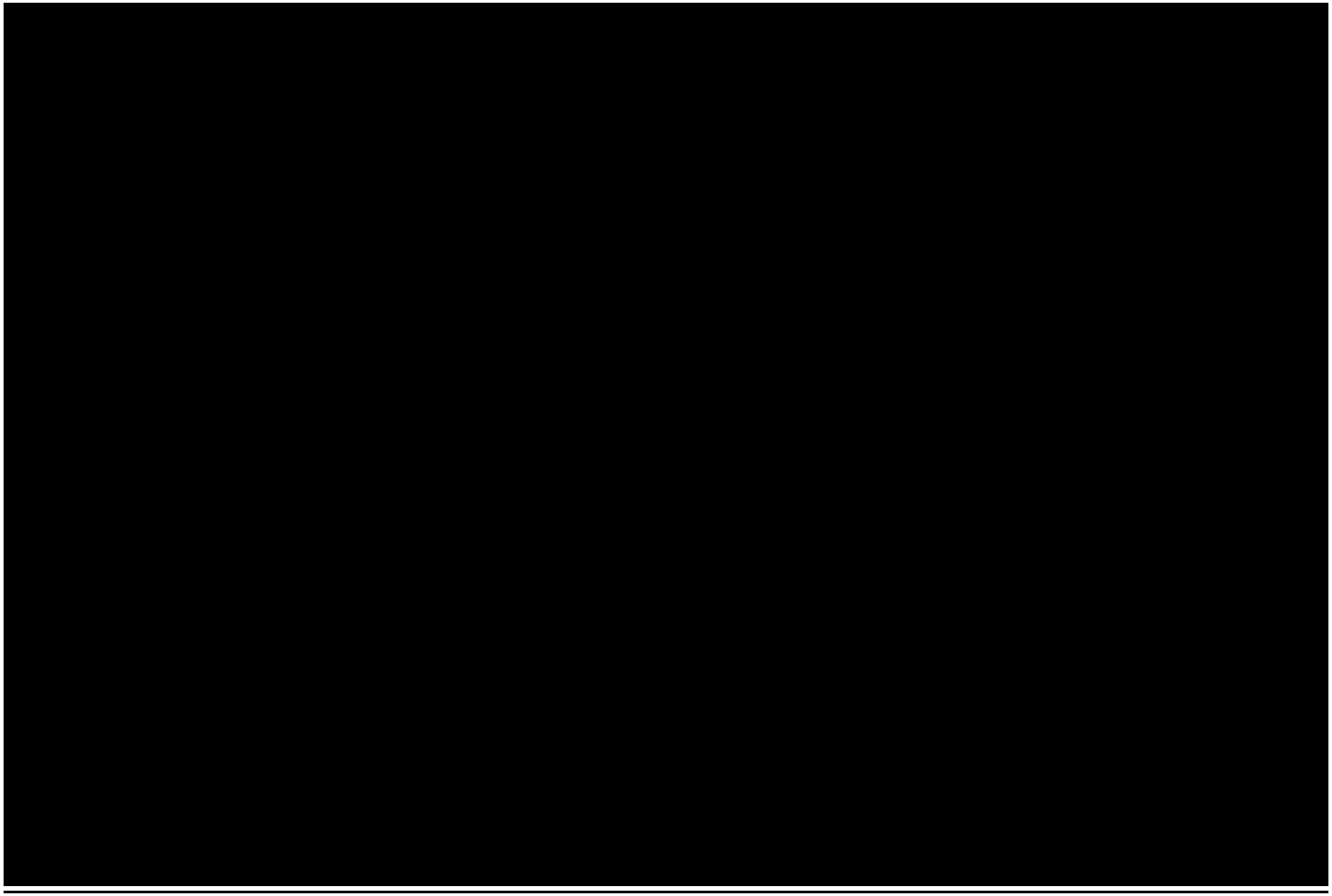
curve provides the best statistical fit to the data and was therefore selected as the base case for the economic model. Additionally, each curve was assessed for validity looking at; whether the curves cross within the CheckMate 238 and CA184-029 trial, the time at which the OS and RFS curves meet in the model for both arms and validation comparing the survival curve against long-term data (Table 14). Figure 27 and Figure 28 present the long-term RFS extrapolations estimated using the log-logistic distribution for treatments within CheckMate 238 and CA184-029, respectively.

Figure 27: CheckMate 238 recurrence-free survival ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 split by treatment

Key: Ipi ipilimumab; ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab.

Notes: KM from baseline is displayed, log-logistic curve is fit from 12 weeks onwards

Figure 28: CA184-029 recurrence-free survival ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 split by treatment



Key: Ipi ipilimumab; ITC, indirect treatment comparison; KM, Kaplan–Meier; PBO, placebo.
Notes: KM from baseline is displayed, log-logistic curve is fit from 12 weeks onwards.

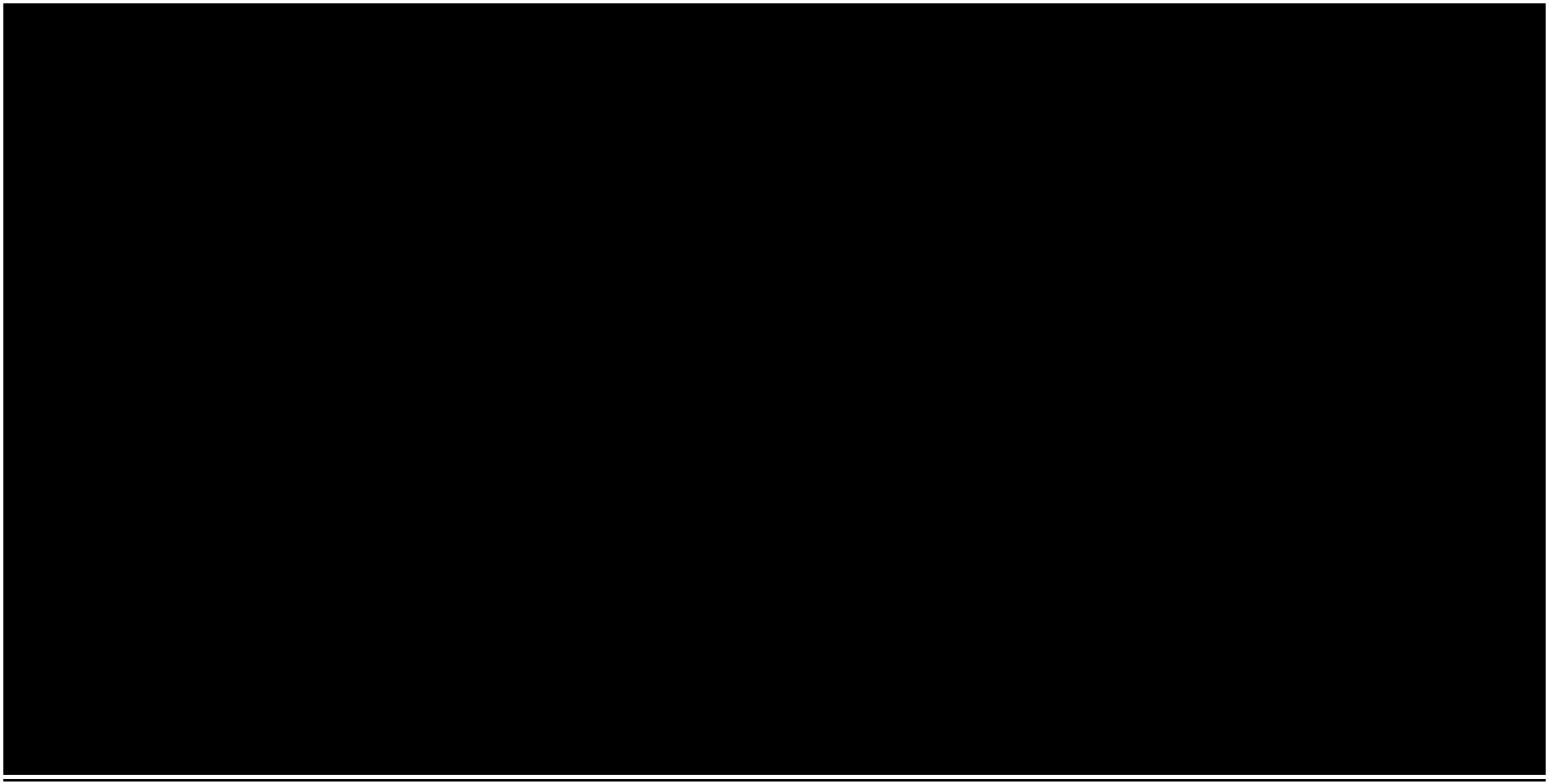
Table 14: 238 and 029 RFS ITC PLD meta-regression model rebased at 12 weeks – model fit statistics

Model	AIC	AIC rank	BIC	BIC rank	Arms cross within trial		Time RFS and OS curves meet (years)*		Validation vs E1697 trial (routine surveillance)**
					CheckMate 238	CA184-029	Nivolumab	Routine surveillance	
Exponential	11651.61	6	11700.00	6	✓ 2 years	×	55	55	✓
Generalised gamma	11369.45	2	11439.34	3	×	×	32	39	✓
Gompertz	11409.57	5	11474.08	4	×	×	7	32	✓
Log-logistic	**11361.84**	**1**	**11426.35**	**1**	×	×	**33**	**39**	✓
Log-normal	11373.61	3	11438.12	2	×	×	30	37	✓
Weibull	11388.23	4	11452.74	5	×	×	37	43	✓

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Notes: Bold text refers to base case selection.
*Post 20 years a patient who remains recurrence-free should be more or less similar to general population mortality
**This is an upper bound reference, so a tick means the curve did not go above this curve

Figure 29 presents the results of the long-term extrapolation using a log-logistic model (the base-case within the economic model) for each treatment using a matched population (i.e. the covariate proportions according to the CGP method is consistent for all treatment groups). The curves indicate that with the matched population, nivolumab gives improved RFS over both ipilimumab and placebo, and ipilimumab gives improved RFS over placebo.

Figure 29: Recurrence-free survival – ITC PLD meta-regression model adjusted long-term survival extrapolation from parametric survival curves rebased at Week 12 split by treatment



Key: Ipi, ipilimumab; ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab; PBO, placebo.

Bucher indirect treatment comparison

An alternative method to using parametric survival models is to perform an adjusted indirect comparison between nivolumab and placebo using the Bucher method.[46] The Bucher method provides a simpler approach to providing an adjusted ITC between nivolumab and placebo than the PLD meta-regression. As RFS is a survival outcome, HRs derived from Cox models were used to form the indirect comparisons using the Bucher method. As Cox models derive a single HR, they assume proportional hazard, which is a reasonable assumption for both the CheckMate 238 and CA184-029 studies.

To estimate the indirect effect of nivolumab compared to placebo, the difference in the relative treatment effect in relation to the ipilimumab arm in each study was estimated. Bucher comparisons assume that the relative treatment effect estimate is normally distributed; HRs are normally distributed on the log scale. The indirect estimate of the HR between treatments placebo and nivolumab was estimated as follows:

$$\log\left(HR_{Nivo\ PBO}^{indirect}\right) = \log\left(HR_{Nivo\ Ipi}^{direct}\right) - \log\left(HR_{PBO\ Ipi}^{direct}\right)$$

With variance (var):

$$\mathrm{Var}\left\{\log\left(HR_{Nivo\ PBO}^{indirect}\right)\right\} = \mathrm{Var}\left\{\log\left(HR_{Nivo\ Ipi}^{direct}\right)\right\} + \mathrm{Var}\left\{\log\left(HR_{PBO\ Ipi}^{direct}\right)\right\}$$

As a scenario analysis, the estimated HR was applied to the nivolumab arm in the CheckMate 238 study within the economic model to estimate the relative effect of placebo. Results of the parametric survival analysis using only CheckMate 238 RFS data are presented in Appendix D.

As discussed previously, there are no clear treatment effect modifiers for RFS, so it is assumed that the treatment effect within each trial is consistent within subgroups. Analysis may therefore be performed without adjustment for patient characteristics. A further analysis was also performed using covariate adjustment to determine whether controlling for small imbalances in prognostic factors changes the treatment effect estimates. The following covariates were included in the covariate adjusted analysis (these are the same as those used in the parametric survival models):

- Sex (male or female)
- Age (<65 or ≥65)
- Stage (Stage IIIA or Stage IIIB or Stage IIIC or Stage IV)

A further point to note is that there is a difference in disease stage between the trials; the CheckMate 238 trial contained Stage IV NED patients but no Stage IIIA, and conversely, the CA184-029 trial contained Stage IIIA patients but not Stage IV NED. Therefore, analyses using only Stage IIIb and IIIc patients were performed to assess whether the treatment effect is consistent across the overlapping disease stages. As randomisation in both trials was stratified by disease stage, randomisation should be maintained in the Stage IIIIB/C population. Although patients' characteristics are reasonably similar between treatment arms within each study, there are some small differences between arms in the trials such as in the proportion of patients with each disease stage and the proportion of patients with tumour ulceration (CheckMate 238 only). A further analysis was therefore performed in the Stage IIIb/c population, controlling for differences in patient characteristics.

In summary, for the ITC using the Bucher comparison method, 4 analyses were performed:

- ITT population with no covariate adjustment
- ITT population with covariate adjustment
- Stage IIIb/c population with no covariate adjustment
- Stage IIIb/c population with covariate adjustment

If the ITT models produced similar relative treatment effect estimates to the Stage IIIb/c models, it would indicate that the difference in the stage between trials does not act as a treatment effect modifier.

Results

Table 15 presents the results of the ITC between nivolumab and placebo using the Bucher method, in both the ITT and Stage IIIb/c population, with and without covariate adjustment. For each of the comparisons, the results indicate that the rate of recurrence or death events is significantly lower for nivolumab patients compared to placebo patients.

The results between populations indicate that the treatment effect is consistent with the estimated HR, decreasing by only [redacted] and [redacted] from the ITT to the Stage IIIb/c populations within the unadjusted and covariate adjusted results, respectively. The results also indicate that covariate adjustment has a small influence on the treatment effect, with the HR increasing by [redacted] with covariate adjustment in the ITT population and remaining unchanged in the Stage IIIb/c population. There was no difference in results in the sensitivity analysis adjusting for lymph node involvement rather than disease stage. Results are consistent with the patient level ITC.

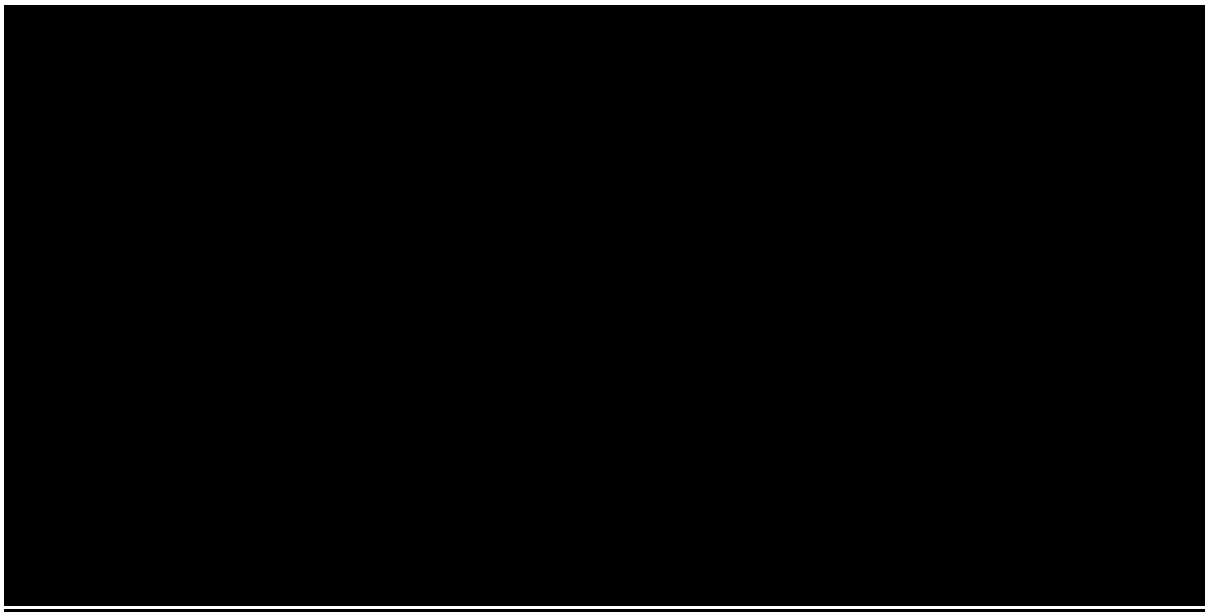
As the covariate adjusted analysis in the ITT population is the most robust analysis, this will be used for the economic model as a scenario analysis to predict routine surveillance RFS. To visually observe the effect of applying the covariate adjusted HR to the ITT population, Figure 30 and Figure 31 present KMs with estimated placebo in CheckMate 238 and estimated nivolumab in CA184-029, respectively. The estimated curves both produce the intuitive result that for RFS nivolumab performs better that ipilimumab and ipilimumab performs better for RFS than placebo, which is in line with the within-trial analysis results.

Table 15: RFS results of the indirect treatment comparison using the Bucher method

Method	Population	TRT 1	TRT 2	HR (95% CI)
Bucher ITC – unadjusted	ITT	Nivo	PBO	[redacted]
Bucher ITC – stage, age, sex adjusted[a]	ITT	Nivo	PBO	[redacted]
Bucher ITC – lymph node, age, sex adjusted	ITT	Nivo	PBO	[redacted]
Bucher ITC – unadjusted	Stage IIIb/c	Nivo	PBO	[redacted]
Bucher ITC – stage, age, sex adjusted	Stage IIIb/c	Nivo	PBO	[redacted]
Bucher ITC – lymph node, age, sex adjusted	Stage IIIb/c	Nivo	PBO	[redacted]
Patient level ITC – exponential curve (for comparison)	ITT	Nivo	PBO	[redacted]

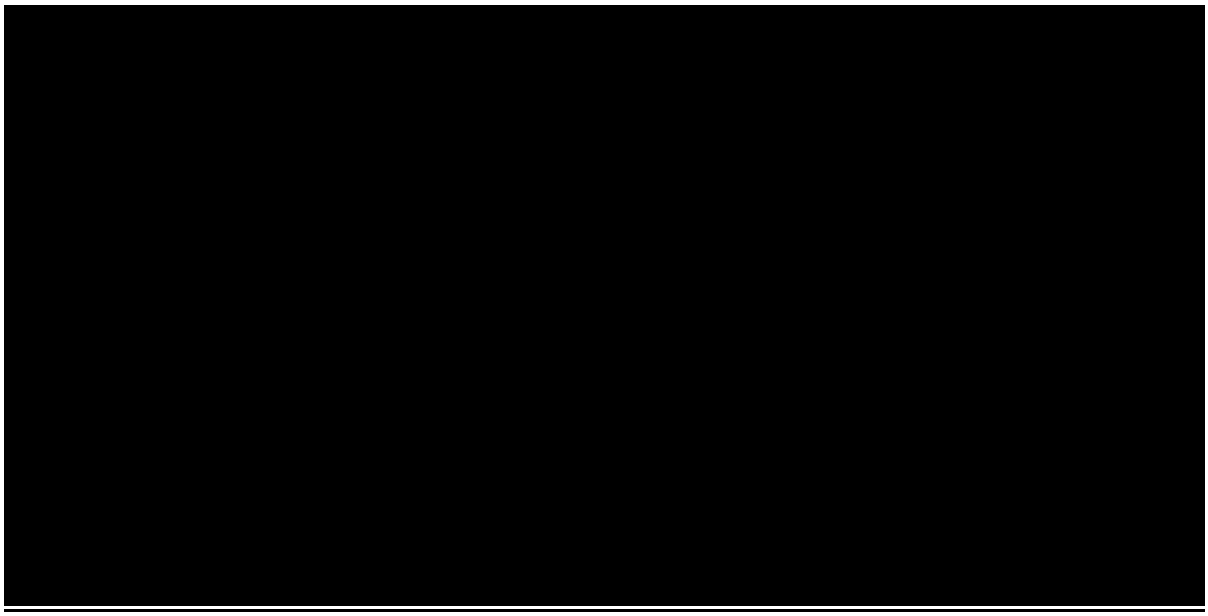
Key: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; Nivo, nivolumab; PBO, placebo; TRT, treatment.
Note: [a], Explored as sensitivity analysis in the economic model.

Figure 30: Recurrence-free survival 238 Kaplan–Meier split by treatment with Bucher estimated placebo



Key: Ipi, ipilimumab; KM, Kaplan–Meier; Nivo, nivolumab; PBO, placebo.
Notes: Dashed line indicates curve is estimated from the Bucher hazard ratio.

Figure 31: Recurrence-free survival 238 Kaplan–Meier split by treatment with Bucher estimated nivolumab



Key: Ipi, ipilimumab; KM, Kaplan–Meier; Nivo, nivolumab; PBO, placebo.
Notes: Dashed line indicates curve is estimated from the Bucher hazard ratio.

Uncertainties in the indirect and mixed treatment comparisons

A limitation of the analyses performed is that the primary definition of RFS differed between the CA184-029 and CheckMate 238 studies. To this end, the RFS analysis in CA184-029 that most closely matched CheckMate 238 was chosen for analysis and is discussed above in more detail. However; as seen in Figure 3 and Table 6 of Appendix D, the choice of RFS definition is unlikely to have a major impact on results. The RFS data used within these analyses for CheckMate 238 relatively immature (median RFS has not been reached), and therefore, the long-term extrapolations made in the patient level ITC should be considered in terms of their validity compared to external data sources. The accuracy of the selected base case model in projecting the results of the most recent data-cut do, however, somewhat reduce the uncertainty surrounding extrapolation (Section B.3.10).

Another source of uncertainty is ipilimumab which was given up to 1 year in CheckMate 238 and 3 years in CA184-029. The impact of this, however, is expected to be limited as the data show similar RFS outcomes for Stage IIIb/IIIc patients across trials, the median number of doses between the two ipilimumab arms in both trials was four and only [redacted]% of patients receiving ipilimumab in CA184-029 had treatment beyond 1 year. This is in line with clinical opinion received at the advisory board where it was expected that the difference in dosing would not impact effectiveness.[1] In addition, any such differences should be adjusted for by the inclusion of the trial covariate in the adjustment.

Furthermore, the staging of patients differed between the CheckMate 238 and CA184-029 studies, that is, the CA184-029 study did not recruit Stage IV NED patients, while the CheckMate 238 study did not recruit Stage IIIa patients. To this end, the Bucher comparison conducted analyses adjusting for this difference in patient characteristics. Although a slight difference in the treatment effect was observed between the ITT and Stage IIIb/c population, this was small, suggesting that the inclusion of Stage IIIa and Stage IV NED patients does not modify the treatment effect. In addition, as the underlying biology across stages is similar, with staging on a continuum that differs only in terms of tumour thickness, number of localised nodes, and presence of ulceration[47], a consistent clinical benefit can be expected to be observed across all stages of disease. This is further discussed in

Section B.2.13. However, assumption was required that the relative treatment effect between nivolumab and ipilimumab is consistent in Stage IIIa patients and is consistent between ipilimumab and placebo in Stage IV NED patients.

It was also not possible to evaluate the effect of B-RAF and PD-L1 status for the CA184-029 trial, as B-RAF status was only collected retrospectively and therefore was not well reported, and PD-L1 was not established at the time of the CA184-029 study. Further, clinical opinion has suggested that due to the changing nature of PD-L1 expression and challenges associated with measuring and assessing PD-L1, it would not be informative to present outcomes by PD-L1 status.[1] PD-L1 status is also not routinely tested in clinical practice.[45] BRAF status is also not relevant in this comparison given that both nivolumab and routine surveillance apply to all patients regardless of mutation status; importantly, retrospective analyses have confirmed that nivolumab has similar efficacy and safety outcomes regardless of BRAF mutation status.[48]

Finally, a comparison of safety data was not conducted due to differing definitions of AEs in the CheckMate 238 and CA184-029 studies, the main difference being the safety window after the last dose of treatment (30 days for CheckMate 238 and 70 days for CA184-029). Additionally in the CA184-029 trial, patients were on treatment longer than in the CheckMate 238 trial and were therefore followed up for longer, increasing the chance AEs, which would impact on the comparison However, safety data were analysed through a simple Bucher comparison. The results of this analysis support the results of the CheckMate 238 study, that is, nivolumab is a well-tolerated treatment, with a safety profile generally comparable to routine surveillance [redacted].

Conclusion

Both the PLD meta-regression and Bucher ITC show consistent results, with a substantial benefit in RFS for nivolumab compared to routine surveillance (HR: [redacted] in the Bucher ITC (adjusted) and [redacted] estimated from the exponential PLD meta-regression model). These results are also consistent with the benefit observed for pembrolizumab, another PD-L1 checkpoint

inhibitor agent (hence with the same mechanism of action as nivolumab), compared to placebo in the KEYNOTE 054 study (HR=0.57 [98.4% CI, 0.43-0.74]; p<0.0001).[49]

In the Bucher ITC, the effect of covariate adjustment made minimal difference to the results; this was expected *a priori* as prognostic variables were generally well balanced between treatment arms. Furthermore, there is no evidence of the KM curves converging after treatment with nivolumab was stopped; therefore, we would expect the benefits seen with nivolumab treatment to continue in the long-term. As the PLD meta-regression model utilises PLD from both studies, it allows estimation of Stage IIIA nivolumab patients and Stage IV NED placebo patients (therefore inclusive of all patients with lymph node involvement and metastatic disease in line with anticipated license), does not require the proportional hazards assumption, and allowed for a more flexible and robust modelling approach; it was therefore used as the base case within the economic model, and the Bucher approach was used as a scenario analysis.

Results of the parametric survival model and Bucher ITCs are used in the economic model, presented in Section B.3.3.

B.2.10. Adverse reactions

No other studies outside of CheckMate 238 were identified that provided additional safety data for nivolumab. All safety data, apart from subsequent therapy, is presented as per the clinical cut-off of 15 May 2017, where median follow-up was 19.5 months. Subsequent therapy data are based on the updated analysis, with a minimum follow-up of 24 months.

Treatment exposure

A summary of treatment exposure is presented in Table 16.

At the time of clinical cut-off (15 May 2017), all 905 treated patients were no longer receiving the trial drug.[4] The median number of doses was 24 (range: 1–26) in the nivolumab group and 4 (range: 1–7) in the ipilimumab group.[4] A total of 397 patients had completed 1 year of treatment (as per protocol): 275 of 452 patients (60.8%) in the nivolumab group and 122 of 453 patients (26.9%) in the ipilimumab group.[4] The

median duration of therapy was [redacted] in the nivolumab group and [redacted] in the ipilimumab group.[3]

Table 16: Treatment exposure, CheckMate 238, 18-month follow-up

	Nivolumab (n=452)		Ipilimumab (n=453)	
	Nivolumab	**Ipilimumab placebo**	**Nivolumab placebo**	**Ipilimumab**
Doses received:				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min–max)	24 (1–26)	7 (1–7)	6 (1–26)	4 (1–7)
Number of doses received, n (%):				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
>7	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative dose, mean mg/kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity, n (%):				
≥110%	[redacted]	[redacted]	[redacted]	[redacted]
90% to <110%	[redacted]	[redacted]	[redacted]	[redacted]
70% to <90%	[redacted]	[redacted]	[redacted]	[redacted]
50% to <70%	[redacted]	[redacted]	[redacted]	[redacted]
<50%	[redacted]	[redacted]	[redacted]	[redacted]

Key: N/A, not applicable; SD, standard deviation.
Source: Weber *et al.*, 2017[4]; CheckMate 238 CSR[3]

After [redacted] follow-up, subsequent anticancer therapy (including radiotherapy, surgery, and systemic therapy) was administered in [redacted] patients ([redacted]) in the nivolumab group and in [redacted] ([redacted]) in the ipilimumab group.[15] A summary of subsequent treatments received is presented in Table 17.

Table 17: Subsequent therapy, ITT population, CheckMate 238, 24-month follow-up

N (%)	Nivolumab (n=453)	Ipilimumab (n=453)
Any	141 (31.1)	186 (41.1)
Surgery	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Systemic therapy	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Anti-PD-1 agent	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
CTLA-4 inhibitor	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Ipilimumab/nivolumab combination	[redacted]	[redacted]
BRAF inhibitor	[redacted]	[redacted]
MEK/NRAS inhibitor	[redacted]	[redacted]
BRAF/MEK combination	[redacted]	[redacted]
Other (experimental agents)	[redacted]	[redacted]
Unassigned	[redacted]	[redacted]

Key: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ITT, intention-to-treat; PD-1, programmed death receptor-1.
Source: Weber et al., 2018[2]; BMS Data on File, 2018[15]

Adverse events

A summary of AEs is reported in Table 18. AEs were reported in almost all patients in both treatment groups, with Grade 3–4 AEs reported by 25.4% of nivolumab patients compared to 55.2% of ipilimumab patients.[4] Drug-related AEs were also reported more frequently with ipilimumab (95.8%) compared to nivolumab (85.2%). In addition, discontinuations due to drug-related AEs were reported in 7.7% of nivolumab patients compared to 41.7% of ipilimumab patients, of which 4.6% and 30.9% were Grade 3–4, respectively.

Table 18: Summary of adverse events, all treated patients, CheckMate 238, 18-month follow-up

	Nivolumab (n=452)	Ipilimumab (n=453)
Any AE, n (%)	438 (96.9)	446 (98.5)
Grade 3–4	115 (25.4)	250 (55.2)
Any SAE, n (%)	79 (17.5)	183 (40.4)
Grade 3–4	[redacted]	[redacted]
Drug-related AE, n (%)	385 (85.2)	434 (95.8)
Grade 3–4	65 (14.4)	208 (45.9)
Drug-related SAE, n (%)	[redacted]	[redacted]
Grade 3–4	[redacted]	[redacted]
Discontinuations due to AEs, n (%)	44 (9.7)	193 (42.6)
Grade 3–4	21 (4.6)	140 (30.9)
Discontinuations due to drug-related AEs, n (%)	35 (7.7)	189 (41.7)
Grade 3–4	16 (3.5)	136 (30.0)
Treatment-related deaths, n (%)	0 (0)	2 (0.4)

Key: AE, adverse event; SAE, serious adverse event.
Source: Weber *et al.*, 2017[4]; CheckMate 238 CSR[3]

Treatment-related select AEs involving the skin, gastrointestinal (GI) tract, liver, and lungs were less frequent in the nivolumab group than in the ipilimumab group.[4] Diarrhoea was reported in 24.3% of nivolumab-treated patients and 45.9% of ipilimumab-treated patients, of which 1.5% and 9.5% were Grade 3–4, respectively. Most endocrine disorders were also reported more frequently in the ipilimumab arm, including pituitary disorder, which was reported in 1.8% of nivolumab-treated patients and 12.4% of ipilimumab-treated patients. However, thyroid disorders were reported more frequently in the nivolumab arm (20.4%) compared to the ipilimumab arm (12.6%).[4]

The median time until the onset of treatment-related select AEs was generally shorter among patients receiving ipilimumab; the time until the resolution of such events was similar in the two groups, with the exception of skin disorders, which took longer to resolve in the nivolumab group.[4] A summary of treatment-related select AEs is presented in Appendix F.

The majority of IMAEs (specific events occurring within 100 days of the last dose, which includes pneumonitis, diarrhoea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine abnormalities [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]) in the nivolumab group were [redacted].[3] Grade 3–4 IMAEs in the [redacted] were less frequently reported in the nivolumab group than the ipilimumab group; [redacted]. The most frequently reported any-grade IMAEs were [redacted]. The most frequently reported Grade 3–4 IMAEs were [redacted].

[redacted].[3] [redacted] A summary of IMAEs is presented in Table 19.

Table 19: IMAEs, safety population, CheckMate 238, 18-month follow-up

	Nivolumab (n=452)		Ipilimumab (n=453)	
	Total	**Grade 3–4**	**Total**	**Grade 3–4**
Endocrine				
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Adrenocortical insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]
Hypopituitarism	[redacted]	[redacted]	[redacted]	[redacted]
Lymphocytic hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Basedow's disease	[redacted]	[redacted]	[redacted]	[redacted]
Primary hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]

	Nivolumab (n=452)		Ipilimumab (n=453)	
	Total	**Grade 3–4**	**Total**	**Grade 3–4**
Type 1 diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]
Fulminant type 1 diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea/Colitis				
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune colitis	[redacted]	[redacted]	[redacted]	[redacted]
Enteritis	[redacted]	[redacted]	[redacted]	[redacted]
Enterocolitis	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis				
ALT increase	[redacted]	[redacted]	[redacted]	[redacted]
AST increase	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increase	[redacted]	[redacted]	[redacted]	[redacted]
Drug-induced liver injury	[redacted]	[redacted]	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis				
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]	[redacted]	[redacted]
Nephritis and renal dysfunction				
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Tubulointerstitial nephritis	[redacted]	[redacted]	[redacted]	[redacted]
Rash				
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity/Infusion				
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]

Key: ALT, alanine transaminase; AST, aspartate transaminase; IMAE, immune-mediate adverse event.
Source: CheckMate 238 CSR[3]

Safety overview

The overall safety profile of nivolumab and ipilimumab in this adjuvant trial was consistent with the safety profile previously observed in other tumours studied, and no new safety concerns were identified in this study. Nivolumab was associated with low rates of drug-related serious AEs and drug-related AEs leading to

discontinuations. Of patients who discontinued treatment with nivolumab, this was due to toxicity in less than a quarter of patients ([redacted]). Importantly, 61% of nivolumab-treated patients completed 1 year of treatment, showing the tolerability of this drug.

The safety profile of nivolumab is already well-established due to its use in advanced/metastatic melanoma, as well as other monotherapy indications including renal cell carcinoma, lung cancer, Hodgkin lymphoma, squamous cell cancer of the head and neck and urothelial carcinoma. AEs seen in the CheckMate 238 study were in line with the immunotherapeutic mode of action, with most IMAEs [redacted].[3] Importantly, no deaths attributable to the study drug occurred in the nivolumab arm of the trial. As experience and familiarity with immunotherapy treatment grows, quick and effective management of common side effects is likely to continually improve; this is supported by risk management measures outlined in the SmPC.

These results are echoed by the British Association of Skin Cancer Specialist Nurses (BASCSN), who have stated that treatment is generally well tolerated, with the majority of patients able to carry out all activities of daily living including going to work.[50] The BASCSN also stated that "*while there are possible adverse effects from this treatment, these are now well identified and can be managed effectively. Overall there are likely to be significant health benefits to those individuals affected by this disease*".

As such, nivolumab demonstrates a favourable benefit–risk profile for the treatment of melanoma patients with involvement of lymph nodes or metastatic disease who have undergone complete resection with well-established and clinically manageable safety data.

B.2.11. Ongoing studies

No relevant studies further to CheckMate 238 are ongoing.

B.2.12. Innovation

Nivolumab is the first checkpoint inhibitor agent licensed for use in the adjuvant setting for melanoma and thus represents a 'step-change' in the management of this

disease for patients. This indication builds upon the value of nivolumab in the systemic melanoma setting as well as more recent indications, which clearly demonstrate the potential of immunotherapies to result in durable response and long-term survival benefit. Due to its novel mechanism of action (see Table 2), nivolumab has the potential to offer an active treatment option for patients in the adjuvant setting, providing significant benefit over the current routine surveillance standard of care by reducing relapse and thus the need for long-term systemic treatment in the post-adjuvant setting. As a treatment for advanced melanoma, nivolumab has made a significant difference in survival for metastatic patients, and according to clinicians this treatment is likely to reduce the risk of patients developing metastatic disease.[50]

By receiving an effective active treatment in the adjuvant setting, patients will gain unprecedented advantages as they are able to benefit from the immunotherapeutic effect earlier in the treatment pathway. In contrast to routine surveillance, which cannot adequately capture metastases until they are large enough to be detected, nivolumab works by priming the immune system to respond to micrometastases in the first instance, thus being a more effective method of preventing progression to advanced disease; consequently, both societal and healthcare costs will be reduced through the use of this intervention.

While we would anticipate health-related benefits, such as improved RFS and response benefits, to be captured in the quality-adjusted life year (QALY) calculation, their significance to patients should be viewed as innovative. The curative potential associated with immunotherapies such as nivolumab, and the possible return to normal living that this offers patients (in contrast to progression to advanced disease and the burden associated with this) is a remarkable advance from what is currently available in the adjuvant setting. Furthermore, as melanoma disproportionately affects a younger population, this has a significant impact on the working-age population, mainly a loss of economic productivity; such an effect is not captured in the QALY calculation. Although this treatment will inevitably have an impact on resources and capacity, the BASCSN believe that this will be mitigated in the future with a reduction in the number of patients needing treatment for metastatic disease.[50]

There are currently no effective adjuvant treatments for melanoma at this earlier stage of disease. As the only active treatment option available to these patients in NHS England, nivolumab meets the need for an effective treatment to be offered to patients, removing the psychological burden and anxiety resulting from waiting for potential recurrence of disseminated disease. As stated by the BASCSN, the use of nivolumab in this setting is likely to provide an innovative opportunity to improve OS for this patient group, and the sooner this treatment is available in an adjuvant setting, the better for NHS patients.[50]

B.2.13. Interpretation of clinical effectiveness and safety evidence

In the adjuvant melanoma setting, patients are currently managed through the use of routine surveillance, which offers no clinical benefit in preventing relapse. This is reflected by the fact that ≥60% of melanoma patients with lymph node involvement or metastatic disease will relapse.[35] As such, there is a clear unmet need for an adequate, active treatment option that has a survival benefit, preventing progression to advanced disease.

In patients with completely resected Stage IIIB, IIIC and IV melanoma, nivolumab demonstrated a statistically significant and clinically relevant improvement in RFS compared to ipilimumab after 24-months follow-up, with a 34% reduction in the risk of recurrence (HR: 0.66; p<0.0001).[2] Median RFS was 30.8 months (95% CI: 30.8, NA) in the nivolumab arm, and 24.1 months (95% CI: 16.6, NA) in the ipilimumab arm, with a 1-year RFS rate of 70.4% and 65.8%, respectively. Importantly, RFS at Year 1 in the ipilimumab arm was consistent with results seen for the CA184-029 study (63.5%[35]) with the same dose, despite the inclusion of patients at more advanced stages in CheckMate 238 (Stage IV NED included and Stage IIIA excluded). Therefore, the efficacy of nivolumab can be expected to translate to Stage IIIA patients and thus provide benefit to all patients with involvement of lymph nodes or metastatic disease.

Nivolumab was also associated with a statistically significant improvement in development of DMFS after 24 months, with a 24% reduction in the risk of DMFS (HR: 0.76 [95% CI: 0.56, 0.98]; p=0.02).[2] At 12 months, DMFS rates were higher in the nivolumab group than in the ipilimumab group (80.1% versus 72.7%,

respectively), and this remained consistent at 18 months (75.2% versus 67.1%, respectively) and 24 months (70.5% versus 63.7%, respectively).

The improvement in both RFS and DMFS with nivolumab was demonstrated consistently across a number of different subgroups, including for PD-L1 status, BRAF status and disease stage; indeed, CheckMate 238 is the first trial in the adjuvant setting to show benefit for patients with resected Stage IV melanoma.

Results of both the parametric survival modelling and Bucher ITCs (described in Section B.2.9), showed an improvement in RFS with nivolumab compared to placebo; in the Bucher ITC this resulted in a HR of [redacted] in the unadjusted ITT population. When adjustments were made for differences in patient populations, nivolumab demonstrated a [redacted] reduction in the risk of recurrence compared to placebo (HR: [redacted]). Furthermore, although the Bucher ITC results for the Stage IIIB/C population [redacted] showed a slight difference in the treatment effect compared to the ITT population, the difference was only small, suggesting that inclusion of Stage IIIA and IV patients does not modify the treatment effect.

The benefits seen with RFS are expected to translate into a long-term survival benefit; this is further discussed in Section B.3.3. The potential for long-term survival is further supported by the extensive clinical evidence for nivolumab and is based on a sound biological rationale that melanoma is a highly immunogenic tumour, making it an ideal target for immunotherapy treatment.[51] A survival plateau representing an immunotherapy-survival tail was first observed in patients with advanced melanoma who were treated with ipilimumab monotherapy.[52] This plateau has since been shown with nivolumab monotherapy and the nivolumab plus ipilimumab combination in melanoma in the post-adjuvant setting and in other indications.[53, 54] Introducing immunotherapy earlier in the treatment pathway, when patients have a better-preserved immune system and a better prognosis, should result in an even greater clinical benefit than seen in the pivotal study in the advanced setting (CheckMate 067).[53] Long-term survival is not a feature of current adjuvant treatment options, with routine surveillance providing no active clinical benefit.

The overall safety profile of nivolumab in CheckMate 238 was consistent with that previously observed in the systemic setting, with no new safety concerns observed, demonstrating that nivolumab is a well-tolerated treatment. Nearly two-thirds of patients (61%) completed 1 year of treatment with nivolumab, further demonstrating the manageable toxicity profile. The manageable safety profile of nivolumab has also been acknowledged by the BASCSN who have stated that treatment is generally well tolerated, with most patients able to carry out all activities of daily living, including going to work.[50]

After treatment with nivolumab, patients' HRQL from baseline was maintained in both the EQ-5D, EORTC QLQ-C30 and WPAI:GH questionnaires. Of note, during the first 12 weeks of ipilimumab induction, there were lower QoL scores in the ipilimumab group than in the nivolumab group; however, this difference was not seen as clinically important. Furthermore, these results were in comparison to ipilimumab. When compared to the current standard of care, routine surveillance, and in addition to the tolerable profile of nivolumab and the improved RFS after 1 year of treatment, a significant, positive impact on QoL can be expected alongside the psychological benefit of receiving an active treatment as opposed to watchful waiting.

Strengths and limitations of the clinical evidence base

Overall, the clinical evidence available provides an appropriate base to inform the assessment of clinical effectiveness and cost-effectiveness of nivolumab for the treatment of completely resected Stage III and IV melanoma.

In CheckMate 238, nivolumab was directly compared to ipilimumab, an active comparator that has previously demonstrated improvements in RFS and OS against placebo. Placebo is the key comparator in this submission and representative of the current practice in England of routine surveillance for patients in the adjuvant setting. Although head-to-head data are not available for direct comparison to routine surveillance, an ITC has been conducted that demonstrates superiority of nivolumab over routine surveillance for the primary outcome of RFS. The results of this ITC are supported by direct evidence of an alternative PD-L1 checkpoint inhibitor agent (hence with the same mechanism of action as nivolumab) being investigated for use

in the adjuvant setting which recently reported an RFS HR of 0.57 compared to placebo.[55]

CheckMate 238 was conducted in line with GCP guidelines, with steps taken to minimise bias and independent monitoring or advisory committees in place to provide oversight of safety and efficacy considerations, study conduct and risk–benefit ratio. As the aim of adjuvant treatment following complete resection of Stage III and IV melanoma is to prevent disease recurrence, RFS is a key outcome of importance in the adjuvant setting and is a standard efficacy measure for adjuvant trials; indeed, previous NICE submissions for the adjuvant treatment of breast cancer and gastrointestinal stromal tumours have used RFS as the primary trial endpoint.[56, 57] RFS was thus chosen as the primary outcome of the study given the established correlation of RFS and OS with immunotherapy (ipilimumab) in adjuvant melanoma and the known safety profile of nivolumab.[36] Although OS is a clinically meaningful endpoint in oncology studies, it requires extended follow-up and in the adjuvant setting is particularly confounded by subsequent treatment, which is why OS was a secondary efficacy endpoint in the trial. OS results are not presented due to the immaturity of follow-up at the time of database lock.

The CheckMate 238 study is generally reflective of patients presenting for treatment of melanoma after complete resection in UK clinical practice.[1] European sites represented 50% of all involved, including eight in England. Furthermore, clinical experts practising in the field of melanoma confirmed that they would be comfortable applying CheckMate 238 trial results to patients presenting in UK clinical practice.[1]

Although CheckMate 238 did not include Stage IIIA patients as per AJCC 7th edition, as a large proportion of these patients will relapse and require treatment in the metastatic setting, the benefit of treating these patients earlier in the treatment pathway is substantial, reducing both patient burden (through preventing the symptoms of more advanced disease) and healthcare costs of drugs in the metastatic setting. Furthermore, as the AJCC staging has recently been amended, some Stage IIIB patients may now be classified as Stage IIIA and vice versa, meaning the CheckMate 238 study may have included Stage IIIA patients as per the 8th AJCC edition. As such, a patient population defined by lymph node involvement and metastatic disease (as per the license terms) more accurately reflects the

patient population in study CheckMate 238 and will mitigate any confusion arising from the change in staging criteria between the AJCC 7th and 8th edition. Importantly, the RFS benefit observed in the CheckMate 238 study was demonstrated consistently across all stages of disease (see Section B.2.7). This consistency is expected to translate to patients with Stage IIIA disease, since the underlying biology across Stages IIIA, IIIB and IIIC is similar, with staging on a continuum that differs only in terms of tumour thickness, number of localised nodes, and presence of ulceration.[5]

To provide clarity, the manufacturer reviewed the pre-defined subgroup analyses within CheckMate 238, and for patients with non-ulcerated, micrometastatic disease (n=[redacted]), nivolumab had a HR of [redacted] versus ipilimumab.[15] Many of these patients would have been considered Stage IIIB in the AJCC 7th edition, but Stage IIIA in the AJCC 8th edition. In patients with non-ulcerated, micrometastatic disease (n=[redacted]) who were defined as Stage IIIB patients per the 7th edition but would be considered Stage IIIA patients per the 8th edition, nivolumab showed a HR of [redacted] compared to ipilimumab based on the earlier database lock (18-month follow-up). With a minimum follow-up of [redacted], one more patient in the ipilimumab group had an event, resulting in a HR of nivolumab over ipilimumab was [redacted]. In summary, applying the new AJCC 8th edition to CheckMate 238, patients with Stage IIIA disease have been included in the CheckMate 238 study; benefit with nivolumab has consistently been observed across all populations. Furthermore, efficacy results with ipilimumab treatment were consistent in CheckMate 238 and CA184-029, which used the same ipilimumab dose and included Stage IIIA patients while excluding Stage IV NED patients (as per AJCC 6th edition)[35]; such consistency can reasonably be expected to be mirrored with nivolumab due to the similar immunotherapeutic mechanism of action.

In light of this, the anticipated license proposes a patient population defined by lymph node involvement and metastatic disease, thus more accurately reflecting the patient population in CheckMate 238. This will also allow clinicians to make more patient-specific treatment decisions, rather than those based on staging, which does not always accurately reflect patient's status.

Finally, completion lymph node dissection is used in current practice for prevention of recurrence in melanoma patients who have been found to have sentinel node involvement; however, this has shown no melanoma specific survival advantage and its use is likely to be reduced.[58] This change in surgical procedure would limit the pathological information available for staging patients and could mean that approximately 20–40% of patients currently categorised Stage IIIB could be classified as Stage IIIA. There would therefore be a requirement for this potentially burdensome surgery and its associated morbidity to be conducted to enable more detailed staging of patients from IIIA to IIIB. This would not be necessary should nivolumab become available for all Stage III patients in line with the anticipated license granted by the EMA.

In conclusion, nivolumab offers an innovative active treatment option with the potential to significantly reduce the risk of progression to metastatic disease and, therefore, improve the life expectancy of melanoma patients with involvement of lymph nodes or metastatic disease who have undergone complete resection.

B.3. Cost effectiveness

- Stage III or IV (no evidence of disease) resectable melanoma is associated with high patient burden and substantial economic cost due to high risk of recurrence and management of systemic disease.
  - Following complete resection, patients are currently being managed through routine surveillance.
- Economic analysis incorporates evidence from CheckMate-238 and CA184-029 Phase III RCTs and trial level association analysis of the relationship between recurrence-free survival (RFS) and overall survival (OS) across adjuvant trials.
- Nivolumab meets the NICE fast track assessment criteria, with a base case incremental cost-effectiveness ratio (ICER) below £10,000/quality-adjusted life year (QALY) and the majority of sensitivity analyses below £20,000/QALY.
- Nivolumab is a highly effective (HR_{RFS} [redacted]) and cost-effective treatment versus routine surveillance in the adjuvant setting:
  - ICER of £8,769 per QALY gained at the current patient access scheme (PAS)
  - 67.8% likelihood of cost-effectiveness at a willingness to pay threshold of £10,000 per QALY
- Nivolumab reduces the likelihood of recurrence, downstream costs and quality of life impacts associated with the management of advanced/metastatic disease while prolonging survival:
  - [redacted] of patients no longer experience a recurrence within their lifetime (NNT = [redacted])
  - An increase of [redacted] life years ([redacted]) over a lifetime versus routine surveillance
  - [redacted] QALY gains for every recurrence prevented
  - Subsequent treatment costs reduce by approximately £[redacted] per patient
- The ICER remained largely insensitive to the parameters and assumptions tested in OWSA and scenario analyses, with the majority of scenarios < £20,000/QALY.
- Threshold analysis shows that nivolumab's efficacy versus routine surveillance would need to be considerably lower than predicted before not being a cost-effective treatment:
  - An increase by [redacted]% in the nivolumab hazard of death would result in it not being cost-effective at the £10,000 threshold ([redacted]% increase at £20,000 threshold)
  - ICER is below £15,000 even when nivolumab OS is no better than ipilimumab (CA184-029)
  - ICER remains below £20,000/QALY when the upper bound of CheckMate-238 RFS is tested
- Key strengths of the analysis include:
  - Certainty of treatment costs due to the 12-month stopping rule included in the trial and license
    - Estimated drug and administration cost reduction of £[redacted] compared to nivolumab monotherapy in the metastatic setting
  - Head-to-head data comparing to an active treatment with proven RFS and OS benefit
  - The model projections based upon the 18-month data-cut predicts well the latest trial information
  - Maturity of evidence available from the CA184-029 trial and registry information
  - The measurement of EQ-5D data throughout the CheckMate 238 trial, including post recurrence
- Nivolumab is a highly cost-effective use of the NHS resources for patients with high risk of recurrence, and therefore, it should be recommended to address the high unmet need in this setting.

B.3.1. Published cost-effectiveness studies

Identification of studies

An SLR was undertaken with the primary aim to identify the available economic evidence for the current treatment options for patients with melanoma in an adjuvant setting. The specific objectives were to identify economic evaluations/studies for patients with adjuvant treatment of melanoma. The secondary objective was to identify utility studies for patients with melanoma in the adjuvant setting (reported in Section B.3.4).

The SLR processes conformed to the specifications of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[59] The SLRs were performed in three parts: a comprehensive and systematic search of the published literature to identify all potentially relevant studies; a systematic selection of the relevant studies based on the explicit inclusion and exclusion criteria; and an extraction of the relevant data from the eligible studies to assess the economic evidence and the impact on a patient's health-related quality of life (HRQL) in terms of utilities.

The review includes searches of standard electronic databases, including:

- Embase®
- The Cochrane Library, including the following:
  - Health Technology Assessment Database (HTAD)
  - National Health Service Economic Evaluation Database (NHSEED)
- MEDLINE®
- EconLit®

Conference proceedings from the last 3 years for a wide range of conferences and HTA websites including NICE were also searched. The search strategies used in the electronic searches are provided in full in Appendix G.

To identify the most recent and relevant data inputs required for an economic model, electronic database searches for economic modelling were restricted to citations published from 2012 onwards (last 5 years). This restriction was applied because the treatment pathway for melanoma has changed substantially for patients downstream

in the metastatic setting; thus, older articles are not considered likely to be relevant. Owing to the scarcity of utility evidence for melanoma, the electronic database/literature searches for the utility review was not limited by publication date.

Bibliographic searches of key systematic review and meta-analysis articles were also conducted to ensure that initial searches captured all the relevant economic studies.

Study selection criteria

The inclusion and exclusion criteria for both the economic evaluations/economic modelling studies and the utility studies are specified in Table 20 in terms of population, interventions, comparators, outcomes and other criteria. The study population assessed included adolescents and adults (≥12 years) with adjuvant treatment of Stage III and IV melanoma. The criteria in terms of interventions are wider than those required for NICE (therapies other than nivolumab are included) as the review was used to identify if there was any relevant evidence for older interventions used outside the UK to inform model development; therefore, active treatments in the adjuvant setting in other countries were included. The included studies were full economic evaluation studies that provide incremental costs and quality-adjusted life years (QALYs) (or any other measure of effectiveness reported together with the costs).

Table 20: Inclusion and exclusion criteria for the economic evaluations/economic modelling and utilities studies

Category	Inclusion criteria		Exclusion criteria	
	Economic studies	**Utility studies**	**Economic studies**	**Utility studies**
Population	• Adolescents and adults (≥12 years) patients with Stage III and IV resected (adjuvant) melanoma		• Healthy volunteers • Paediatric population (<12 years) • Disease other than melanoma • Stage I and II melanoma patients	
Interventions	• Nivolumab, either alone or in combination with any other therapy • Ipilimumab, either alone or in combination with any other therapy • Interferon, either alone or in combination with any other therapy	• No specific inclusion criteria	• Non-drug treatments (e.g. surgery, radiotherapy) • Studies assessing interventions not in included list of intervention	• None
Comparators	• No restriction; all therapies were included.	• No specific inclusion criteria	• No exclusion based on comparator	• None
Outcomes	• Incremental costs, LYs gained and QALYs, and any other measure of effectiveness (in term of which ICER is reported like RFS/PFS/OS/DMFS) reported together with costs • Model inputs • Sensitivity analysis	• Studies reporting utility data (EQ-5D®, SF-6D, HUI, etc.)	• Cost-only outcomes	• Studies not reporting utility values will be excluded

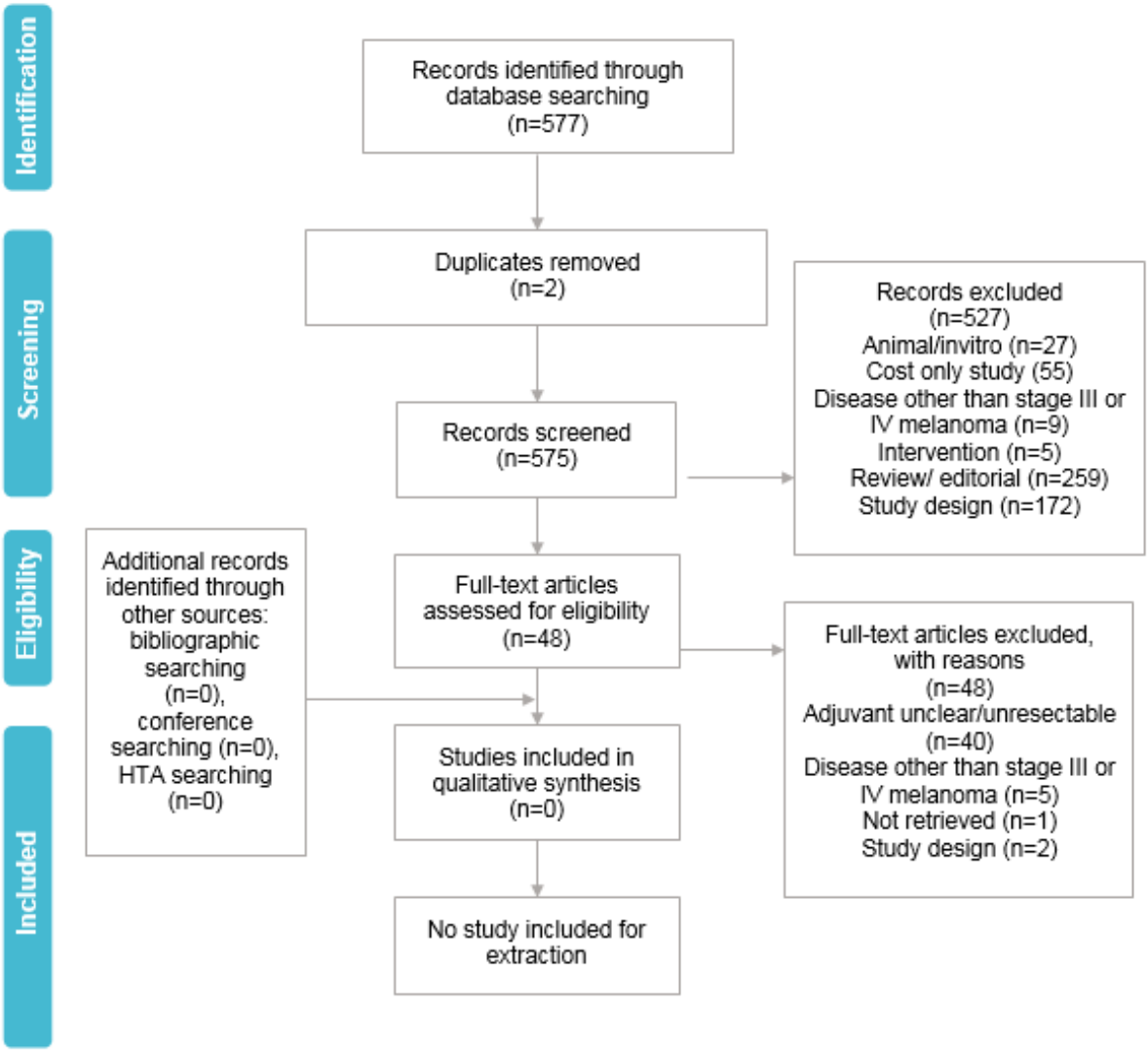
Category	Inclusion criteria		Exclusion criteria	
	Economic studies	**Utility studies**	**Economic studies**	**Utility studies**
Study design	• Full-economic evaluations (cost-consequence, cost-effectiveness, cost–utility, cost–benefit, cost-minimisation, budget impact, all economic evaluation studies based on models)/HTA evaluations • Economic evaluations alongside a trial	• Utility studies • Observational studies	• Reviews, letters, and comment articles • Simple cost analysis	• Reviews, letters, and comment articles
Time limit	• Studies published in the last 5 years were included	• No restriction	• Studies published before 2012	• None
Language	• English and French language		• Other than English and French	
Country of study	• No restriction		• Not excluded on basis of country	

Key: HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LY, life year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year.

PRISMA flow diagram for the economic SLR

Searches were conducted on 29 August 2017 (data provided in Appendix G). No citations were included for cost-effectiveness review. The details for the flow of studies are presented in Figure 32 using a PRISMA flow diagram.

Figure 32: PRISMA diagram for economic modelling studies



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HTA, health technology assessment.

B.3.2. Economic analysis

Owing to the lack of cost-effectiveness studies that met the inclusion criteria for the SLR, no cost-effectiveness studies were used to inform the economic analysis. A *de*

novo economic model was constructed for this submission based on PLD from the CheckMate 238 and CA184-029 trials. Model design was based on a targeted review of prior adjuvant submissions, data availability, clinical input and previous submissions in the metastatic setting (see Model structure Section).

Patient population

The proposed indication for nivolumab in the UK is adults with melanoma with involvement of lymph nodes or metastatic disease that has undergone complete resection.

The patient characteristics in the model are taken from both the CheckMate 238 and CA184-029 trials. The population of CheckMate 238 includes Stage IIIB–IV NED patients; Stage III patients must have had clinically detectable lymph nodes. The population in CA184-029 includes Stage IIIA–C patients only according to the AJCC 7 criteria; all patients were required to have confirmed lymph node involvement. The efficacy of nivolumab demonstrated within CheckMate 238 can be expected to translate to all patients regardless of stage or lymph node involvement given that there is no evidence of an interaction between stage or lymph node involvement and effectiveness in the trial (see Section B.2.7) and that the 2-year RFS rate for ipilimumab is consistent between the CA184-029 and CheckMate 238 studies (Section B2.9). To adjust for potential differences in long-term prognosis, PLD analysis was conducted with stage as a covariate that allows the use of CA184-029 to inform long-term prognosis for both RFS and OS.

Both the CheckMate 238 and CA184-029 trial populations consisted of adults (≥18 years) who had their tumours completely resected. Patients aged ≥15 years were part of the inclusion criteria within the CheckMate 238 study; however, no subjects under the age of 18 were enrolled in the trials. This is due to the limited number of patients in this age category.

Table 22 provides a summary of the patient characteristics used for prediction within the model. The proportion of patients in each group are based on the combination of patients in the ITT populations of the CheckMate 238 and CA184-029 trials. The staging distribution was adjusted to account for the lack of Stage IIIA patients in CheckMate 238 and the lack of Stage IV NED patients in CA184-029 using the

relative proportion with Stage IIIA or Stage IV NED within the respective trials compared to the Stage IIIB and Stage IIIC proportions (Table 21).

Table 21: Stage distribution from CA184-029 and CheckMate 238

Stage	CA184-029	CheckMate 238	Total	Adjusted for the overall population
Stage IIIA	186 (19.6%)	0 (0%)	186 (10.0%)	364* (16.5%)
Stage IIIB	420 (44.2%)	311 (34.5%)	731 (39.4%)	731 (33.1%)
Stage IIIC	345 (36.3%)	422 (46.8%)	767 (41.4%)	767 (41.4%)
Stage IV NED	0 (0%)	169 (18.7%)	169 (9.1%)	345** (15.6%)
Notes: *364 is 19.6% of total Stage IIIA, IIIB and IIIC (364/(364+731+767)) in line with CA184-029 distribution. **345 is 18.7% of total Stage IIIB, IIIC and IV (345/(731+767+345)) in line with CheckMate 238 distribution.				

Table 22: Patient population

Group	%
Stage= IIIA, Sex= M, Age category = < 65	8.4%
Stage= IIIA, Sex= M, Age category = >= 65	0.6%
Stage= IIIA, Sex= F, Age category = < 65	6.4%
Stage= IIIA, Sex= F, Age category = >= 65	1.1%
Stage= IIIB, Sex= M, Age category = < 65	15.0%
Stage= IIIB, Sex= M, Age category = >= 65	4.4%
Stage= IIIB, Sex= F, Age category = < 65	11.5%
Stage= IIIB, Sex= F, Age category = >= 65	2.2%
Stage= IIIC, Sex= M, Age category = < 65	16.9%
Stage= IIIC, Sex= M, Age category = >= 65	5.3%
Stage= IIIC, Sex= F, Age category = < 65	9.2%
Stage= IIIC, Sex= F, Age category = >= 65	3.4%
Stage= IV, Sex= M, Age category = < 65	6.2%
Stage= IV, Sex= M, Age category = >= 65	2.7%
Stage= IV, Sex= F, Age category = < 65	5.6%
Stage= IV, Sex= F, Age category = >= 65	1.2%

Patient weight data were also taken from the CheckMate 238 and CA184-029 trials with individual patient weights from the Western European region used to predict vial wastage for nivolumab [redacted]. The mean weight of Western European patients in both trials used

within the model was [redacted]. A scenario is included within the analysis which also uses UK patient weight data from the metastatic melanoma trials.

Model structure

Choice of model health states

In line with prior NICE submissions for adjuvant treatment for breast cancer, gastrointestinal stromal tumours, and colon cancer, and the primary endpoint of the CheckMate 238 trial, the economic model used to evaluate the cost effectiveness of nivolumab as an adjuvant therapy for metastatic melanoma has been structured around recurrence.[56, 57, 60, 61] During model development, the following factors were considered:

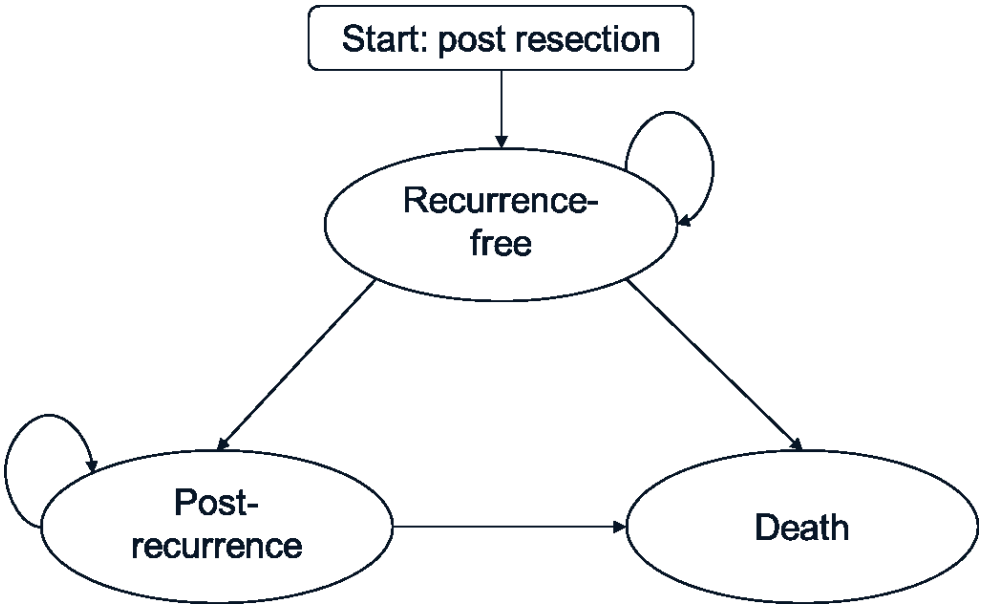
- Is it important to look at different types of recurrences separately?
- Is it important to track more than one type of recurrence?
- What data sources are available to populate model transitions?
- What evidence is there for surrogacy between the different potential health states?

Based upon the above, a three-health state partition survival model was selected for the base case (Figure 33) as:

- There was very little difference in the rates of the different types of recurrence between the 2 arms, indicating that splitting by recurrence type would be unlikely to impact results ([redacted]).[3]
- While a large amount of data exists on historical outcomes for RFS for the routine surveillance arm from prior IFN trials, these data are not split by recurrence type.
- Data are available on the strength of RFS as a surrogate endpoint for OS; however, the recurrence is again not split by type.
- The model is still able to assign costs according to the type of recurrence without tracking recurrence type in a time-dependent manner, allowing sufficiently accurate costing of subsequent therapies.
- Feedback on a prior more complex adjuvant submission was that extrapolating relapse in an overcomplicated manner lacked clinical validity and made the model difficult to critically appraise.[60]

- The feedback provided by clinical experts at the UK advisory board was that it was not necessary to split by recurrence type in order to maintain the clinical plausibility of the model. Indeed, splitting by recurrence type risked incorporating unnecessary complexity within the model.[1]
- Incorporating time dependency would require a Markov structure, which would lead to artificially increased uncertainty due to the limited amount of data available to inform individual transitions (the patient numbers for each type of recurrence and death recurrence free within the CheckMate 238 trial are small).
- Patients can experience more than one recurrence (e.g. local followed by distant); however, the follow-up available within the CheckMate 238 trial does not provide sufficient information to model this (and natural history data for a second recurrence are not available).

Figure 33: Cost-effectiveness model structure



Markov versus partitioned survival model

Once the three-health state model structure had been selected, both Markov model and partitioned survival model structures and the data sources available to inform post-recurrence transitions were considered in line with NICE DSU TSD 19 and included within the model.[62]

Partitioned survival models allow the proportion of patients in each health state to be defined by the individual survival curves extrapolated from the trial data or hazard ratios. This structure is most commonly used within oncology models and is an established method with straightforward implementation and explanation.[62] It does not require the definition of explicit transitions between health states and automatically incorporates time dependencies in the event rates. However, a partitioned survival model can be limited by the validity of projection within the extrapolation period, which would need to be assessed for its clinical and biological plausibility. There are also concerns with these models if the RFS and OS curves cross, and scenarios around the assumptions of long-term extrapolations are limited. In this analysis, nivolumab OS data are not yet available; therefore, any assumptions around the OS of nivolumab are carried forward within the partitioned survival model, and the ability to produce scenarios around post-recurrence survival is restricted. Markov models, on the other hand, although lacking “memory” within health states, allow sensitivity around the PRS of nivolumab to be more formally tested. The downside here is that additional data (and assumptions) are required as the three endpoints now require separate modelling. As of a result, this may reduce the applicability of the results when informing the decision problem given that different evidence sources would need to be used to inform these models.

Given the uncertainty around PRS due to the lack of OS data in the CheckMate 238 trial, scenario analysis has been provided using information on expected survival in the metastatic setting to explore the impact of using different assumptions for PRS. Scenario analysis is also provided testing the impact of moving from a partitioned survival to a Markov structure when the same dataset is used (limited impact). Table 23 summarises the different options and highlights some of the key strengths and weaknesses of each approach.

The partitioned survival model was selected as the base case model structure. Partitioned survival models are more commonly used within oncology models and fit with the three-health state structure. This is also one of the simplest approaches and uses the trial data directly to inform RFS and OS. The other Markov options are presented as scenario analyses to explore structural uncertainty and the uncertainty

around post-recurrence survival given the evolving pathway of metastatic melanoma, and the effects these have on the model results.

Table 23: Summary of post-recurrence survival options

Model option	Explanation	Strengths	Weaknesses
Partitioned survival model (base case)	This option uses RFS data as described in Section B.3.3 and information from a predictive equation for the treatment effect on OS given the treatment effect on RFS based upon available published literature. The HR OS derived from the predictive equation using CheckMate 238 HR RFS (nivo vs ipi) is then applied to the HR OS (ipi vs placebo) from CA184-029 trial to produce HR OS nivo vs placebo. This HR is then applied to the curve used for routine surveillance. Routine surveillance OS is taken from parametric curves fitted to CA184-029 data. Post-recurrence survival is calculated based on the difference between OS and RFS: $PRS = OS - RFS$	• The simplest approach for which the most data are available. • The most recently available correlation equation based upon aggregate data uses the [redacted].	• Most of the trials used to derive the OS/RFS relationship included patients with Stage II melanoma and no Stage IV patients and are over 10 years old. However, the correlation equation uses [redacted], showing a good estimation of the OS compared to the observed OS within these trials. • Despite the uncertainty associated with using OS/RFS relationship; KOLs have previously commented on accuracy of algorithm.
Markov option 1: OS/RFS correlation	This option uses the same RFS and OS curves as the partitioned survival model. RFS curves inform the transitions from RF to PR survival or death. A hazard ratio is derived from CA184-029 trial comparing OS and PRS, which is applied to the OS curves to estimate the post-recurrence transitions to death.	• Relatively simple approach • Allows structural uncertainty around the parametric survival model to be tested.	• As above, but the transitions from post-recurrence to death are estimated from OS curves. • This assumes that PRS and OS has proportional hazards, which appears appropriate (see Appendix N), and the PRS vs OS HR derived from CA184-029 translates to nivolumab.

Model option	Explanation	Strengths	Weaknesses
	This option is included to test for structural uncertainty around the partitioned survival model.		
Markov option 2: PRS from weighted metastatic melanoma survival and local/regional recurrence survival	This option uses RFS data described in Section B3.3. Data informing the transitions from the post-recurrence health state are taken from the weighted survival curves of CA184-029 local/regional recurrence and literature data from metastatic melanoma treatments.	• Not reliant on OS/RFS correlation. • More reflective of clinical practice post-recurrence for distant recurrence patients.	• Adds complexity to the model. • Requires the assumption that adjuvant treatment does not affect survival outcomes post-recurrence. • Data are derived from a variety of sources within the metastatic setting and lack of PLD for comparisons introduces bias in estimates used within the model.

Key: HTA, health technology assessment; KM, Kaplan–Meier; NMA, network meta-analysis; OS, overall survival; PLD, patient-level data; PRS, post-recurrence survival; RFS, recurrence-free survival.

How patients move through the model

Within the model, all patients start post resection in the 'recurrence-free' health state. In each model cycle, patients can either remain in their current health state or progress to a subsequent health state. Patients can move to death from either the 'recurrence free' or the 'post-recurrence' health state. Upon recurrence, patients will move to the 'post-recurrence' health state.

At the recurrence event, patients can either have a local/regional recurrence or a distant recurrence. Both types of recurrence are pooled in the 'post-recurrence' health state. However, for the costing of subsequent treatments and disease monitoring, this health state is split into two groups based on the proportions experiencing each recurrence type to account for the different costs. Model option 2 also splits recurrence by local/regional or distant and weights the OS using these proportions.

Modelling utility

Utilities for the recurrence-free and post-recurrence health states were based on the observed EQ-5D-3L data from CheckMate 238, with published literature used to inform the impact of AEs in the model base case.

Modelling drug cost

In line with the CheckMate 238 trial, the expected marketing authorisation for nivolumab is that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient until 12 months. Nivolumab drug and administration costs are therefore applied as one-off costs within the first model cycle.

Modelling subsequent therapies

The cost of active subsequent anti-cancer therapies that may be used in UK clinical practice were included within the model based upon usage in the CheckMate 238 trial, which was considered by clinicians at the advisory board as reflective of current practice.[1] The dose and time on treatment for these subsequent therapies for both local and distant recurrences were sourced from the trial data and literature.

Individual PLD from CheckMate 238 were used to calculate the proportion of patients post-recurrence who experienced a local/regional or distant recurrence within the

whole trial population (See Section B.3.3). This proportion was then applied to the patients who transitioned into the post-recurrence health state to model the subsequent therapy as a one-off cost upon transition.

Modelling resource use

In line with NICE clinical guidance[63], resource use costs were defined according to the length of time a patient stays recurrence-free (5 years being classed as long-term survivorship) and also, within the post-recurrence state, the type of recurrence. Resource use information was derived from a survey of 6 UK clinicians. AE costs were calculated as a one-off cost applied at the first model cycle based upon CheckMate 238 and CA184-029 trial data.

Summary

Table 24: Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	60 years	General population survival was modelled based on ONS life-tables for the age-range included in CheckMate 238 with patients enrolled from the age of 18 upwards. Just under 5% of the general population are alive after 60 years (assuming all patients die at age 100); therefore, it is long enough to capture any additional costs or benefits throughout the patient's lifetime.
Cycle length	28 days	28 days was considered appropriate given that: (i) the maximum number of patients moving between health states based upon this cycle length is always <5% of the starting total; and (ii) that the frequency of planned follow-up for disease assessment and quality of life is every 12 weeks during the period where data collection is most frequent. Treatments are given for a fixed duration in the adjuvant setting, and therefore, the consideration of different treatment cycle lengths was not required.
Half-cycle correction	Yes	NICE Guide to the Methods of Technology Appraisals, 2013[63]
Were health effects measured in QALYs? If not, what was used?	Yes	
Discount of 3.5% for utilities and costs	Yes	
Perspective (NHS/PSS)	Yes	
Key: PSS, Personal Social Services; QALYs, quality-adjusted life years.		

Figure 34: Detailed model summary diagram

Key: OS, overall survival; RFS, recurrence-free survival.

Intervention technology and comparators

The nivolumab dosing regimen within the model is 3mg/kg every 2 weeks intravenously, as used in the CheckMate 238 trial and as recommended as monotherapy in the summary of product characteristics (SmPC).[64]

The continuation rules recommended within the marketing authorisation are that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient, with the maximum treatment duration with nivolumab as monotherapy for adjuvant melanoma for 12 months. This is in line with the CheckMate 238 study (where subjects were treated with a maximum of 1-year total duration of study medication until recurrence of disease, unacceptable toxicity, or subject withdrawal of consent).[4] Within the model, the PLD for CheckMate 238 time on treatment are used to produce a one-off cost for nivolumab use per patient.

Per the NICE final scope and NICE current adjuvant melanoma guidelines, the comparator within the model is routine surveillance.[65] There are no drug costs associated with this; however, monitoring costs are accrued within the model due to repeat follow-up visits associated with routine surveillance.

B.3.3. Clinical parameters and variables

Clinical evidence

Table 25 summarises the key sources of clinical evidence used to populate the model. The NICE DSU model selection algorithm was used to select the most appropriate structure for all fitted parametric curves.[66]

Information is presented within the main submission text for the model base case long-term extrapolation option. All other options are presented in Appendix N.

Table 25: Sources of key clinical evidence used to populate the model

Clinical evidence	Brief description	Use in the model
CheckMate 238[4]	Phase III trial in fully resected Stage IIIB–IV (no evidence of disease) melanoma patients that investigates the efficacy of nivolumab 3mg/kg (n=452) compared with ipilimumab 10mg/kg (n=453). Only RFS was available at time of developing the submission.	• PLD were used to fit RFS parametric curves • ToT and the number of patients receiving each dose was taken from this study • EQ-5D-3L data were used for trial-based utility analysis • QLQ-C30 data used to map to EQ-5D utility data within scenario analysis • Used for modelling the frequency of AEs for nivolumab • Patient characteristics from the trial were used to populate covariate-adjusted OS and RFS curves • Validation of model outcomes for RFS for nivolumab • Subsequent treatment frequencies used in the base case
CA184-029[35]	Phase III trial in fully resected Stage III melanoma patients that investigates the efficacy of placebo (n=474) compared with ipilimumab 10mg/kg (n=471). RFS and OS were both available with 5 years minimum follow-up.	• PLD were used to fit RFS and OS parametric curves • Patient characteristics from the trial to populate covariate-adjusted OS and RFS curves • PRS for local/regional recurrence patients were used within OS Markov modelling options • QLQ-C30 data used to map to EQ-5D utility data within scenario analysis • Subsequent treatment frequencies used within scenario analysis • AE frequencies used for routine surveillance, with ipilimumab used to link the trials • Validation of model outcomes for OS and RFS for routine surveillance
Long-term OS[14, 42, 43]	Long-term OS based on registry from AJCC 7 (up to 15 years)[43] or AJCC 8 (up to 10 years)[14] Agarwala et al. 2017 study[42]	• Used to model long-term OS from Year 10 onwards • Validation of long-term model outcomes for routine surveillance

Clinical evidence	Brief description	Use in the model
		• Used as upper bound validation for OS and RFS validation due to lower risk patients included
General population mortality[67]	Latest England general population mortality by single year of age	• Used to supplement long-term registry OS from AJCC. • Used to set the minimum threshold of age-matching mortality rates for modelled patients in all treatment arms
Literature based relationship between RFS and OS[37]	Two studies are available: [redacted] • Published study using individual PLD [redacted][37]	• Used to predict the treatment effect for nivolumab on OS given the impact on RFS
Key: AE, adverse events; AJCC, American Joint Committee on Cancer; OS, overall survival; PLD, patient-level data: PRS, post-recurrence survival; RFS, recurrence free survival; ToT, time on treatment.		

Recurrence-free survival

As presented in Section B2.9, given that PLD were available for both studies, a patient level meta-regression was conducted for RFS for nivolumab versus routine surveillance using ipilimumab as the treatment link between the two studies, CheckMate 238 and CA184-029. This methodology represents the "gold-standard" ideal scenario for this type of comparison as it allows for maximum utilisation of available data to inform the comparison and long-term projection.[40] Additionally, use of this method allows for covariate adjustments to predict RFS within the full licensed population. As discussed in Section B2.9, a source of uncertainty with this method is the fact that ipilimumab was given up to 1 year in CheckMate 238 and 3 years in CA184-029. The impact of this, however, is expected to be limited as the data show similar RFS outcomes for Stage IIIb/IIIc patients across trials, the median number of doses between the two ipilimumab arms in both trials was four and only [redacted]% of patients receiving ipilimumab in CA184-029 had treatment beyond 1 year.

The outcome from this analysis is the fitted parametric curves described in Section B2.9. A scenario is also presented which uses parametric curve fit directly to CheckMate 238 data (Appendix D) and the Bucher ITC HR (Section B.2.9) is used to produce the RFS curve for routine surveillance.

Again, as previously mentioned in Section B2.9, a later data cut of RFS from CheckMate 238 recently became available (December 2017 data cut-off). The new KM data were overlaid onto the model predictions based upon the older data cut (May 2017 data cut-off) and demonstrated that the curves still provide a good fit with the latest data cut (see Section B.3.10). The newer data cut was not used for model population as only RFS was updated at this point; safety and quality of life was not updated.

The corrected group prognosis (CGP) method was used to calculate the final parametric survival curves used within the economic model.[69] The CGP method calculates a survival curve for each unique combination of covariates. The proportion of patients in each group (Table 22) are then used to weight the individual survival curves to create a weighted average curve for the entire population.

Use of PLD from both trials allows the model to predict survival curves for the total population of interest (Stages III–IV), although neither trial covers the entire licensed population. RFS benefit observed in CheckMate 238 is expected to translate to patients with Stage IIIA disease, since the underlying biology across Stages IIIA, IIIB and IIIC is similar, with staging on a continuum that differs only in terms of tumour thickness, number of localised nodes, and presence of ulceration.[5] The ITC described in Section B2.9 uses PLD from both CheckMate 238 and CA184-029 to make a comparison between both trial populations for RFS.

To produce estimates of RFS (and additionally OS and PRS) for the patient population of interest (completely resected Stage III and IV (NED) melanoma), the following assumptions were made:

- **Nivolumab is equally effective across all disease stages.** No evidence of difference in effect across stages was found in the CheckMate 238 trial and the Bucher ITC shows a similar outcome when subgroup analysis was conducted using only the overlapping stages between the CheckMate 238 trial and the CA184-029 trial compared to the ITT (see Section B2.9)
- **OS for Stage IV NED patients can be informed using data for Stage IIIC patients.** No data are available on OS for Stage IV NED patients. In the CheckMate 238 trial, Stage IV NED RFS was found to be similar to Stage IIIC RFS (See Figure 35). This was also evident from the CheckMate 238 RFS parametric models and the ITC, which showed little difference between the covariate coefficients. Clinical experts agreed that if resection is possible with Stage IV NED patients, then outcomes would be very similar to Stage IIIC patients. Therefore, it is reasonable to assume equal outcomes between the two stages in terms of RFS and OS.[1, 44] Consequently, the Stage IV NED covariate coefficient in the CA184-029 parametric models for OS and RFS was included and assumed to be the same as the Stage IIIC coefficient.
- Stage IIIA patients' natural history RFS prognosis is not expected to have changed between the CA184-029 and CheckMate 238 trials. The Stage IIIA covariate coefficient included in the CheckMate 238 RFS parametric models was assumed to be the same as the Stage IIIA coefficient from the ITC.

- The most relevant patient population to model is the CheckMate 238 population once stage and other covariates included are adjusted for. The trial covariate, included in the ITC to account for differences between trials that could not be measured, was included in the CA184-029 parametric models and is assumed to be the same as the trial coefficient in the ITC. This is set to predict survival outcomes for the CheckMate 238 trial, which is our main trial of interest and is more recent.

Figure 35: CheckMate 238 RFS split by disease stage

Key: Ipi, ipilimumab; RFS, recurrence-free survival.

Figure 36 shows the final curves using the log-logistic distribution and estimated survival of our matched population of interest (i.e. Stage IIIA – Stage IV NED) using the CGP method. The KM data are taken from the trials for the initial 12 weeks. For nivolumab, the KM curve is taken directly from CheckMate 238. Due to the difference in survival between the two trials in the initial 12 weeks, a HR between the two ipilimumab arms to estimate trial effect was calculated and applied to the placebo

CA184-029 KM curve to predict outcomes for placebo in the population of interest. This HR, [redacted], was estimated using a Cox regression model comparing the ipilimumab arms in CheckMate 238 and CA184-029, censoring patients after 12 weeks.

Figure 36: ITC RFS final curve using matched population

Key: ITC, indirect treatment comparison; RFS, recurrence-free survival.

Overall survival – estimation of treatment effect

For the partitioned survival model, nivolumab OS is generated using a predictive equation for the OS treatment effect based on the RFS treatment effect derived from multiple adjuvant melanoma trials and applied to the routine surveillance OS curve generated from the CA184-029 placebo OS (see Section below). Use of this trial level association analysis provides a simple approach to estimate the OS of nivolumab using data from previous adjuvant melanoma studies. Routine surveillance OS is based on the parametric models derived from the CA184-029 placebo arm. The partitioned survival model uses the difference between the OS curve and RFS to calculate PRS: OS – RFS = PRS.

A recent publication concluded that RFS appears to be a valid surrogate endpoint for OS in Stage II–III melanoma adjuvant therapy.[37] This study used 13 interferon trials to derive a regression equation to estimate HR_{OS} from HR_{RFS}. [redacted]. The first step of this [redacted][68] The framework of this new study is based on the approach described by Burzykowski et al. for two time-to-event endpoints.[70, 71] Due to the lack of individual patient data for some of the adjuvant trials, the first step in this analysis uses [redacted]. The primary analysis of this study uses [redacted]. Several sensitivity analyses were also conducted, [redacted] Table 26 summarises the studies that were included in the surrogacy relationship equation. Further details of this analysis can be found in a separate report.[68]

Table 26: Studies included in the base case correlation relationship

Study	Intervention (dose)	Comparator (dose)	Included in Suciu et al.[37]	Number of patients	HR RFS	HR OS	Included in analysis
ECOG1684[73]	High dose IFN alpha-2b (20MU/m^2 IV for 5 days/week for 4 weeks, then 10MU/m^2 SC 3 days/week for 48 weeks)	Observation	Y	287	0.76	0.84	Y
ECOG1690[74]	High dose IFN alpha-2b (20MU/m^2 IV for 5 days/week for 4 weeks, then 10MU/m^2 SC 3 days/week for 48 weeks) and low dose IFN (3MU a day for 3 days a week for 2 years)	Observation	Y	642	0.88	0.95	Y
NCCTG83-7052[75]	High dose IFN alfa-2a (20MU/m^2 IM 3 days/week for 12 weeks)	Observation	Y	264	0.89	0.92	Y
EORTC18952[76]	Intermediate dose IFN alfa-2b (10MU SC 5 days/week for 4 weeks, then 10MU SC 3 days/week for 1 year or 5MU SC 3 days/week for 2 years)	Observation	Y	1388	0.88	0.9	Y
WHO16[77]	Low dose IFN alfa-2a (3MU SC 3 days/week for 3 years)	Observation	Y	444	0.95	0.96	Y
UKCCCRAIM-High[78]	Low dose IFN alfa-2a (3MU 3 days/week for 2 years)	Observation	Y	674	0.94	0.93	Y
DeCOG[79]	Low dose IFN alfa-2a (3MU SC 3 days/week for 2 years)	Observation	Y	293	0.72	0.63	Y
Scottish MG[80]	Low dose IFN alfa-2b (3MU SC 3 days/week for 6 months)	Observation	Y	94	0.78	0.81	Y
EORTC18871[81]	Low dose IFN alfa-2b (1MU SC every other day for 1 year)	Observation	Y	281	0.94	0.88	Y
DKG80-1[81]	Low dose IFN alfa-2b (1MU SC every other day for 1 year)	Observation	Y	203	1.09	1.09	Y
EORTC18991[82]	PEGylated IFN-alfa-2b (6µg/kg SC per week for 8 weeks, then 3µg/kg SC per week for 5 years)	Observation	Y	1256	0.87	0.96	Y

Study	Intervention (dose)	Comparator (dose)	Included in Suciu et al.[37]	Number of patients	HR RFS	HR OS	Included in analysis
ECOG1694[83]	High and low dose IFN alfa-2b (20MU/m^2 IV for 5 days/week for 4 weeks, then 10MU/m^2 SC 3 days/week for 48 weeks)	GMK vaccine (1mL SC on Days 1, 8, 15 and 22, then every 12 weeks until l96 weeks)	Y	882	0.84	0.86	Y
ECOG2696[84]	High and low dose IFN alfa-2b (20MU/m^2 IV for 5 days/week for 4 weeks, then 10MU/m^2 SC 3 days/week for 48 weeks) and GMK vaccine	GMK vaccine alone (30µg of GM2 and 100µg SC on Weeks 1, 2, 3, 4, 12, 24, and 36)	Y	107	0.72	1.11	N
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: GMK, GM2-KLH/QS-21; HR, hazard ratio; OS, overall survival; Q3W, every three weeks; RFS, recurrence free survival; SC, subcutaneously.

The sensitivity analysis [redacted] is used in the model base case to derive nivolumab OS [redacted] Figure 37). This analysis was chosen as it contains [redacted] most relevant trials:

[redacted]

The HR_{RFS} from CheckMate 238 of nivolumab vs ipilimumab (0.65)[4] is used in the equation to derive the HR_{OS} of nivolumab vs ipilimumab [redacted]. This hazard ratio is then compared to the HR_{OS} of ipilimumab vs placebo (0.72) from the CA184-029 trial to produce the HR_{OS} of nivolumab vs placebo [redacted]. This hazard ratio is then applied to the routine surveillance curve estimated from the CA184-029 placebo OS data.

The equation derived from the previous Suciu et al. surrogacy analysis is explored as a scenario:

$$HR_{OS} = \exp(0.0106 + 0.9874 \times \ln(HR_{RFS}))$$

Using this equation and the same method as above gives HR_{OS} = 0.48 for nivolumab compared to routine surveillance.

The key differences between these equations are the trials used to inform the equation and the type of data used. The new analysis used in the base case [redacted]

Table 20 presents the fit of the predicted OS to the actual OS for all trials included within the trial level association analysis. [redacted]

[redacted]

Figure 37: Treatment effects on RFS vs treatment effects on OS (sensitivity analysis 4)

Notes: [redacted]

Overall survival – prediction of underlying survival

As for RFS, survival curve fitting was conducted in line with NICE DSU guidance; with covariate adjusted curves with the same covariates as for RFS included for consistency and the same assumptions and methodology used for prediction for the population of interest.

Figure 26 presents the long-term survival extrapolation for placebo estimated using parametric survival models fit to the CA184-029 OS data fit from baseline for ipilimumab and placebo, respectively. The survival curve fits were conducted using both treatment arms to allow the maximum amount of data to inform projections (Section B.2.9).

These curves are fit to the CA184-029 population, i.e. Stage III patients. The final parametric model was re-weighted to match our intended patient population (Stage III – IV NED) from the CGP method by adding a Stage IV NED covariate (assumed to be the same as the Stage IIIC covariate) and adding a trial covariate (assumed to be the same as the ITC trial covariate). Figure 38 shows the KM data from the CA184-029 trial with the generalised gamma curves based upon the CA184-029 patient population (also shown in Figure 26) and the final curves after adjusting for the proportion of patients in each group within the full population of interest (i.e. including Stage IV NED patients).

Figure 38: CA184-029 overall survival – base case curve selected and final curve

Key: KM, Kaplan–Meier; PBO, placebo.

Overall survival – use of external long-term survival data within model

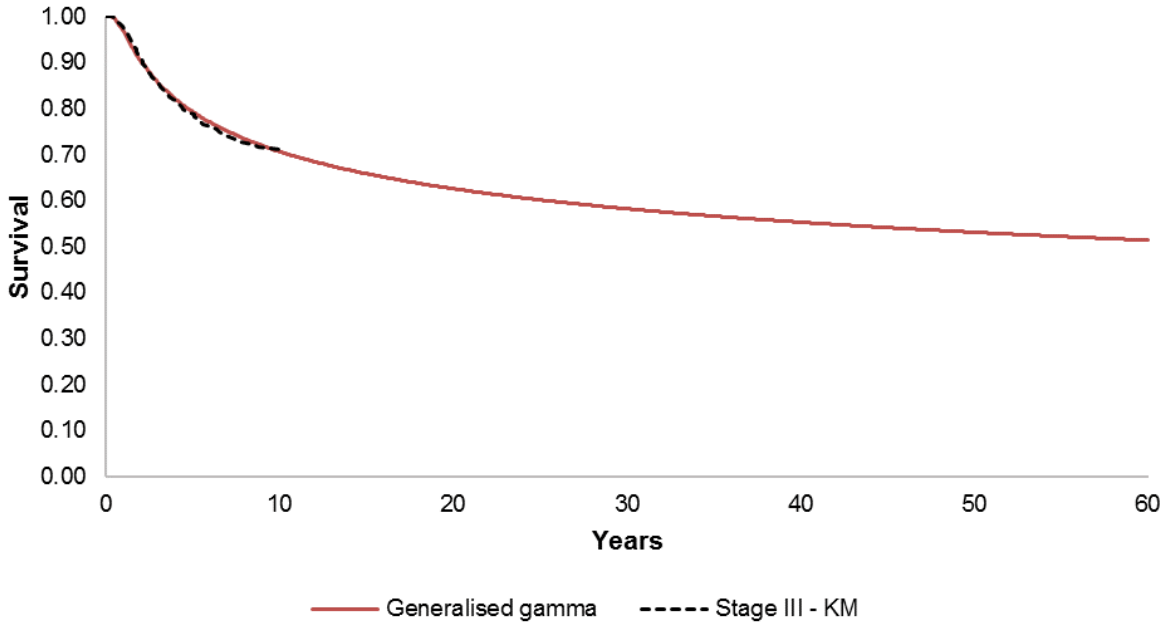
As discussed in Section B.2.9, one of the key issues surrounding the long-term extrapolation of outcomes within adjuvant melanoma is the conflict between the long-term nature of a dataset and its generalisability to current practice. Even following selection of the most clinically plausible curve, the extrapolated parametric survival curves produced from the trial data appeared to produce low estimates of survival compared to long-term sources available; 10-year OS from the CA184-029 placebo arm is estimated to be approximately [redacted] compared to 70% in AJCC version 8[14], 39% in AJCC version 7[43] (weighted stage III curve) and 75% from E1697.[42] Therefore, the model includes the functionality to apply long-term registry data to both treatment arms after a certain time point. From this time point onwards no ongoing treatment effect is assumed.

For the model base case, this scenario is applied at 10 years using data from AJCC version 8 as most clinically reflective of current practice.[14] The availability of better treatments post-recurrence in the metastatic setting and more accurate staging (therefore better outcomes) means that the AJCC v8 is more reflective of current clinical practice. The10-year time point was selected as this is approximately when long-term melanoma survival outcomes begin to plateau[42, 43], suggesting that the risk of death due to melanoma is reduced at this time. This was also the view of clinicians at the UK advisory board who suggested that the risk of recurrence is reduced at this time, and mortality should be trending towards the general population at this time.[1] Alternative time points of 5 years and 20 years are included in the scenario analysis.

The AJCC version 8 registry data are considered to be the most up-to-date melanoma data due to changes in the treatment pathway, with more efficacious treatments becoming available in the metastatic setting, and the more accurate staging, and therefore would be more representative source for outcomes in current clinical practice. As such, AJCC v8 is used in the base case to capture these changes in melanoma clinical practice. The Stage III survival outcomes from the publication were digitised, and pseudo PLD were created using the Guyot algorithm[85]; parametric survival curves were then fit to the data to extrapolate the survival outcomes. Based on AIC/BIC and visual fit (Appendix D), and the

description of the expected long-term hazard function provided at the clinical advisory board[1], the generalised gamma was selected as the base case (Figure 39).

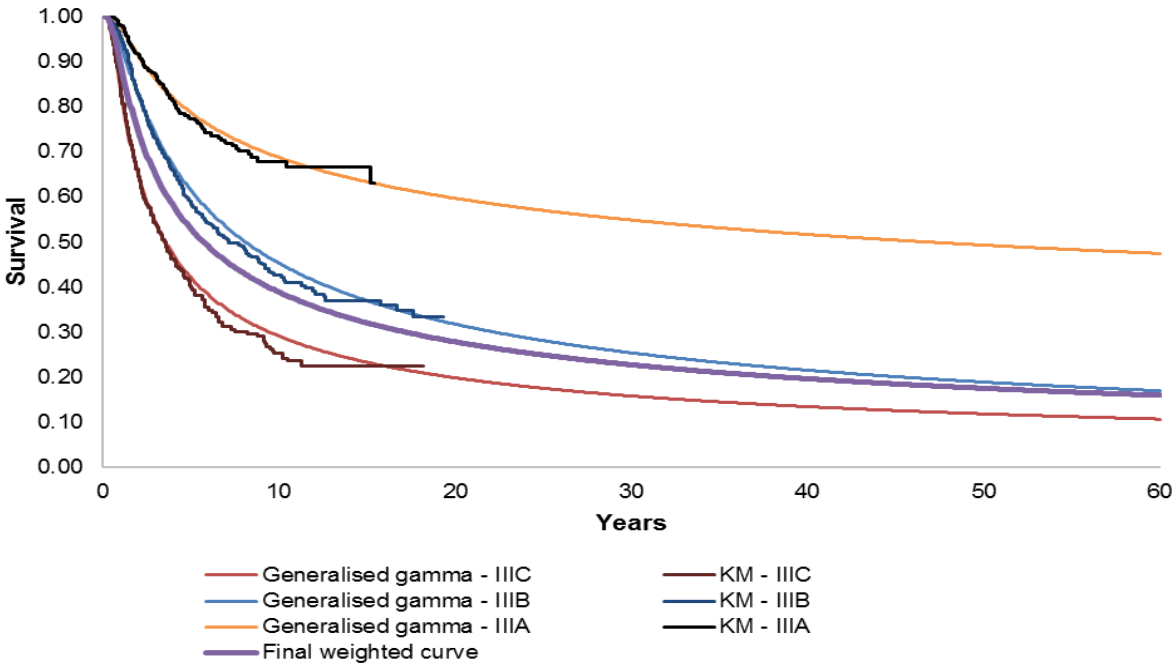
Figure 39: AJCC 8th edition registry data – Stage III with generalised gamma curve



Key: KM, Kaplan–Meier.

Alternatively, the 7th edition AJCC data can be used as a long-term data source. The Stage IIIA, IIIB, and IIIC curves were digitised, and parametric models were fit to pseudo PLD. The AIC/BIC and visual fit showed that generalised gamma was the best fitting curve for each stage sub type (Appendix D). The overall Stage III curve weighted the subtype curves using the distribution of stage in the model (Table 21) with the Stage IV NED patients incorporated into the Stage IIIC population. The final curves for each Stage subtype and overall weighted curve are shown in Figure 40 for this scenario.

Figure 40: AJCC 7th edition registry data – Stage III with generalised gamma curves and final weighted curve



Key: KM, Kaplan–Meier.

To estimate the RFS curve once these long-term data are applied, a HR was calculated comparing RFS and OS. Pseudo PLD were created from digitised observation OS and RFS curves from the E1697 trial.[42] A Cox regression was used to estimate the HR, [redacted]. This HR is applied to the long-term OS curve to produce the long-term RFS curve. An alternative HR can be calculated using the CA184-029 trial [redacted] as a scenario. This method assumes that the hazard between RFS and OS from the previous adjuvant trials holds in this setting and is constant.

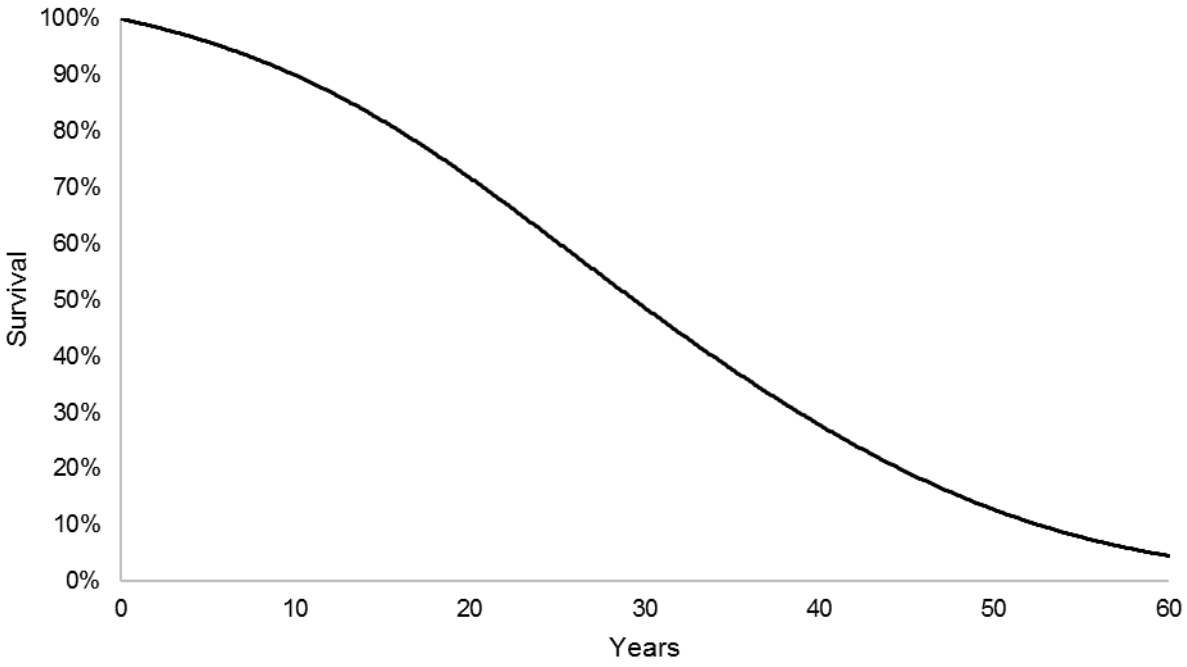
Overall survival – use of general population mortality data

The patients' age in the CheckMate 238 and CA184-029 trials ranged between 18 and 86 years.[4, 35] Because of the large range of patient ages, the model incorporates a maximum time horizon of 60 years in order to capture lifetime costs and benefits associated with melanoma for the whole population. Scenario analysis explores alternative time horizons of 40 and 50 years.

General population survival was modelled based on the Office of National Statistics life tables[67] and used the trials' age distribution to determine the average survival of the general population reflective of the modelled population.

Within the model, the transition to death is modelled as the maximum of the predicted OS, and the general population mortality is derived from the national life tables.

Figure 41: General population survival



Final model predictions

Table 27 summarises the data used for the base case for the projection of RFS and OS within the model.

Table 27: Summary of survival extrapolations and data used within the model

RFS	OS
• Parametric survival models from the PLD meta-regression of CheckMate 238 and CA184-029 (up to 10 years). • HR applied to melanoma registry OS data (from Year 10 onwards).	• Routine surveillance uses parametric survival models for CA184-029 trial data. Nivolumab OS estimated from OS/RFS relationship using nivo vs routine surveillance HR (up to 10 years) • Melanoma registry data used for transition probabilities on both arms from 10 years.

RFS	OS
	• Background mortality using general population data used if extrapolations predict a lower mortality.
Key: HR, hazard ratio; OS, overall survival; PLD, patient-level data; RFS, recurrence-free survival.	

Figure 42 presents the final model projections for OS and RFS. As expected by clinical advisors, in the very long-term, the RFS and OS curves meet, and at all times, projections remain lower than general population mortality. The [redacted].[1] Within the model it is estimated that [redacted] remain recurrence free in the routine surveillance arm and [redacted] in the nivolumab arm. This is broadly in line with the clinician estimates.

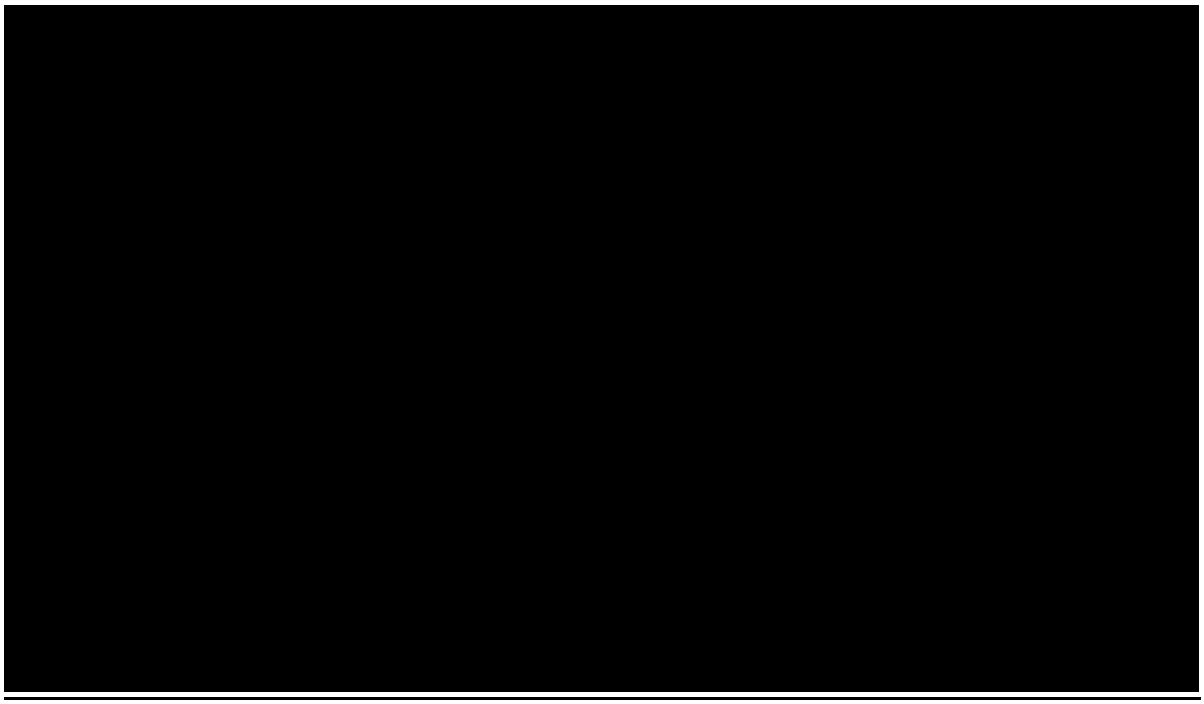
At the UK advisory board, the clinicians suggested that at around 15 years, patient mortality should be nearer that of the general population, and by 20 years should be more or less the same[1]; therefore, if a patient remains recurrence-free by [redacted], it seems reasonable that at this point their risk of recurrence is extremely low and the risk of mortality from other causes would instead be the driving factor.

Figure 43 shows the long-term transition probabilities used for mortality compared to general population data. The maximum of the long-term projection mortality or general population mortality was used throughout the model to ensure that the hazard of death was never greater than the general population.

Figure 42: Final model projections for RFS and OS

Key: OS, overall survival; RFS, recurrence-free survival.

Figure 43: Projection of mortality transition probability over time



Time on treatment

Time on treatment (ToT) for nivolumab was taken from the CheckMate 238 PLD, which recorded the proportion of patients receiving each dose up to the maximum duration of 1 year. These values are reported in Table 28.

Table 28: Final ToT for nivolumab in the base case model

Number of doses received				
Week	**Dose**	**Patients (n)**	**Patients (%) receiving this exact number of doses**	**% receiving dose**
1	1	[redacted]	[redacted]	[redacted]
3	2	[redacted]	[redacted]	[redacted]
5	3	[redacted]	[redacted]	[redacted]
7	4	[redacted]	[redacted]	[redacted]
9	5	[redacted]	[redacted]	[redacted]
11	6	[redacted]	[redacted]	[redacted]
13	7	[redacted]	[redacted]	[redacted]
15	8	[redacted]	[redacted]	[redacted]
17	9	[redacted]	[redacted]	[redacted]
19	10	[redacted]	[redacted]	[redacted]
21	11	[redacted]	[redacted]	[redacted]
23	12	[redacted]	[redacted]	[redacted]
25	13	[redacted]	[redacted]	[redacted]
27	14	[redacted]	[redacted]	[redacted]
29	15	[redacted]	[redacted]	[redacted]
31	16	[redacted]	[redacted]	[redacted]
33	17	[redacted]	[redacted]	[redacted]
35	18	[redacted]	[redacted]	[redacted]
37	19	[redacted]	[redacted]	[redacted]
39	20	[redacted]	[redacted]	[redacted]
41	21	[redacted]	[redacted]	[redacted]
43	22	[redacted]	[redacted]	[redacted]
45	23	[redacted]	[redacted]	[redacted]
47	24	[redacted]	[redacted]	[redacted]
49	25	[redacted]	[redacted]	[redacted]
51	26	[redacted]	[redacted]	[redacted]
	Total:	**452**		
Key: n, number; ToT; time on treatment.				

Recurrence rates

Subsequent treatment costs and monitoring costs are split by recurrence type and weighted by the proportion of patients who had a local/regional recurrence or a distant recurrence from CheckMate 238. The proportion of patients who had a local/regional recurrence only includes these patients, whereas the proportion of patients who had a distant recurrence also includes patients who had a local/regional recurrence first and then went on to have a distant recurrence. This is more reflective of what would be expected in current practice[1] given that more patients have a distant recurrence compared to local recurrence and is similar to the proportions from the CA184-029 trial and across treatments (Table 29). These proportions are also similar to a retrospective study looking at real-world treatment outcomes in the UK, Germany and France for Stage IIIB/IIIC melanoma patients. In the UK, 120 (61.5%) patients had a recurrence, with 18.3% having only a local/regional recurrence and 81.6% having a distant recurrence at some point.[23] Given that the proportions between treatments is similar across the CheckMate 238 trial, the pooled data were used in the model and applied to both nivolumab and routine surveillance.

Table 29: Recurrence type for CheckMate 238 and CA184-029

Recurrence type	CheckMate 238			CA184-029		
	Nivolumab	Ipilimumab	Total	Ipilimumab	Placebo	Total
Local/regional only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Local/regional then distant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distant only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Safety

Adverse events (AEs) of treatments were included to account for extra costs incurred due to treatment. The AEs considered within the model are: immune-related (any grade), diarrhoea (Grade ≥2) and any other Grade ≥3 AE. Previous metastatic melanoma NICE submissions of immunotherapy treatments had a similar approach except endocrine disorders of any grade were extracted instead of immune-related AEs.[86, 87] Immune-related AEs were felt to be more appropriate in this case as the

main comparison is routine surveillance, so it was key to highlight the differences and broaden the potentially treatment-related AEs included within the model.

Nivolumab and ipilimumab AEs were based on all cause AE data from the CheckMate 238 trial, which also recorded the number of patient hospitalisations for each AE category. Immune-related AEs taken from the trial were based on the PLD using the 'Body system' category and were defined as 'Immune system disorders'; diarrhoea incidence was based on the 'dictionary-derived term' excluding any already captured within the immune-related category. Immune-related AEs (any grade) and diarrhoea (Grade ≥2) for routine surveillance were based on the relative difference in AEs between ipilimumab and placebo in CA184-029 and between ipilimumab and nivolumab in CheckMate 238. AE data from both trials are shown in Table 30.

For the 'other Grade ≥3 AE', the comparison of nivolumab and placebo AEs between CheckMate 238 and CA184-029 produced clinically implausible results, suggesting that more placebo patients have AEs compared to nivolumab. The ipilimumab arm from both trials is used to adjust for differences between the trials to compare AEs (see below):

$$Routine\ surveillance\ other\ grade\ 3\ AEs\ \% = \frac{029\ placebo\ \%}{029\ ipi\ \%} \times 238\ ipi\ \%$$

$$= [redacted] \times [redacted] = 38.1\%$$

Data from CheckMate 238 estimate the % of patients having other Grade ≥3 AEs on nivolumab is [redacted] which is lower than the estimated proportion for routine surveillance using the trials. This is likely because in the CA184-029 trial, patients were on treatment longer than in the CheckMate 238 trial and were therefore followed up for longer, which increases the chance of capturing more AEs. [1]

Due to the implausibility of the suggestion that patients on active treatment would experience fewer AEs than on routine surveillance, and given immune-related AEs are separated out, an assumption is made in the base case that the 'other grade ≥3' AEs for routine surveillance are the same as nivolumab. Another scenario can be considered, which assumes that there are no other Grade ≥3 AEs for the routine surveillance arm to determine the impact of both extremes on the model results.

In line with previous advanced melanoma NICE submissions, the majority of costs associated with AEs would be hospitalisation costs. The proportion of patients requiring inpatient visits for nivolumab were based on the CheckMate 238 trial. However, the mean number of inpatient hospital visits was not recorded in either the CheckMate 238 or CA184-029 trials; therefore, both inpatient and outpatient visits per AE were estimated from the Oxford Outcome study, which looks at advanced melanoma resource use and costs in the UK.[88] Clinical expert opinion suggests that the costs associated with AEs between advanced melanoma and adjuvant melanoma would be similar; however, the timing of the report may not reflect current clinical practice within melanoma.[1] The limitation of this reference is the age of the report and that melanoma practice may have changed; however, more recent studies or costs data have not been found. The proportion of patients requiring outpatient visits was also based on the Oxford Outcomes study; 22.3% of patients had immune-related AEs requiring outpatient visits, 19.2% for diarrhoea and 21.3% for other AEs.

The expected proportion of patients being hospitalised for routine surveillance is calculated by applying the ratio of the proportion of patients hospitalised versus the proportion of patients with AEs derived from the nivolumab AE data in CheckMate 238. The number of hospitalisation days per patient per AE are assumed to be the same as for patients in the nivolumab arm based on the Oxford Outcomes study. The overall AE incidence rates and hospitalisation days used in the analysis are shown in Table 30.

Table 30: Base case modelled adverse events based upon the CheckMate 238 and CA184-029 trials

Adverse Event	CA184-029		CheckMate 238		
	Placebo	Ipilimumab	Nivolumab	Ipilimumab	Routine surveillance
Total patient numbers for AE analysis	[redacted]	[redacted]	[redacted]	[redacted]	
Immune-related (any grade)					
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	
% of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][a]

Adverse Event	CA184-029		CheckMate 238		
	Placebo	Ipilimumab	Nivolumab	Ipilimumab	Routine surveillance
Number of patients hospitalised	NR	NR	[redacted]	[redacted]	[redacted]
% of patients hospitalised	NR	NR	[redacted]	[redacted]	[redacted][b]
Total hospitalisation days	NA	NA	[redacted]	[redacted]	[redacted][e]
Mean hospitalisation days per patient in safety pop.	NA	NA	[redacted]	[redacted]	[redacted][f]
Diarrhoea (Grade ≥2)					
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	
% of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][a]
Number of patients hospitalised	NR	NR	[redacted]	[redacted]	[redacted]
% of patients hospitalised	NR	NR	[redacted]	[redacted]	[redacted][b]
Total hospitalisation days	NA	NA	[redacted]	[redacted]	[redacted][e]
Mean hospitalisation days per patient in safety pop.	NA	NA	[redacted]	[redacted]	[redacted][f]
Other adverse events (Grade ≥3)					
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	
% of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients hospitalised	NR	NR	[redacted]	[redacted]	[redacted]
% of patients hospitalised	NR	NR	[redacted]	[redacted]	[redacted]
Total hospitalisation days	NA	NA	[redacted]	[redacted]	[redacted]
Mean hospitalisation days per patient in safety pop.	NA	NA	[redacted]	[redacted]	[redacted]

Key: NA, not applicable; NR, not reported.
Notes: [a] Estimated by weighting the CA184-029 placebo value as a ratio of the 029 ipilimumab arm %AE to the CheckMate 238 ipilimumab arm %AE (%029-placebo/029-ipi)*238-ipi).
[b] Estimated by applying the relative ratio: % of patient hospitalised (nivolumab)* (% of patient with AE (routine surveillance) / % patient with AE (nivolumab).
[c] Assumed same as nivolumab in the base case.
[d] % of patients hospitalised x number of AE patients in nivo arm ([redacted])
[e] Average hospitalisation days from Oxford outcomes x number of patients hospitalised
[f] Total hospitalisation days/total patients in AE analysis

B.3.4. Measurement and valuation of health effects

As agreed by clinical experts, patients who are recurrence-free are similar to the general population despite having a risk of recurrence.[1] As discussed in Section B.1.3, this increased risk of a melanoma recurrence may cause anxiety while waiting for a recurrence, and in addition to the actual recurrence when it occurs, impacts the quality of life of melanoma patients; thus making a treatment that reduces the risk of recurrence compared to no treatment preferable to patients. After treatment with nivolumab, patients' HRQL was maintained in the CheckMate 238 quality-of-life questionnaires, with lower quality-of-life seen in the ipilimumab arm. In comparison to routine surveillance, the extension of RFS seen with nivolumab and the additional psychological benefit of receiving active treatment is anticipated to positively impact patient quality of life, the benefits of which may not be explicitly captured within the strict QALY framework. RS Health conducted a discrete choice experiment (DCE) that evaluated patient preferences in terms of trade-offs among treatments for adjuvant melanoma in the US.[89] This study found that over two thirds of patients prefer treatment versus none, and treatment effectiveness was of the highest importance for both patients and physicians in the advanced stage.

Another study, which looked at patient and physician preferences for treatments with longer-term survival profiles, also found that patients place a high value on therapies with a "tail-of-the-curve" survival and are even willing to give up a proportion of mean survival in favour of durable survival.[90] NICE guidance is clear that when deciding on recommending interventions, that NICE "must consider other factors" such as patient preferences and that "cost-utility cannot be the sole basis for NICE's decisions".[91]

Nivolumab demonstrates clear potential for long-term survival given the significant difference in RFS compared to another active treatment in the CheckMate 238 trial in addition to the overall mechanism of action where significant and durable OS has been demonstrated in the metastatic melanoma setting. These factors, including the improved quality of life due to extended RFS, are key considerations for the decision problem.

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

EQ-5D-3L data were collected in the CheckMate 238 trial, and EORTC QLQ-C30 data were collected in both CheckMate 238 and CA184-029. Based on NICE guidelines[92], EQ-5D data are the preferred utility measure; therefore, in the model base case, data from the CheckMate 238 trial alone are used. EORTC QLQ-C30 data from both trials were also mapped to EQ-5D and are used in sensitivity analysis.

- The CheckMate 238 trial collected both EQ-5D-3L and QLQ-C30 data. QoL data were scheduled to be collected at Weeks 1, 5, 7, 11, 17, 25, 37 and 49, and additionally at two follow-up visits, first 30 days after last dose and 84 days after first follow-up.
- The CheckMate 029 trial only collected EORTC QLQ-C30 data. These data were scheduled to be collected within 1 week prior to the first treatment administration, on Day 22, 43 and 64 (± 3 days) prior to study drug medication, and at Week 24 and every 12 weeks thereafter in maintenance therapy for up to 2 years independent of disease progression.

Exploratory analyses were first performed to determine the effect on post-baseline utility of each covariate individually, and to identify covariates to be considered for regression analysis. For potential categorical prognostic factors, the following exploratory analyses were performed:

- Univariate descriptive summaries (number of patients, number of observations, mean, standard deviation [SD], median, inter-quartile rage [IQR] and range) of utility by each variable
- Where appropriate, bivariate descriptive summaries of utility by two variables

For continuous prognostic factors, the following exploratory analysis were performed:

- Scatter plots comparing the variable with utility score
- Univariate descriptive summaries (number of patients, number of observations, mean, SD, median, IQR and range) of utility by the continuous variable split by tertiles

The following potential prognostic factors were explored using descriptive summaries:

- Health state (pre-recurrence, post-recurrence or unknown [note: once a patient is censored, it is not known what their health state is])
- Treatment (nivolumab or ipilimumab)
- Time to event (recurrence or death; continuous characteristic)
- Baseline utility
- Patient characteristics:
  - Age (< 65 or ≥ 65 years old)
  - Gender (male or female)
  - Stage (IIIa [mapped analysis only], IIIb, IIIc or IV)
  - B-RAF status (mutant, wildtype or not reported)
  - PD-L1 status (< 5% / unknown or ≥ 5%)

For the same reason as described in Section B2.9, lymph node involvement and ulceration status were not included within the analysis. Melanoma subtype was also not considered as a covariate due to the low number of non-cutaneous patients.

Variables explored were then considered for addition to the regression model based on forward selection, which was performed by adding the characteristics into the model one by one based on which variable produced the model with the lowest AIC, which is a measure of statistical fit. All models within the regression include a random effect for patients, to adjust for the correlation between multiple observations, and a fixed effect for baseline utility, to account for any differences between treatments at baseline.

The final regression model presented in this report was used in the economic model to predict utility by health state. All statistical analyses were performed using R, and mixed effect regression models were performed using the "lme" function from the package 'nlme'.

Analysis datasets were derived using SAS® version 9.4 software, using the following assumptions:

- Only patients who received treatment were included in this analysis.
- All observations in the ADAM datasets were considered, with the exception of duplicate observations on the same day.
- Baseline flags in the ADAM datasets were used to define the baseline observation for each patient. Any observations before this baseline flag were removed. Where there was no flag for a patient, their first observation was used as the baseline utility value.
- Only patients who had a baseline observation and at least one other post-baseline observation in a defined health state (that was not after a censored-recurrence) were included in the analysis.

In the CheckMate 238 trial, [redacted] of observations were incomplete for EQ-5D. These observations were removed without imputation.

The number of patients and mean number observations included in the utility analysis by treatment arm and trial are presented in Table 31. Twenty-three patients in the intention-to-treat (ITT) population were not considered in the utility analysis due to insufficient utility information (due to the reasons specified above). On average, patients receiving nivolumab had more observations per person than patients receiving ipilimumab.

Table 31: Number of patients and EQ-5D observations by treatment

TRT	Patients (ITT population)	Patients (analysis)	Observations	Mean number of observations
All	[redacted]	[redacted]	[redacted]	[redacted]
Ipi	[redacted]	[redacted]	[redacted]	[redacted]
Nivo	[redacted]	[redacted]	[redacted]	[redacted]
Key: Ipi, ipilimumab; ITT, intention-to-treat; Nivo, nivolumab; TRT, treatment.				

Table 32 presents univariate and bivariate descriptive summaries of utility by health state and treatment. Observations that occurred after a censored recurrence were put into the unknown health state category and were removed from the bivariate summaries.

Utility observations post-recurrence are lower than those pre-recurrence by roughly [redacted]. Observations in an unknown health state are higher than the pre-recurrence observations; however, as there is a small number of records in this category ([redacted]%) and utility in this health state is not of interest for the economic model, it was not considered further. These observations were removed from the exploratory regression models. Patients who received ipilimumab had a lower pre-recurrence mean utility value ([redacted]) compared to patients who received nivolumab ([redacted]). The bivariate descriptive summaries show that the difference between pre-recurrence and post-recurrence is larger for patients receiving nivolumab (mean difference=[redacted]) compared to ipilimumab (mean difference=[redacted]). This indicated that there may be an interaction between health state and treatment. Therefore, an interaction term was considered within the stepwise regression model (Appendix O). This change between treatment and health state could be explained by the differences in subsequent therapies received by the two treatment arms which impact the post-recurrence health state utility.

Table 32: Utility summaries by health state and treatment

Health state	TRT	Patients	Observations	Mean (SD)	Median (IQR)	Range
Pre-recurrence	All	868	5624	[redacted]	[redacted]	[redacted]
Post-recurrence	All	290	909	[redacted]	[redacted]	[redacted]
Unknown[a]	All	196	251	[redacted]	[redacted]	[redacted]
All	Ipi	434	3093	[redacted]	[redacted]	[redacted]
All	Nivo	449	3691	[redacted]	[redacted]	[redacted]
Pre-recurrence	Ipi	423	2443	[redacted]	[redacted]	[redacted]
Post-recurrence	Ipi	162	527	[redacted]	[redacted]	[redacted]
Pre-recurrence	Nivo	445	3181	[redacted]	[redacted]	[redacted]
Post-recurrence	Nivo	128	382	[redacted]	[redacted]	[redacted]

Key: Ipi, ipilimumab; IQR, inter-quartile range; Nivo, nivolumab; SD, standard deviation; TRT, treatment.

Health state	TRT	Patients	Observations	Mean (SD)	Median (IQR)	Range
Note: [a], Observations after recurrence-free survival censoring.						

Table 33 presents descriptive summaries of utility by time to recurrence or death with a separate group for observations from censored patients. There is a positive correlation between time to event and utility, as time to event increases (time of utility observation is further away from the event), so does utility with a mean difference of approximately [redacted] between the three groups.

Although time to event appears to be predictive of utility, there is a large number of patients (n=529) who have not experienced an event (censored), so their time to event is unknown. This group is not of interest in the economic model, since we do not need to predict utility for this group. Therefore, these patients would need to be removed from the regression model, which is problematic since there is such a large proportion of the patients in this group and much information from these patients' utility will be lost. Therefore, time to event was not considered as a covariate in the regression model.

Table 33: Pre-recurrence utility summaries by time to event

Time to event	Number of patients	Number of observations	Mean (SD)	Median (IQR)	Range
≤76	257	442	[redacted]	[redacted]	[redacted]
77–193	202	435	[redacted]	[redacted]	[redacted]
>193	126	439	[redacted]	[redacted]	[redacted]
Censored	529	4308	[redacted]	[redacted]	[redacted]
Key: IQR, inter-quartile range; SD, standard deviation.					

Along with differences in the treatment effect and health state, patient characteristics may influence utility score. Table 34 presents univariate summaries of utility by patient characteristics. Mean utility score appears very similar between patients <65 years ([redacted]) and patients ≥65 years ([redacted]). A slight difference is observed between the two genders: on average, women had a lower mean utility score ([redacted])

compared to men ([redacted]). The summaries indicate a relationship between disease stage and utility, with patients who had more advanced disease having a lower utility score. The Stage IV NED group has a lower utility score ([redacted]) than the Stage IIIc group ([redacted]), who in turn has a lower utility than the Stage IIIb group ([redacted]). Patients with other or not reported disease stage have a higher mean utility score ([redacted]) than all other disease stage categories. Due to the low patient numbers and the inability to interpret results within this group, patients with other or not reported disease stage were excluded from the regression analysis. B-RAF status does not appear to influence a patient's utility score, as B-RAF-mutation positive patients had a marginally higher mean utility ([redacted]) than wildtype patients ([redacted]). Patients whose B-RAF status was not reported had a mean utility score matching those of B-RAF-positive patients ([redacted]). Due to the reasonably large number of patients whose B-RAF status was not reported, these records were not excluded from the regression analysis and were considered as a separate subcategory. PD-L1 status also does not appear to have a strong influence on utility scores. Patients with PD-L1 <5% or unknown PD-L1 had a marginally lower mean utility score ([redacted]) than patients with PD-L1 ≥5% ([redacted]).

Although the univariate summaries give an indication of which patient characteristics are prognostic for utility (namely stage and gender), each of the summarised patient characteristics were considered for regression analysis.

Table 34: Utility summaries by patient characteristics

Characteristic	Level	Patients (%)	Observations	Mean (SD)	Median (IQR)	Range
Age (years)	< 65	657 (0.74)	4910	[redacted]	[redacted]	[redacted]
	≥ 65	226 (0.26)	1623	[redacted]	[redacted]	[redacted]
Sex	F	370 (0.42)	2767	[redacted]	[redacted]	[redacted]
	M	513 (0.58)	3766	[redacted]	[redacted]	[redacted]
Disease Stage	IIIB	302 (0.34)	2323	[redacted]	[redacted]	[redacted]

Characteristic	Level	Patients (%)	Observations	Mean (SD)	Median (IQR)	Range
	IIIC	415 (0.47)	3018	[redacted]	[redacted]	[redacted]
	IV	162 (0.18)	1156	[redacted]	[redacted]	[redacted]
	Other/ NR	4 (0.00)	36	[redacted]	[redacted]	[redacted]
B-RAF	Mutant	373 (0.42)	2773	[redacted]	[redacted]	[redacted]
	Wildtype	114 (0.13)	2924	[redacted]	[redacted]	[redacted]
	NR	396 (0.45)	836	[redacted]	[redacted]	[redacted]
PD-L1	< 5% / unknown	583 (0.66)	4270	[redacted]	[redacted]	[redacted]
	≥ 5%	300 (0.34)	2263	[redacted]	[redacted]	[redacted]
Key: F, female; IQR, inter-quartile range; M, male; NR, not reported; SD, standard deviation.						

To summarise, the following covariates were considered for the regression model:

- Treatment (nivolumab or ipilimumab)
- Health state (pre-recurrence or post-recurrence)
  - Treatment-health state interaction term
- Baseline utility
- Age group (<65 or ≥65)
- Sex (female or male)
- Disease stage (Stage IIIb or Stage IIIc or Stage IV NED)
- B-RAF status (mutant or wildtype or not reported)
- PD-L1 status (< 5% / unknown or ≥ 5%)

Table 35 presents the results of the regression model, which includes covariates for treatment, health state, an interaction between health state and treatment, and disease stage. This model is the final observed model and has been used to predict utility for the base case of the economic model. All coefficients within the model are

statistically significant ($p<0.05$). The AIC values for each step in the regression and diagnostic plots are presented in Appendix O.

The disease stage coefficient values indicate that the Stage IV NED group has a utility decrement of [redacted] compared to the Stage IIIb group, while the Stage IIIc group has a utility decrement of [redacted] compared to the Stage IIIb group. While statistically significant, these differences are small.

As the model contains an interaction term between treatment and health state, each of the coefficients should not be considered in isolation. As the reference category for the recurrence coefficient is pre-recurrence, the treatment coefficient only relates to the treatment difference between nivolumab and ipilimumab in the pre-recurrence period. Similarly, as nivolumab is the reference category for the treatment coefficient, the recurrence coefficient only relates to recurrence in patients who received nivolumab. The interaction term then gives an estimate of the relative difference in utility between nivolumab post-recurrence and ipilimumab post-recurrence.

To more clearly see how the treatment, recurrence and interaction term influence utility score, Table 36 presents the estimated utility for each treatment by health state, which has been used in the economic model based upon the patient characteristics within the decision problem population.

After controlling for baseline utility, disease stage and repeated measures, the model estimates that in the pre-recurrence health state, the ipilimumab group had a utility decrement of [redacted] compared to nivolumab. However, in the post-recurrence health state, the model estimates that the ipilimumab group had a [redacted] higher utility relative to the nivolumab group. This is likely explained by the uptake of more effective subsequent therapies (anti-PD-1 therapies) post ipilimumab compared to nivolumab, which had more ipilimumab uptake post-recurrence in the CheckMate 238 trial (see Table 48). However, these differences in utilities are small and should be interpreted with caution given the caveats stated above.

As no Stage IIIA patients were included within the CheckMate 238 study, it is assumed for the calculation of utilities only a decrement would be included for Stage IIIC and IV, and Stage IIIA will have the same utility as the reference Stage IIIB.

Table 35: Regression model coefficients

Coefficient	Value	Standard error	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility	[redacted]	[redacted]	[redacted]	[redacted]
Treatment: Ipi (ref: Nivo)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence: post (ref: pre-recurrence)	[redacted]	[redacted]	[redacted]	[redacted]
Disease Stage: IIIc (ref: IIIb)	[redacted]	[redacted]	[redacted]	[redacted]
Disease Stage: IV (ref: IIIb)	[redacted]	[redacted]	[redacted]	[redacted]
Interaction: post*Ipi	[redacted]	[redacted]	[redacted]	[redacted]
Key: CI, confidence interval; Ipi, ipilimumab; Nivo, nivolumab.				

Table 36: Estimated utilities from the final regression model

Health state	Nivolumab*	Ipilimumab
Pre-recurrence	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]
Notes: Nivolumab utilities are applied to both nivolumab and routine surveillance in the base case		

Mapping

EORTC QLQ-C30 data from both trials were also mapped to EQ-5D and are used in sensitivity analysis. The key benefits of using the mapped data are that:

- Mapping of the QLQ-C30 allowed for a utility score to be estimated for nivolumab, ipilimumab and placebo, and notably, it allowed an indirect relative treatment effect to be derived between nivolumab and placebo (not possible with observed data alone as the 029 study did not collect EQ-5D).
- Mapping of the QLQ-C30 provides more observations and longer follow-up, allowing time dependency to be more thoroughly investigated and validation of the observed EQ-5D information.

The mapped data are used in sensitivity analysis rather than the base case as the NICE DSU TSD 10 states: "*in most cases, mapping should be considered a second-best solution to directly collected EQ-5D values, as the use of mapping will lead to increased uncertainty and error around the estimates of health-related utility*".[93]

To derive estimates of utility using QLQ-C30, a mapping algorithm was applied to the data in 029 and 238 in order to map the QLQ-C30 responses to the EQ-5D index score. The University of Oxford Health Economics Research Centre (HERC) mapping database was used to identify a suitable mapping algorithm.[94] Details of the mapping algorithm selection process and analysis conducted on the mapped data are provided in Appendix O.

Table 37 presents the results of the forward selection model, which includes covariates for treatment, health state, an interaction between health state and treatment, and sex. This model is the final mapped model and has been used to predict utility in scenario analyses in the economic model. The AIC values for each step in the regression and fit of the regression model are Appendix O

The model indicates that patients who were in the 238 trial had a significant utility decrement of [redacted] compared to patients in 029. The model also estimates that women had a near significant (p-value = [redacted]) utility decrement of [redacted] compared to men.

After controlling for baseline utility, sex and repeated measures, the model estimates that in the pre-recurrence health state, the ipilimumab group had a significant utility decrement of [redacted] compared to nivolumab. However, the placebo group had a utility decrement of [redacted] compared to nivolumab in the pre-recurrence period; note this comparison is not significant. In the post-recurrence state, the model estimates that patients who received either ipilimumab or placebo have utility scores [redacted] higher than patients who received nivolumab. As per the EQ-5D analysis, the difference in post-recurrence utility value between the treatment arms could be explained by the differences in subsequent therapies received upon recurrence (Table 48); however, this difference is minimal.

Table 37: Forward selection regression model – mapped utility

Coefficient	Value	Standard error	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility	[redacted]	[redacted]	[redacted]	[redacted]
Trial: 238 (ref: 029)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment: Ipi (ref: Nivo)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment: PBO (ref: Nivo)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence: post (ref: pre-recurrence)	[redacted]	[redacted]	[redacted]	[redacted]
Sex: male (ref: female)	[redacted]	[redacted]	[redacted]	[redacted]
Interaction: post* Ipi	[redacted]	[redacted]	[redacted]	[redacted]
Interaction: post* PBO	[redacted]	[redacted]	[redacted]	[redacted]
Key: Ipi, ipilimumab; Nivo, nivolumab; PBO, placebo.				

Table 38 presents the estimated utility for each treatment by health state based upon the mapped data, which has been used as a sensitivity analysis in the economic model. Placebo post-recurrence utility is the same as the ipilimumab post-recurrence utility. This could be due to small differences between subsequent therapies upon recurrence in the CA184-029 trial; more patients on the placebo arm received ipilimumab post recurrence, whereas more patients in the ipilimumab arm received dacarbazine post recurrence.

Table 38: Estimated utilities from the final regression model – mapped utility

Health state	Nivolumab	Ipilimumab	Placebo
Pre-recurrence	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]	[redacted]

Health-related quality-of-life studies

To inform the utility estimates that are used in the model, a SLR was performed to identify published utility values associated with melanoma. The identification of studies process and search strategy is described in Section B.3.1. Details of the SLR are presented in Appendix H.

Three studies were extracted from four publications; the fourth publication was a secondary publication of one of the three extracted studies.[95] The summaries of these three studies are shown in Table 39. Two of the publications were cost-

effectiveness studies of interferon[96, 97], and the other publication was a poster reporting preference based utilities for adjuvant melanoma in the UK and Australia.[98]

One of the cost-effectiveness studies was a Canadian-based hypothetical cohort reflective of the Eastern Cooperative Oncology Group (ECOG) trial E1684. The utility estimates in the study used time-trade-off methods from a sample of 104 respondents in Quebec; it is noted that these estimates reflect urban populations, and large variations were observed resulting in large standard deviations.[96]

The other study used a hypothetical cohort reflective of the same ECOG 1684 trial. It was noted that the utility assessments of individual trial patients were not prospectively collected; therefore, in recognition of this limitation, they performed the analysis with and without utility adjustments for interferon (IFN) toxicity (although the source of these is not noted).[97]

Given the age of these studies, the lack of actual patient data contained within them, and therefore the uncertainty of the methods used to collect these utility estimates, these will not be used as evidence within the cost-effectiveness analysis.

Middleton et al. presents a specific utility-based study using the adult population in the UK and Australia; 87 participants from the UK and 85 participants from Australia took part in the study using the standard gamble technique. Utilities were obtained from 14 health states (five treatment-related health states and nine toxicities). The following health states were captured within this study: induction treatment, no treatment and recurrence.

Given the relevance of this study to the decision problem and the UK-specific sample, these utilities and disutilities can, however, be used within the analysis as a scenario. The overall utilities from Middleton et al. were used in the model as a scenario given that these utilise all the patients in the study (n=155) and are in between the utilities reported from the UK and Australia individually; the UK generally had lower estimates compared to Australia.

Table 39: Summary of utility values reported in identified utility studies

Study	Mean utilities		Mean disutility for toxicity*	
Middleton et al., 2016[98]		(Overall/UK/Australia)	Diarrhoea	-0.09
	Adjuvant no toxicities	0.890/0.840/0.942	Toxicity-hospital	-0.16
	Induction treatment	0.878/0.845/0.914	Hypophysitis	-0.13
	No treatment	0.855/0.837/0.875	Depression	-0.11
	Recurrence	0.620/0.581/0.662	Toxicity-outpatient	-0.11
	Recurrence long-term treatment survival	0.737/0.703/0.774	Flu	-0.08
			Rash	-0.08
			Nausea	-0.08
			Fatigue	-0.06
Crott et al., 2004[96]		Mean (SD), median	NR	
	IFN treatment	0.52 (0.29), 0.58		
	Recurrence	0.23 (0.23), 0.08		
	RFS	1		
	Death	0		
Hillner et al., 1997[97]		Mean (range)	NR	
	Induction IFN	0.7 (0.0–1.0)		
	Maintenance IFN	0.8 (0.0–1.0)		
	Recurrent disease	0.5 (0.0–1.0)		
	Disease-free, no treatment			

Key: IFN, interferon; NR, not reported; RFS; recurrence-free survival; SD, standard deviation.
Note: *No toxicity disutilities differed by country.

Adverse reactions

The utility decrements from Middleton et al. are applied within the cost-effectiveness analysis, dependant on the AE frequencies and the average AE durations as reported in the CheckMate 238 PLD. Using this approach there is some potential for double counting with adverse events experienced by patients in the CheckMate 238 trial at the same time as EQ-5D collection, however, the level of double counting is expected to be low and given that utilities are assumed equal across treatment arms therefore, use of literature to inform the impact of adverse events was considered to be appropriate. Scenario analysis is provided to test the impact of potential double counting.

The utilities extracted from Middleton et al. and a description of their use within the model are presented in Table 40. The proportions of patients experiencing each AE

(as reported in Section B.3.3) and the average AE duration were considered for the nivolumab and routine surveillance to produce a weighted disutility by arm. The average AE duration for immune-related disorders was 41 days, and 18 days for both diarrhoea and other AEs.[99] These disutilities are incorporated in the model as a one-off impact at the start of the model (-0.009 for nivolumab versus -0.006 for routine surveillance).

Table 40: Summary of utility values reported in Middleton et al. (2016) applied within the model

Mean disutility for toxicity		Disutility use in model
Diarrhoea Toxicity-hospital Toxicity-outpatient	-0.09 -0.16 -0.11	Diarrhoea Immune-related AEs and other AEs weighted by inpatient visits per AE (Table 30)
Key: AE, adverse event.		

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

Given that data on the treatment effect on utility was only available for nivolumab versus ipilimumab using the EQ-5D within the model base case and only small differences were observed between treatments, therefore all treatment are assumed to have the same utility within each health state as nivolumab and AE decrements are applied based upon Middleton et al. 2016[98] (see section on Adverse reactions).

The final mean utility values based upon the EQ-5D-3L trial data for the recurrence-free and post recurrence health states are [redacted], respectively, where the baseline EQ-5D value of [redacted] from the patient data was used for the calculation [redacted] for recurrence-free health state, with [redacted] being added on for post-recurrence).

The regression models including the treatment specific covariates, mapped data and health state data from Middleton et al. are used within scenario analysis. Results based upon the mapped data provide longer follow-up and are supportive of the results produced based upon the EQ-5D; recurrence-free utility of [redacted]) and post-recurrence utility of [redacted] with the EQ-5D).

When data are used that take into account the treatment effect covariate, AE decrements are not applied on top to avoid double counting.

Utilities presented within Middleton et al. are consistent with those obtained within the clinical trial in the recurrence-free health state (range of 0.84–0.89 in Middleton et al. [redacted]) but are lower within the recurrence health state (range of 0.58–0.73 within the Middleton et al. study [redacted] in the trial), which may be reflective of the limited follow-up available within the CheckMate 238 study and a function of the different methodology used. Given that utilities within the metastatic setting (progression-free 0.795 and post progression 0.7625)[87] and derived from the CA184-029 longer-term evidence are more similar to those within the CheckMate 238 trial, we would consider it likely that the utilities in recurrence are under-estimated in Middleton et al.

Age was not found to be a significant predictor of quality of life and was therefore not included in the regression models or within the economic model.

Table 41 summarises the utilities used in the base case model including the utilities for different health states defined by progression status, and utility decrements for different treatment arms including their AEs that were applied within the cost effectiveness model. AE data were taken from Middleton et al. as detailed previously.

Table 41: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Utility values for health states defined by progression status				
Recurrence-free	[redacted]	Sampling using variance-covariance matrices assuming multivariate-normal distribution	Section B.3.4, page 137	Assumed equal across treatments. Based on statistical models fitted using EQ-5D data collected in CheckMate 238 trial and covariate for routine surveillance based on mapping from QLQ-C30 to EQ-5D using data collected in
Post-recurrence	[redacted]			

				both CheckMate 238 and CA184-029 trials
Utility decrements for adverse events				
Immune-related disorders	-0.11**	-0.134, -0.09***	Section B.3.4, page 147	Based on the Middleton et al. (2016) poster, which looks at disutilities due to AE in the adjuvant melanoma setting[98]
Diarrhoea	-0.09	-0.108, -0.073***		
Other AEs	-0.137**	-0.165, -0.111***		
Key: AE, adverse event; CI, confidence interval; SE, standard error. **Note:** * Routine surveillance utility was assumed at the same as placebo utility. ** Toxicity-hospital and toxicity – outpatient disutility used weighted by % patients hospitalised. *** 95% CI were not reported in the literature, SE assumed to be 10% mean.				

B.3.5. Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

A literature review identifying costs and healthcare resource use was deemed unnecessary owing to the PLD available for both CheckMate 238 and CA184-029 trials and the fact that treatment pathways in the metastatic setting have changed considerably over recent years rendering published information highly likely to be out of date. Moreover, six UK clinical experts participated in a resource use survey that was designed to collect recent UK costs and confirm resource use type and frequency specifically to the reference patient population. Initial targeted searches and consultation with clinicians indicated that there are unlikely to be any published sources of cost and resource use information for adjuvant melanoma in England. This inference is supported by the lack of identification of any economic evaluations in the cost-effectiveness search.

Intervention and comparators' costs and resource use

The unit drug cost of nivolumab is based on the list price (Table 42). The previously accepted PAS discount of [redacted] for nivolumab has been included in all analyses.

Table 42: Unit nivolumab costs

Nivolumab vial options		
Concentration	10mg/ml	10mg/ml
Vial volume	4ml	10ml
Dose per vial	40mg	100mg
Price per vial (no PAS)	£439.00	£1097.00
Price per vial (with PAS) – base case	[redacted]	[redacted]
Source for prices without PAS	MIMS September 2017[100]	
Key: MIMS, Monthly Index of Medical Specialities; PAS, patient access scheme.		

The proportion of patients receiving each dose was recorded in the CheckMate 238 data and implemented to give an average cost per patient per administration cycle.

The administration cost for nivolumab was taken from NHS reference costs with the treatment assumed to be given in a day case setting. The cost implemented was £259.76 (cost ref. SB12Z)[101] per administration in line with a recent nivolumab appraisal.[102]

Using the Western European weight of the patients in the CheckMate 238 and CA184-029 trials in the base case, the method of moments technique is used to calculate the average number of vials that would be required to satisfy one administration of nivolumab based on the weight of the population of interest.[103] A scenario is presented that uses UK specific weight data from metastatic melanoma trials. Clinicians at the advisory board felt that there would be little difference between the weights of patients between the adjuvant and metastatic setting[1]; therefore, this scenario makes use of specific UK patient population weights.

The method of moments first derives a log-normal distribution for the patient weight within the trial based upon the mean and standard deviation of the body weight measured. It then uses the log-normal distribution for weight to predict what proportion of patients require each number of vials to administer the required dose. This method assumes that patients only receive whole vials (no vial sharing), and thus accounts for drug wastage (estimated average number of 40mg vials is [redacted]).

The number of nivolumab vials needed per administration per each patient weight is calculated based on the possible combinations of vial sizes. All the possible vial

combinations (up to 9 vials) and their respective doses were calculated; where there were more than one of the same dose, only the cheaper of the options was carried forward.

Health-state unit costs and resource use

Medical resource use was identified via a survey of [redacted] UK clinicians. [redacted] were invited to participate in the survey based upon experience in the adjuvant melanoma setting and geographical spread covering England and Scotland [redacted] clinicians completed the survey via a self-administered questionnaire and were paid for their services (see Appendix I). All clinicians surveyed were consultant oncologists who were currently working within melanoma and had at least 3 years' experience with melanoma, and [redacted] of the clinicians had over 10 years' experience managing patients with melanoma. [redacted] of the clinicians work in university hospitals, [redacted] of the other clinicians work in a cancer hospital [redacted] clinician works in a tertiary cancer hospital, [redacted] (for a template of the HCRU survey questionnaire, please refer to Appendix I).

Resource use was recorded for the following health states, which were determined based upon the results of a pilot survey and clinical input: recurrence-free, local/regional (unresectable), local/regional (resectable), and distant recurrences. The proportion of patients who were categorised as having local/regional recurrence and distant recurrence was based on the CheckMate 238 study. Patients who experienced a distant recurrence at any point (not just the first recurrence) were grouped with the distant recurrence patients ([redacted]%), and patients who only had a local/regional recurrence were categorised into the local/regional group ([redacted]%). The proportion of patients experiencing a local/regional recurrence who were resectable vs unresectable was also taken from the CheckMate 238 study based on the proportion of patients who had curative surgery ([redacted]% vs [redacted]%).

The percentage of patients who used the resource and the frequency per month of the resource use was reported for Year 1, Year 2, Year 3–5 and Year 5+ time frames as per NICE guideline NG14, which reflects current recommendations of routine surveillance[65]; these frequencies were then multiplied by the unit costs, as reported

in Table 43, obtained from the most recent NHS Reference costs or the Personal Social Services Research Unit (PSSRU). The overall costs for each timeframe and health state are reported in Table 44. The recurrence-free and weighted post-recurrence costs are applied at each month of the model per patient depending on health state. The full results of the resource use survey and the proportions of patients receiving each resource are presented in Appendix P. The costs for distant recurrence and unresectable local/regional recurrence are higher than local/regional recurrence, which is consistent with the retrospective study of Stage IIIB and IIIC patients which found that resource utilisation was higher for patients in the distant metastatic phase.[23]

Table 43: Medical resource use unit costs

Resource	Cost (£)	Reference
Outpatient visits		
Oncologist/ Surgeon	107.00	PSSRU 2017 - Hospital Based Doctors. Consultant Surgical cost per working hour[104]
GP/PCP	28.00	PSSRU 2017 - General Practitioners cost per 9.22-minute consultation without qualifications[104]
Dermatologist	106.00	PSSRU 2017 - Hospital Based Doctors. Consultant Medical cost per working hour[104]
Nurse visits	37.00	PSSRU 2017 - Band 5 Hospital based Nurse cost per working hour[104]
Imaging		
Chest x-ray	85.69	NHS reference costs 16/17 - RD20A - Computerised Tomography Scan of One Area, without Contrast, 19 years and over[101]
PET-CT (chest and abdomen)	334.28	NHS reference costs 16/17 - RN02A - Positron Emission Tomography with Computed Tomography (PET-CT) of Two or Three Areas, 19 years and over[101]
CT (chest and abdomen)	112.33	NHS reference costs 16/17 - RD24Z - Computerised Tomography Scan of Two Areas, with Contrast[101]
MRI (head)	139.30	NHS reference costs 16/17 - RD01A - Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over[101]
CT (head)	97.39	NHS reference costs 16/17 - RD21A - Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over[101]
Other*	118.35	Average between NHS reference costs RD01A and RD21A
Laboratory tests		
CBC	1.69	NHS reference costs 16/17 - DAPS03 - Integrated Blood Services[101]

Resource	Cost (£)	Reference
Comprehensive metabolic panel	1.13	NHS reference costs 16/17 - DAPS04 - Clinical Biochemistry[101]
LDH	1.13	
Albumin	1.13	
Calcium	1.13	
C-reactive protein	1.13	
Liver function test	1.13	
Key: CBC, complete blood count; CT, computed tomography; GP, general practitioner; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCP, primary care physician; PET, positron emission tomography; PSSRU, Personal Social Services Research Unit. **Notes:** *, One clinician reported that the 'other' was a CT scan of the neck; the other clinicians did not specify. It is assumed that 'other' is a single scan of one area either by MRI or CT.		

Table 44: Monitoring costs for patients split by timeframe and health state applied within the model

Health state	Year 1 cost (£)	Year 2 cost (£)	Year 3–5 cost (£)	Year 5+ cost (£)
Recurrence-free	[redacted]	[redacted]	[redacted]	[redacted]
Local/regional recurrence (unresectable)	[redacted]	[redacted]	[redacted]	[redacted]
Local/regional recurrence (resectable)	[redacted]	[redacted]	[redacted]	[redacted]
Distant recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Weighted average for post-recurrence monitoring costs*	[redacted]	[redacted]	[redacted]	[redacted]
Notes: *, Weighted average for post-recurrence monitoring costs based on post-recurrence patient proportions as reported in the CheckMate 238 patient-level data.				

Adverse reaction unit costs and resource use

As discussed in Section B.3.3, resource use for AEs is based on PLD in CheckMate 238 and CA184-029 and considered for immune-related disorders (any grade), diarrhoea (Grade ≥2) and other AEs (Grade ≥3). These costs are split into hospitalisation and outpatient visits in line with the recent nivolumab and ipilimumab combination therapy NICE submission.[87]

Nivolumab AEs were based on data from the CheckMate 238 trial, which also recorded the number of patient hospitalisations for each AE category. The AEs used for routine surveillance were based on the relative difference in AEs between ipilimumab and placebo in CA184-029 and ipilimumab and nivolumab in CheckMate 238, with the exception of the 'other Grade ≥3', which is assumed to be the same as

nivolumab in the base case (See Section B.3.3). AE data from both trials are shown in Section B.3.3, which also reports the calculated routine surveillance AEs used within the model.

AE costs were captured as inpatient and outpatient events for the percentage of the patient population who experience the AEs considered in the model. The inpatient costs were calculated per hospital bed day depending on the AE and were taken from the NHS reference costs[101], as shown in Table 45. Outpatient costs were based on the predicted percentage of patients who would elect to become an outpatient and the average cost to treat. Since the mean number of inpatient hospital visits was not recorded in either CheckMate 238 or CA184-029 trials, both inpatient and outpatient visits per AE were estimated from the assumptions made in the Oxford Outcomes study (Table 46).[88] This study was designed to estimate the frequency and characteristics of resource use, and associated costs for advanced melanoma in the UK, Italy, Sweden, Spain and Portugal. UK resource use and costs were used from the study as per previous metastatic melanoma HTA submissions.[86, 87] Costs from the Oxford Outcomes study have been adjusted for use in the model according to 2016/17 PSSRU inflation indices.[104]

Table 45: Adverse event inpatient costs

Treatment	Hospital cost (£)	Type of stay	Reference
Hospital bed day (immune-related)	£297.41	Non-elective excess bed days	Weighted average between KA08A, DZ29H and FD01C- NHS reference costs 2016/17[101]
Hospital bed day (other AEs)	£305.85	Total HRGs - Non-elective inpatients	Excess bed days - NHS reference costs 2016/17[101]
Key: AE, adverse events; HRG, healthcare resource group; NHS, National Health Service. **Note:** Endocrine disorders used as costs for immune-related disorders.			

Table 46: Adverse event outpatient costs

Outpatients and unit costs	Value	Reference
% Treated as outpatient (immune-related disorders)	24.2%	Oxford Outcomes.[88] Table 91
Unit outpatient cost (immune-related disorders)	£428.08	Oxford Outcomes.[88] Table 17
% Treated as outpatient (diarrhoea)	19.2%	Oxford Outcomes.[88] Table 91
Unit outpatient cost (diarrhoea)	£649.85	Oxford Outcomes.[88] Table 17
% Treated as outpatient (other Grade 3+ AEs)	21.7%	Oxford Outcomes.[88] Table 91
Unit outpatient cost (other Grade 3+ AEs)	£403.68	Oxford Outcomes.[88] Table 16/17
Key: AE, adverse events.		

The unit costs are applied to the number of hospital days and outpatient visits for each treatment arm and a final per patient (accounting for patients who do not have AEs) average AE cost is calculated to be used in the economic model (Table 47). For simplicity, treatment arm-specific per patient AE resource use is applied at the start of the model.

Table 47: Summary of per patient AE costs in the economic model

	Nivolumab	Routine surveillance
Hospitalisation costs – immune-related disorders (any grade)	[redacted]	[redacted]
Hospitalisation costs – diarrhoea (Grade ≥2)	[redacted]	[redacted]
Hospitalisation costs – other AEs (Grade ≥3)	[redacted]	[redacted]
Hospitalisation costs – subtotal	[redacted]	[redacted]
Outpatient costs – immune-related disorders (any grade)	[redacted]	[redacted]
Outpatient costs – diarrhoea (Grade ≥2)	[redacted]	[redacted]
Outpatient costs – other AEs (Grade ≥3)	[redacted]	[redacted]
Outpatient costs – subtotal	[redacted]	[redacted]
Total cost (per trial patient)	[redacted]	[redacted]
Key: AE, adverse event.		

Miscellaneous unit costs and resource use

Subsequent treatment frequencies and costs are applied according to the recurrence type experienced and the initial adjuvant treatment received. Both CheckMate 238 and CA184-029 recorded the subsequent therapies that were administered to both

the local/regional and the distant recurrence patients. However, clinical expert opinion suggested that CheckMate 238 is more reflective of current clinical practice given the changes in the metastatic melanoma treatment pathway over the last 5 years and was therefore used as the main data source.[1, 44] Therefore, CheckMate 238 data were used in the base case and data collected from CA184-029 is presented as a scenario. The data from CheckMate 238 demonstrate that immune checkpoint inhibitors were given to some patients after a recurrence in the nivolumab arm. Clinicians also reported within the resource survey that the adjuvant therapy treatment would be repeated but would depend on the gap between the end of adjuvant therapy and recurrence as well as commissioning policy.[105]

The full list of subsequent therapies that were captured in the model, along with the percentage of records are reported in Table 48. Nivolumab is assumed to have the same distribution of subsequent treatments as the nivolumab arm in the CheckMate 238 trial, and routine surveillance is assumed to have the same distribution as ipilimumab. The unit costs for the subsequent therapies deemed to be of most interest based on frequency of use, cost and clinical opinion of their activity levels are presented in Table 49. Other subsequent anti-cancer therapies were not explicitly modelled but are included in 'other' and are modelled with the same costs as dacarbazine. To extract the maximum records from the CheckMate 238 trial, while also being able to accurately cost therapies given in combination, the following assumptions were made:

- The start date of the subsequent therapy was used to determine whether subsequent treatment was post local/regional recurrence or post distant recurrence.
- Records with a missing start date were excluded (5 records in total).
- Duplicate records were removed after assessment (by matching patient ID, start date and treatment).
- For records that were known combination therapies with missing end dates (e.g. nivolumab + ipilimumab), if the records started within 14 days of each other, then they were classed as the combination.
  - 14 days is the shortest cycle length of the treatments considered (nivolumab).

- For records that were not known to be combination therapies, or the treatments did not start within 14 days of each other, they were considered separate records.
- Combination therapies were identified for records that had matching start or end dates.
  - These could include any combination of treatments; however, overlapping records of the same treatment were considered separately.

Within both trials, some patients who had a local/regional recurrence later had a distant recurrence; therefore, subsequent treatment records for these patients were classed according to the timing of their recurrence relative to the timing of receipt of subsequent treatment. Any subsequent therapies received post distant recurrence were categorised into the distant group. A PAS discount of [redacted] has been included for nivolumab and [redacted] for ipilimumab. Functionality is included within the economic model to incorporate additional PAS discounts for alternative subsequent treatments not known by BMS.

Dosing for treatments for local/regional and distant recurrences were sourced from the literature. Dosing for subsequent therapies post local/regional recurrence were assumed to be in the adjuvant setting. Where there were incomplete data for local/regional subsequent therapy dosing, it was assumed that the dosing was the same as in the distant setting. ToT was also sourced from the literature due to the immaturity of the CheckMate 238 dataset. The dosing schedule and ToT used within the model for both local/regional and distant recurrences are reported in Appendix Q.

Table 48: Subsequent treatment splits by treatment arm from CheckMate-238

	Local/regional recurrence		Distant recurrence	
	Nivolumab	**Routine surveillance***	**Nivolumab**	**Routine surveillance**
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]

	Local/regional recurrence		Distant recurrence	
	Nivolumab	**Routine surveillance***	**Nivolumab**	**Routine surveillance**
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Note: * Subsequent treatment data from ipi arm following recurrence.				

Table 49: Subsequent treatment unit costs

Drug name	Unit size	Pack size (n)	Pack cost at list price	Source
Nivolumab	40mg	1	£439.00	MIMS[100]
	100mg	1	£1,097	
Ipilimumab	50 mg	1	£3,750.00	MIMS[106]
	200 mg	1	£15,000.00	
Interferon	10 MU	1	£41.55	MIMS[107]
	18 MU	1	£74.83	
	25 MU	1	£103.94	
PEGylated interferon	90 µg	1	£76.51	MIMS[108]
	135 µg	1	£107.76	
	180 µg	1	£497.60	
Dabrafenib	50 mg	28	£933.33	MIMS[109]
	75 mg	28	£1,400,00	
Trametinib	0.5 mg	7	£280.00	MIMS[110]
	0.5 mg	30	£1,200.00	
	2 mg	7	£1,120.00	
Pembrolizumab	50 mg	1	£1,315.00	MIMS[111]
	100 mg	1	£2,630.00	
Vemurafenib	240 mg	56	£1,750.00	MIMS[112]
Talimogene laherparepvec	1,000,000 PFU	1	£1,670.00	MIMS[113]
	100,000,000 PFU	1	£1,670.00	
Dacarbazine	100 mg	10	£46.15	eMIT[114]
	500 mg	1	£22.48	

Drug name	Unit size	Pack size (n)	Pack cost at list price	Source
	1000 mg	1	£44.05	
Cisplatin	10 mg	1	£1.84	eMIT[114]
	50 mg	1	£4.48	
	100 mg	1	£10.13	
Temozolomide	100 mg	5	£25.69	eMIT[114]
	140 mg	5	£35.59	
	250 mg	5	£53.36	
Interleukin	22 MU	1	£112.00	MIMS[115]
	22 MU	10	£1036.00	
Paclitaxel	30 mg	1	£3.44	eMIT[114]
	100.2 mg	1	£9.85	
	150 mg	1	£10.52	

Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities; n, number.

Subsequent surgery and radiotherapy are also included within the costs. Curative and palliative surgery and radiotherapy records were collected in the CheckMate 238 trial and split between recurrence type. Similarly, it is assumed that routine surveillance has the same subsequent surgery/radiotherapy pattern as ipilimumab in CheckMate 238. Table 50 shows the records collected in the trials for subsequent surgeries and radiotherapy with unit costs. Outpatient and day case costs were selected from a limited reference list of costs based upon clinical feedback that surgery for recurrent disease would not routinely require inpatient stays. These costs approximately match the expected types of surgery received by patients upon recurrence. Surgical options are restricted to patients with limited disease recurrence as patients with wide spread disease would not be eligible for surgery and would instead receive systemic treatment.

Table 50: Subsequent surgery and radiotherapy from the trials

Subsequent treatment	Local/regional recurrence		Distant recurrence		Unit cost	Reference
	CheckMate 238		CheckMate 238			
	Ipi	Nivo	Ipi	Nivo		
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	£100.72	NHS reference costs 16/17 – 160 Plastic surgery – total outpatients[101]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£297.09	NHS reference costs 16/17 – SC29Z – other radiotherapy – day case[101]
Key: Ipi, ipilimumab; Nivo, nivolumab; NHS, National Health Service.						

The mean costs of subsequent treatments including surgeries and radiotherapy per recurrence per arm are presented in Table 51. The proportion of records per subsequent treatment was multiplied by the calculated drug cost. This cost was then multiplied by the proportion of subsequent treatment records compared to how many patients are in each recurrence type to generate the total subsequent treatment cost per recurrent patient. These overall subsequent treatment costs are then weighted by the proportion of patients who only have a local/regional recurrence ([redacted]) and distant recurrence ([redacted]) applied to patients upon recurrence.

Table 51: Total subsequent treatment cost applied per recurrence in the model per adjuvant treatment

Recurrence type	Nivolumab	Routine surveillance
Local/regional	[redacted]	[redacted]
Distant	[redacted]	[redacted]

A one-off, end-of-life cost, was applied to patients at the point of dying to reflect the cost of terminal care. The end-of-life cost in the base case was calculated based on a total cost derived from the Round et al. (2015) modelling study, which estimated the cost of caring for cancer during the final phases of life (Table 52).[116] The study presented the end of life cost from health, social or informal care service for breast, colorectal, lung or prostate cancer individually in England and Wales. Table 52

summarises the costs used from Round et al. All costs have been uplifted to 2016/17 costs using indices from the PSSRU.[104]

Table 52: End-of-life costs from Round et al. (2015)

Category	Breast	Colorectal	Lung	Prostate	Average
Health care	4,346	4,854	3,157	6,687	4,254
Social care	2,843	1,489	1,358	2,728	1,829
Informal care – indirect costs*	4,868	2,850	2,420	4,814	3,265
Note: All costs are in GBP. *Indirect costs are those costs arising from the illness but where a payment is not made, such as lost wages due to time off work. This has been valued using the human capital approach.					

B.3.6. Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A summary of all base-case analysis inputs is provided in Appendix R.

Assumptions

Table 53: Summary of model assumptions

Category	Assumption made	Justification/reason
ITC between CA184-029 and CheckMate 238	Ipi duration of treatment is different between the two trials. An assumption was made that the difference in durations does not impact efficacy for the comparison.	Ipi in 238 received 1 year of treatment, ipi in 029 received 3 years of treatment. Median number of doses in both trials was 4 (Section B.2.9). Additionally, outcomes were similar in Stage IIIB and Stage IIIC patients across the trials and only a small proportion [redacted] doses of ipi treatment in the 029 trial.
Survival outcomes for population of interest	Stage IV (NED) patients are assumed to have the same outcomes as Stage IIIC patients.	Stage IV (NED) patients were not included in the CA184-029 trial which is used to predict OS data and for the comparison of nivo with placebo. CheckMate 238 RFS data showed little difference between Stage IIIC and Stage IV RFS (See Figure 35), clinical opinion also suggested they should be similar in outcomes.[1, 44]
	The trial covariate for CheckMate 238 vs CA184-029 included in the ITC was included in the CA184-029 parametric models and assumed to have same effect.	This was done in order to predict 029 survival outcomes in the CheckMate 238 trial, which is more recent and the main trial of interest.

Category	Assumption made	Justification/reason
	Nivo is equally effective across all disease stages.	No evidence of difference in effect across stages was found in the CheckMate 238 trial and the Bucher ITC shows a similar outcome when subgroup analysis was conducted using the only the overlapping stages between the CheckMate 238 trial and the CA184-029 trial compared to the ITT population.
AEs	Routine surveillance 'other Grade 3+' AEs were assumed to be the same as nivo.	Comparison of AEs between both trials suggested placebo has more AEs than nivo (see Section B.3.3). It is clinically implausible to suggest patients on no treatment will have more AEs than active treatment.
Subsequent treatments	All subsequent treatments in the local/regional group were assumed to have the adjuvant dose and duration. If dosing and duration of treatment for a subsequent treatment in the local/regional group was not available in the literature, then it was assumed to have the same dose and duration as in the distant recurrence group.	No dosing information on subsequent treatments were available in the CheckMate 238 or CA184-029 trials; therefore, literature data were used to inform the dosing. Some subsequent treatments in the local/regional recurrence group are not indicated in the adjuvant setting and trial publications were not available; therefore, metastatic data were used.
Utilities	Equal health-state utilities were assumed for all treatments in the base case, based on nivo observed EQ-5D-3L in CheckMate 238 and disutilities from the literature.	Utility regression equations did not show a large difference in utility, and data were not available to compare all treatments based upon treatment effects. Mapped and literature data are used in sensitivity analysis.
Key: AEs, adverse events; ITC, indirect treatment comparison; ipi, ipilimumab; ITT, intention-to-treat; NED, no evidence of disease; OS, overall survival; PRS, post-recurrence survival; nivo, nivolumab; RFS, recurrence-free survival.		

B.3.7. Base-case results

Base-case incremental cost-effectiveness analysis results

Table 54 and Table 55 present the base case incremental cost-effectiveness results for nivolumab versus routine surveillance at the NHS list price and the with-PAS price, respectively, for the partitioned survival model. At the with-PAS price, nivolumab is cost-effective at the fast-track threshold of £10,000.

Table 56 presents the LYs gained by health state. These results show that there are more LYs for routine surveillance patients compared to nivolumab in the post-

recurrence health state due to fewer patients in the nivolumab arm having a recurrence ([redacted] patients avoided recurrence).

Table 54: Base case results (based on list price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 55: Base case results (based on PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.87	[redacted]	[redacted]	[redacted]	[redacted]	£8,769
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 56: Summary of LY gain by health state

Health State	Nivolumab	Routine surveillance	Incremental LY	Absolute increment	% Absolute increment
Recurrence-free	[redacted]	8.68	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	5.20	[redacted]	[redacted]	[redacted]
Total	[redacted]	**13.87**	[redacted]	[redacted]	**100.00%**
Key: LY, life year.					

As discussed in Section B.3.2, Markov models have also been explored to test the structural uncertainty of the PSM and to enable expected survival post-recurrence to be incorporated into the analysis. Further details of these alternative structures can be found in Appendix N). Table 57 presents the results of the Markov models.

Markov option 1 gives a similar ICER to the partitioned survival model suggesting that model structure alone is not a key driver of the ICER. Markov option 2 gives ICERs less than the £20,000 threshold. The reason that ICERs are higher in Markov option 2 versus the base case are that a lower absolute survival is estimated post recurrence and less survival benefit is anticipated for nivolumab relative to routine surveillance which is in contrast to the durable responses observed with nivolumab in the systemic disease. Another major weakness of this model scenario of course is that additional assumptions are required as data is taken from a wide variety of sources which are not specific to this setting. These assumptions include: prior adjuvant therapy does not affect PRS, for many of the metastatic treatments a constant HR is applied, and long-term melanoma data is applied to all treatments in line with previous methodology submitted to NICE (see Appendix N.2). Additionally, as there were issues producing clinically plausible projections for PRS using Markov 2 due to lower survival estimates projected for routine surveillance compared to placebo PRS in CA184-029 (discussed in Appendix N.2), additional adjustments were required, this scenario should be therefore be considered less robust in light of this.

Table 57: Summary of base case results testing structural uncertainty using the Markov models (with PAS)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Markov option 1 – base case							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	11.16	[redacted]	[redacted]	[redacted]	[redacted]	£8,381
Markov option 2 – base case							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.03	[redacted]	[redacted]	[redacted]	[redacted]	£17,947
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PRS, post-recurrence survival; QALY, quality-adjusted life year.							

B.3.8. Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed within the cost-effectiveness analysis, conducted for 1,000 iterations. The average (mean) incremental QALYs gained from nivolumab across the 1,000 iterations are displayed in Table 58. The visual results of the PSA runs are presented in Figure 44. The results show that the results of the probabilistic analysis are similar to those of the deterministic analysis.

Table 58: Mean results of PSA (1,000 runs) and comparison with deterministic results

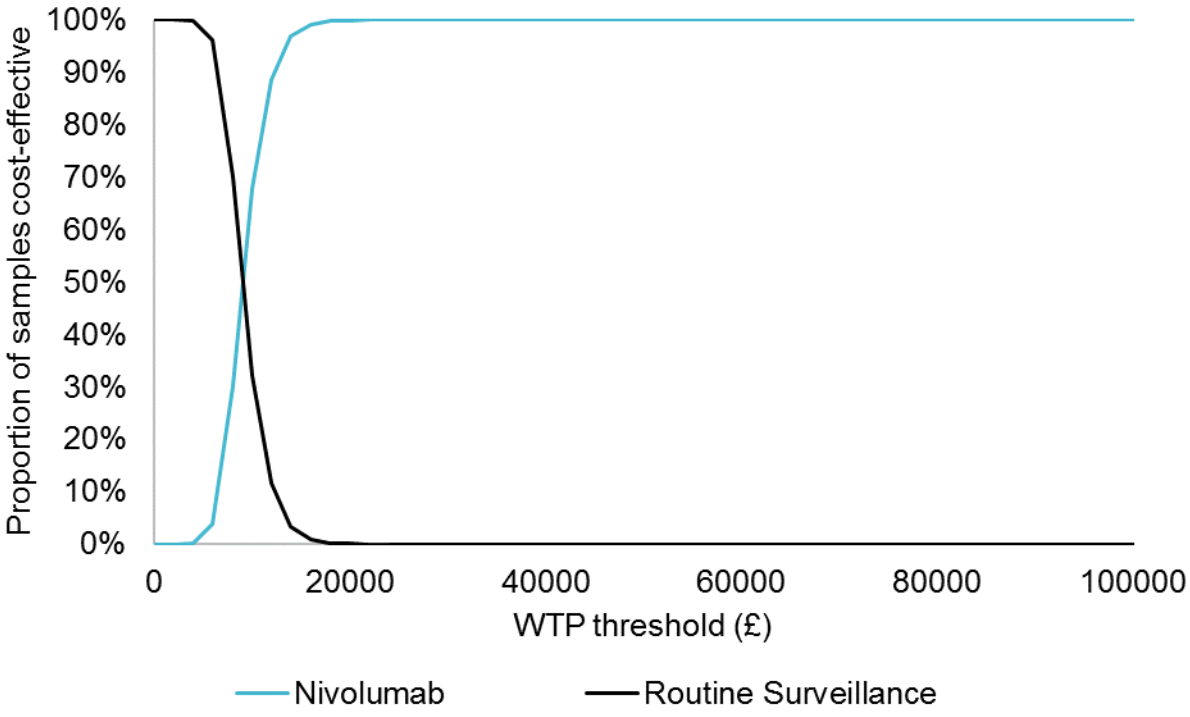
Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA (95% CI)	Deterministic
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]		
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	9,002 (4,981–13,022)	8,769
Key: CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.						

Figure 44: Cost-effectiveness plane (1,000 runs)

Key: QALYs, quality-adjusted life years; WTP, willingness to pay.

Figure 45 presents the cost-effectiveness acceptability curve (CEAC) for nivolumab compared to routine surveillance based on the 1,000 PSA iterations at different willingness to pay (WTP) thresholds. The probability of nivolumab being cost-effective is 67.8%, 99.9% and 100% at WTP thresholds of £10,000, £20,000 and £30,000, respectively.

Figure 45: Cost-effectiveness acceptability curve



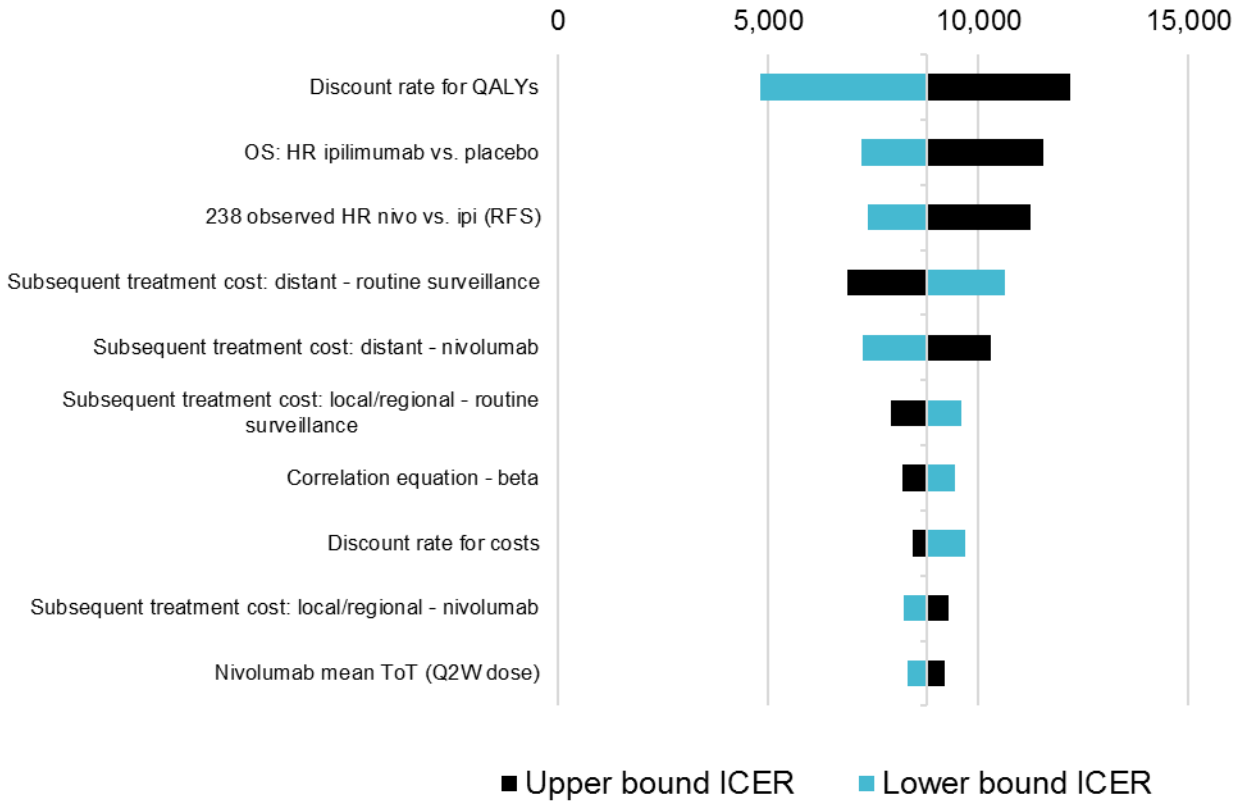
Key: WTP, willingness to pay.

Deterministic sensitivity analysis

One-way sensitivity analysis

Figure 46 presents a tornado diagram showing the parameters with the greatest impact on the ICER with descending sensitivity from one-way sensitivity analysis (OWSA). The ICER was most sensitive to the discount rate applied to QALYs, the HR between nivolumab and ipilimumab and between ipilimumab and placebo (this is used to estimate the HR between nivolumab and routine surveillance to derive the OS), and subsequent treatment costs. The ICER ranged from £4,802 to £12,181, demonstrating that values tested at their upper and lower bounds still produced ICERs below £20,000, and in the majority of cases remained below the £10,000. The results of the extensive sensitivity analyses performed provide confidence that this technology is relevant for a fast track appraisal by NICE.

Figure 46: Tornado diagram of the 10 most influential parameters on the ICER



Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; RFS, recurrence-free survival; ToT, time on treatment.

Threshold analysis

Sensitivity analysis testing the survival projections for nivolumab was done to determine the lowest survival projection required for nivolumab not to be cost-effective versus routine surveillance at the £10,000 and £30,000 WTP threshold. Various HRs were applied to the nivolumab OS and RFS data, which were chosen to reflect the range of uncertainty within the CheckMate 238 RFS HR of 0.65 (97.56% CI: 0.51–0.83). The HR applied as [redacted]; the HR applied within this range went up in increments of 0.05. These hazards were then applied to the survival projections for nivolumab to decrease/increase the probability of death or recurrence depending on the scenario. The following scenarios where a HR was applied are as follows:

- Scenario 1 – HR applied to OS after defined timepoint
- Scenario 2 – HR applied to RFS after defined timepoint
- Scenario 3 – HR applied to OS and RFS after defined timepoint

The hazard ratios were applied separately in each scenario, and the ICER was reported as the output of each analysis. The timepoint default was set at 0 to test the uncertainty from the start of the model. The results of the threshold analysis with the defined timepoint set to 0 are reported in Table 59.

The results show that the hazard of death for nivolumab would need to increase by [redacted]% before nivolumab is no longer cost-effective at the £10,000 threshold and by [redacted]% to be no longer cost-effective at the £20,000 threshold. A scenario was also tested which assumed that the OS benefit between nivolumab and routine surveillance was the same as the OS benefit seen in the CA184-029 trial between ipilimumab and placebo (i.e. nivolumab OS is the same as ipilimumab OS). This resulted in an ICER of £14,920. This scenario is a conservative assumption given that there is evidence from the metastatic setting that nivolumab has a significant OS benefit compared to ipilimumab which increases over time[53], and the RFS benefit seen in CheckMate 238 is also evidence of a benefit compared to ipilimumab; however, this scenario is still under the £20,000 threshold.

Additionally, the hazard of RFS for nivolumab would need to be towards the upper bound of the CI before nivolumab is no longer cost-effective at the £10,000 threshold and all other ICERs within the uncertainty range remained less than £10,000.

Even when OS and RFS were adjusted at the same time, the ICERs remained less than £20,000, demonstrating that even within the uncertainty range, nivolumab remains cost-effective compared to routine surveillance.

Table 59: Threshold analysis results – ICER with PAS price

Scenario	Hazard ratio applied									
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. HR applied to OS	7,094	7,541	7,917	8,324	8,769	9,256	9,791	10,383	11,039	12,205
2. HR applied to RFS	7,132	7,653	8,037	8,408	8,769	9,120	9,460	9,793	10,116	10,596
3. HR applied to OS and RFS	5,855	6,626	7,277	7,988	8,769	9,632	10,594	11,669	12,884	15,094
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; RFS, recurrence-free survival.										

Scenario analysis

Table 60 presents the scenario analysis performed to assess the structural uncertainty within the model using the base case portioned survival model. For all scenarios tested, the ICER remained below £20,000 per QALY.

Table 60: Results of scenario analysis (with PAS)

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	8,769
Population	Patient characteristics: (029 and 238) Stage proportions: 029 & 238 adjusted RFS for nivolumab and routine surveillance: ITC (029 and 238)	CheckMate 238 CheckMate 238 Nivo: 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	8,309

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	8,469
Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	9,070
		50 years	[redacted]	[redacted]	[redacted]	8,832
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	8,740
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	8,357
Subsequent treatment data source	Trial '238 data	Trial '029 data	[redacted]	[redacted]	[redacted]	7,067
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	12,464
		Gompertz*	[redacted]	[redacted]	[redacted]	4,613
		Log-normal	[redacted]	[redacted]	[redacted]	8,334
		GGamma	[redacted]	[redacted]	[redacted]	8,490
		Weibull	[redacted]	[redacted]	[redacted]	9,272
Long-term survival adjustment	Gershenwald, applied after10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	8,010
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	10,886
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	8,055
		Balch, 5 years	[redacted]	[redacted]	[redacted]	14,789
		Balch, 10 years	[redacted]	[redacted]	[redacted]	10,239
		Balch, 20 years	[redacted]	[redacted]	[redacted]	8,454
		OS/RFS HR from '029 trial	[redacted]	[redacted]	[redacted]	8,928
		Balch, OS/RFS HR from '029 trial	[redacted]	[redacted]	[redacted]	10,491

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Source for correlation equation RFS/OS	Coart et al. 2018	Suciu et al.	[redacted]	[redacted]	[redacted]	8,189
OS for routine surveillance	Generalised Gamma	Exponential*	[redacted]	[redacted]	[redacted]	8,278
		Gompertz	[redacted]	[redacted]	[redacted]	8,722
		Log-normal	[redacted]	[redacted]	[redacted]	8,539
		Log-logistic	[redacted]	[redacted]	[redacted]	8,536
		Weibull*	[redacted]	[redacted]	[redacted]	8,770
Long-term-data curve selection	Gershenwald, GGamma	Balch, Exponential**	[redacted]	[redacted]	[redacted]	14,077
		Balch, GGamma	[redacted]	[redacted]	[redacted]	10,239
		Balch, Log-normal	[redacted]	[redacted]	[redacted]	11,576
		Balch, Log-logistic	[redacted]	[redacted]	[redacted]	11,561
		Balch, Weibull**	[redacted]	[redacted]	[redacted]	12,312
		Exponential**	[redacted]	[redacted]	[redacted]	10,597
		Gompertz	[redacted]	[redacted]	[redacted]	8,497
		Log-normal	[redacted]	[redacted]	[redacted]	9,518
		Log-logistic	[redacted]	[redacted]	[redacted]	9,712
		Weibull**	[redacted]	[redacted]	[redacted]	10,075
End-of life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	8,623
Utilities source		Include AE disutilities: No	[redacted]	[redacted]	[redacted]	8,761
		Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	8,826

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
	Observed EQ-5D Apply same utility to across treatments Separate stage covariate Include AE disutilities: Yes	Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	8,834
		Middleton et al.	[redacted]	[redacted]	[redacted]	8,312
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	8,769
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	8,834
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	8,768
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	8,834
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	8,846
Post-recurrence survival	Treatment specific PRS (using PSM)	Assume same PRS (using Markov option 2)	[redacted]	[redacted]	[redacted]	12,112

Key: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; LY, life year; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival.
Note: The curve fits that are indicated (*) are those which do not meet the validation criteria as displayed in Table 13 and Table 14. (**) are those that fit the data poorly.

Summary of sensitivity analyses results

The probabilistic sensitivity analysis demonstrates that the conclusion that nivolumab is cost-effective versus routine surveillance is robust. The CEAC based on 1,000 runs estimates that the probability of nivolumab being cost-effective at WTP thresholds of £10,000, £20,000 and £30,000 is 67.8%, 99.9% and 100%, respectively. The OWSA identified parameters that have the biggest impact on the ICER and qualified the impacts of taking extreme values of each parameter on the cost-effectiveness results. The OWSA showed that the cost-effectiveness results were not overly sensitive to these parameters, and the ICERs were below £20,000 for all parameters tested and, in the majority of cases, remained below the £10,000 applicable to the fast track route.

Further sensitivity was tested around the survival projections of nivolumab by testing the within uncertainty range from the CheckMate 238 trial and seeing what impact this had on the cost-effectiveness result. This analysis shows that even at the upper bounds of the uncertainty range, nivolumab is still cost-effective versus routine surveillance, and the ICER is still under £20,000. A conservative assumption was also made by assuming no OS benefit between nivolumab and ipilimumab, which had an ICER under £15,000.

A wide range of scenario analyses were performed on key model assumptions and alternative choices including structural assumptions to test the robustness of the base case results. All scenarios tested resulted in an ICER less than £20,000, with the majority of scenarios staying below £10,000.

B.3.9. Subgroup analysis

In line with the final scope, no subgroups were modelled within the economic evaluation.

B.3.10. Validation

Validation of cost-effectiveness analysis

The following key aspects of the model methods and inputs were validated by health economics and clinical experts[1, 44]:

- The model structure and its appropriateness to reflect the clinical pathway;
- The type of models considered in this economic evaluation to model RFS and OS;
- The techniques used to compare nivolumab to routine surveillance using the CheckMate 238 and CA184-029 trials;
- Extrapolation beyond the trial period and availability of long-term data;
- Exploring different data sources considered to model post-recurrence in the Markov model and the partitioned survival model selected as the base case (see Section B.3.2);
- The treatments that patients are most likely going to receive upon recurrence;
- The use and clinical validity of utilities derived from the clinical trials based upon recurrence;
- Modelling impacts of the safety and AEs on resource use.

Both internal and external data sources were used to validate the model survival projections.

Internal validation

Internal validation used the RFS KM data from CheckMate 238 and CA184-029 to compare the RFS outputs from the model. Table 61 shows the model-projected RFS compared to the KM-projected RFS from the trial. Median RFS for CA184-029 is stated as reported in the CSR[39]; median RFS for CheckMate 238 had not yet been reached. Figure 47 and Figure 48 show the KM RFS from the trials compared to the model RFS when patient characteristics were changed to reflect the trial specific population; i.e. when comparing to data from a given trial, only patient characteristics from that trial were used. The modelled RFS shows good estimates when overlaid with the actual trial data.

Table 61: Trial RFS versus model RFS

	Data median (years)	Year 1	Year 2	Year 3	Year 4
CA184-029					
Trial '029 RFS – Placebo (KM)	1.43	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – Routine surveillance*	1.53	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 238					
Trial '238 RFS – Nivolumab (KM)	NA	[redacted]	[redacted]	NA	NA
Model RFS – Nivolumab**	NA	[redacted]	[redacted]	NA	NA

Key: KM, Kaplan–Meier; RFS, recurrence-free survival.
Note: Trial data medians were sourced from trial CSR.
* Patient characteristics were based on CA184-029.
** Patient characteristics were based on CheckMate 238.

Figure 47: CheckMate 238 KM versus model RFS

Key: KM, Kaplan–Meier; RFS, recurrence-free survival.
Note: Patient characteristics were based on CheckMate 238 for this validation assessment.

Figure 48: CA184-029 KM versus model RFS

Key: KM, Kaplan–Meier; RFS, recurrence-free survival.
Note: Patient characteristics were based on CA184-029 for this validation assessment.

Table 62 shows the proportion of patients alive at each year based on the CA184-029 trial data compared to the projected proportions based on the model. Figure 49 displays the KM curves from CA184-029 overlaid with the projected OS from the model, which demonstrates a good fit compared to the trial data when patient characteristics are changed to reflect the CA184-029 population. As no OS data are yet available in the CheckMate 238 trial, only the routine surveillance modelled OS has been compared to the placebo arm in the CA184-029 trial.

Table 62: Trial CA184-029 versus model OS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Trial '029 OS – Placebo (KM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model OS – Routine surveillance*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: KM, Kaplan–Meier; OS, overall survival.
Notes: *Patient characteristics were based on CA184-029.

Figure 49: CA184-029 KM versus model OS

Key: KM, Kaplan–Meier; OS, overall survival.
Note: Patient characteristics were based on CA184-029 for this validation assessment.

Both the RFS and OS comparisons shows the modelled outcomes, both regarding absolute predictions and comparable benefit, appear plausible and in line with observed clinical trial data.

External validation

Long-term OS data were sourced for routine surveillance using AJCC version 7 data (Balch et al., 2009[43]) and AJCC version 8 data (Gershenwald et al., 2017[14]). These data sources were compared to the active routine surveillance survival from the model by comparing the proportion of patients alive at different time points (Table 63) and plotting survival curves (Figure 50).

The final modelled OS for routine surveillance compared to the long-term survival of the external sources shows lower estimates in comparison. This is due to the following:

- As previously mentioned in Section B.3.3, the long-term data available are not entirely reflective of the intended population, making comparisons with the model results difficult.
- It is unknown what treatments these patients in the long-term data would have received and whether adjuvant therapy was given.
- As the OS data for routine surveillance is based on the CA184-029 placebo arm, Balch et al. is more comparable in terms of expected survival, and the modelled results sit between the Stage IIIB and Stage IIIC curves, which is expected given the inclusion of Stage IV NED patients in our population; however, as clinical practice has changed significantly since the time of these data sources, the projected outcomes from melanoma patients should have improved making our estimates conservative. This improvement is seen in the Gershenwald et al. curves with the latest data which is also supported by clinicians as the most relevant source of long term registry data for validation.

Table 63: Long-term OS data for external validation

	Year 1	**Year 2**	**Year 5**	**Year 10**	**Year 15**
Balch 2009 Stage IIIA	97.8%	91.6%	77.3%	67.7%	66.5%
Balch 2009 Stage IIIB	95.5%	83.0%	58.4%	42.6%	37.1%
Balch 2009 Stage IIIC	85.5%	64.5%	40.3%	25.3%	22.6%
Balch 2009 Stage III (weighted) - AJCC 7v	**89.0%**	**74.4%**	**52.9%**	**38.9%**	**32.1%**
Balch 2009 Stage IV abnormal LDH	33.3%	19.4%	9.7%	7.5%	NA
Balch 2009 Stage IV normal LDH	69.4%	44.1%	24.2%	18.8%	NA
Gershenwald 2017 Stage III - AJCC 8v	**97.8%**	**91.3%**	**79.3%**	**71.7%**	**NA**
Routine surveillance OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: LDH, lactate dehydrogenase; OS, overall survival.
Note: Data not collected after 10 years for Gershenwald et al. (2017).

Figure 50: Long-term OS data for external validation

Key: LDH, lactate dehydrogenase; OS, overall survival.

One of the key limitations of the internal and external comparisons is that OS data from CheckMate 238 are not yet available, and therefore, validation of the nivolumab OS is difficult. Nivolumab OS would be expected to be greater than AJCC v7 predictions and more in line with the AJCC v8 given the age of the data, however nivolumab OS projections in the model are currently lower than AJCC v8 suggesting that the model OS predictions are conservative (as is the routine surveillance prediction).

Threshold analysis shows that the projected modelled hazard of death for nivolumab would need to increase by 15% before it is no longer considered cost-effective at the £10,000 threshold; additionally, the ICER remained under £20,000 for the HR's tested within the range of uncertainty from the Checkmate 238 and 029 trials. Assuming the same OS benefit as ipilimumab also produced ICER below £20,000, which further supports the cost-effectiveness of introducing nivolumab for adjuvant treatment. Another key limitation is that the long-term sources available to validate

model extrapolations are restricted given the considerable changes in clinical practice within the metastatic setting over the last 5 years, making it impossible to have both long-term and clinically relevant data.

CheckMate 238 December 2017 data cut

As previously mentioned in Section B.2, a new data cut for RFS became available from the CheckMate 238 trial during the model build (December 2017 data cut). To assess the validity of the model projections, the modelled projected RFS outcomes were overlaid with the new KM data using only patient characteristics from CheckMate 238 (Figure 51). Figure 51 demonstrates that the projected model outcomes are in line with the newest data cut of the CheckMate 238 trial and therefore are still valid.

Figure 51: CheckMate 238 December 2017 data cut KM versus model RFS

Key: KM, Kaplan–Meier; RFS, recurrence-free survival.

B.3.11. Interpretation and conclusions of economic evidence

The economic analysis performed is based on a *de novo* economic model with a structure designed to reflect the adjuvant melanoma setting in the most simplistic form while still capturing the relevant outcomes. The model structure is consistent with previous adjuvant models. The model brought together the most relevant efficacy and safety clinical data and used robust statistical techniques to establish the comparative efficacy of nivolumab and routine surveillance through the use of bespoke PLD meta-regression: the "gold-standard" for ITC. The model makes use of the most recent adjuvant melanoma trials and utilises results from trial-based utility and safety analysis. The model uses clinical input for resource use inputs from clinicians mostly with over 10 years' experience in melanoma and assumptions around model structure, and inputs were validated in face-to-face validation meetings. The key limitations of the analysis are the lack of availability of OS data for nivolumab and the considerable recent changes in the melanoma treatment pathway, which lead to difficulties in sourcing appropriate long-term sources to validate projections. To overcome the lack of OS data, the model estimates OS based on the relationship between RFS and OS from the wealth of adjuvant trials conducted ([redacted]), including the [redacted]). Longer follow-up OS data are also available from the CA184-029 trial and are used as a basis for the routine surveillance arm.

To determine model sensitivity to changes in the treatment pathway and assumptions around PRS, structural analysis was conducted using Markov modelling to test the impact of data from metastatic melanoma treatments previously submitted to NICE to estimate post-recurrence survival.

OS projections for routine surveillance were validated against long-term registry data showing that the base case projection may be conservative compared to what would be expected in current practice, thereby making the OS projections of nivolumab also conservative. Although the projections of OS for nivolumab cannot be validated against any data, threshold analysis tested the cost-effectiveness if these projections were lower than the model predicts; the results show that nivolumab is still cost-

effective against routine surveillance under all clinically plausible scenarios including assumption of equal OS to ipilimumab and RFS at the lower bound of the trial CI.

The structure and key assumptions and modelling options were validated with health economic experts.[44] No previous economic analysis was identified through the systematic literature review in the adjuvant melanoma setting; therefore, the modelling assumptions or results could not be externally validated with previous studies.

Nivolumab treatment in the adjuvant setting following complete resection of Stage III or IV melanoma is a highly effective ([redacted]) and cost-effective treatment option versus routine surveillance:

- ICER of £8,769 per QALY gained at the current patient access scheme (PAS)
- 67.8% likelihood of cost-effectiveness at a WTP of £10k per QALY

Treating upfront with nivolumab in the adjuvant setting reduces the likelihood of disease recurrence and downstream costs and quality of life impacts associated with management of advanced/metastatic melanoma while prolonging expected survival:

- [redacted] of patients no longer experience a recurrence within their lifetime (numbers needed to treat [NNT] = [redacted])
- An increase of [redacted] life years ([redacted]) is projected over a lifetime
- Subsequent treatment costs reduce by approximately [redacted] per patient
- A gain of [redacted] QALYs for every recurrence prevented.

The key strengths of the analysis are:

- Certainty around treatment costs given the 12-month stopping rule included in both trial and license.
  - Estimated drug and administration cost reduction of [redacted] compared to nivolumab monotherapy in the metastatic setting.
- Availability of head-to-head data comparing to another active treatment
- The model presented based upon the earlier CheckMate 238 data-cut predicts well the latest information

- The maturity of the patient level evidence available from the CA184-029 trial and registry information
- The measurement of EQ-5D data throughout the CheckMate 238 trial, including post recurrence

In conclusion, the *de novo* economic analysis brings together the best available clinical data to establish the comparative efficacy and safety of nivolumab versus routine surveillance. We consider that nivolumab meets the criteria for a fast track assessment by NICE with a base case ICER below £10,000/QALY gained and with all of the sensitivity analyses below £20,000/QALY gained. If nivolumab was to be appraised through the FTA process, patients could potentially gain quicker access to an effective adjuvant treatment option for the first time in the NHS.

There is currently no treatment option for patients with resected melanoma. It is of key importance for patients to have the option of treatment to reduce the chance of a recurrence requiring further chemotherapy and potentially shorter life. Following complete surgical resection, patients are currently managed through routine surveillance due to lack of adjuvant treatment options with a proven efficacy benefit and tolerable safety profile available. Nivolumab demonstrates significant RFS benefit compared to another active treatment in the adjuvant setting. Further, nivolumab has already demonstrated OS benefit within the metastatic setting with the latest data from the CheckMate 067 trial showing significant OS benefit of nivolumab compared to ipilimumab which increases over time.[53] Having an option of such treatment compared to nothing in the adjuvant setting can result in substantial gains in patient relevant outcomes, reduce the anxiety of a recurrence and significantly improve patient's quality of life.

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Health technology appraisal

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

Dear Dio,

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received on 15 May 2018 from Bristol-Myers Squibb. 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 22 June 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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 [redacted] in turquoise, and all information submitted as [redacted] 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 Juliet Kenny, Technical Lead (Juliet.Kenny@nice.org.uk). Any procedural questions should be addressed to Thomas Feist, Project Manager (Thomas.Feist@nice.org.uk).

Yours sincerely

Eleanor Donegan
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

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Section A: Clarification on effectiveness data

A1. **Priority question:** Please carry out the indirect treatment comparisons (ITCs), both patient level data (PLD) meta-regression and Bucher methods, for recurrence-free survival (RFS) incorporating data from the updated database lock of 19 December 2017 (24 month follow-up) for CheckMate 238 and the data from CA184-029.

A2. **Priority question:** Please carry out the ITCs, both PLD meta-regression and Bucher methods, using CheckMate 238 and CA184-029 to generate an effect estimate for overall survival (OS) for the comparison of nivolumab versus placebo at 24 months or using the latest available data from CheckMate 238.

A3. **Priority question:** Please confirm that the sensitivity analyses for RFS where the definition of RFS for CA184-029 was matched to CheckMate 238 in terms of censoring for subsequent therapy is based on censoring those in CA184-029 at the time of last disease assessment prior to receipt of subsequent therapy.

A4. **Priority question:** Please carry out the ITCs, both PLD meta-regression and Bucher methods, incorporating data from the updated database lock of 19 December 2017 (24 month follow-up) for CheckMate 238 (or the latest available data) and the data from CA184-029 for the following outcomes:

a. recurrence-free survival (RFS) using the independent review data for both CheckMate 238 and CA184-029;

b. RFS for CheckMate 238 and the subgroup of people who received up to 1 year of ipilimumab in CA184-029;

c. RFS for CheckMate 238 using the subgroup of people PD-L1 status ≥ 5% and the whole CA184-029 study population;

d. RFS for CheckMate 238 using the subgroup of people PD-L1 status < 5% or indeterminate and the whole CA184-029 study population.

A5. **Priority question:** Please provide the baseline characteristics for:

a. the subgroup of people who received up to 1 year of ipilimumab in CA184-029;

b. the subgroup of people PD-L1 status ≥ 5% in CheckMate 238;

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c. the subgroup of people PD-L1 status < 5% or indeterminate in CheckMate 238.

A6. **Priority question:** Please provide the absolute number of events and patients at risk, using data from the updated database lock of 19 December 2017 (24 month follow-up) for CheckMate 238 (or the latest available data) and the data from CA184-029 for the following outcomes:

a. adverse events outcomes reported in the economic model;

b. adverse events outcomes reported in the economic model using the censoring of adverse of events data at 30 days after last treatment dose (rather than 70 days in CA184-029) for both CheckMate 238 and CA184-029;

c. adverse events outcomes reported in the economic model for CheckMate 238 and the subgroup of people in CA184-029 who received up to one year treatment of ipilimumab;

d. adverse events outcomes reported in the economic model for CheckMate 238 and the subgroup of people in CA184-029 who received up to one year treatment of ipilimumab with censoring of adverse events at 30 days after last treatment dose.

A7. **Priority question:** Please provide the rationale for assuming that the relationship between RFS and OS are the same across different drug classes in the calculation of OS for nivolumab using the 'surrogacy relationship equation'.

A8. **Priority question:** Please provide further details on the origin of the 'surrogacy relationship equation' used to calculate the OS of nivolumab and details of the trials included in the calculation used in the economic base case to supplement the information provided in the Company Submission Document B pages 118 to 124.

A9. **Priority question:** Please provide mean, with accompanying 95% confidence interval, OS for nivolumab and ipilimumab at 12, 18 and 24 months of follow-up, together with the number of events and number of people at risk at each time point in the individual groups for CheckMate 238 and the equivalent data for ipilimumab and placebo in CA 184-029.

Staging

A10. Reclassifying patients using the Version 8 AJCC definitions of stage III and IV melanoma, please carry out the ITCs, both PLD meta-regression and Bucher methods, incorporating data from the updated database lock of 19 December 2017 for CheckMate 238 (or the latest available data) and the data from CA 184-029 for the RFS for the following subgroups:

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a. Stage IIIa;

b. Stage IIIb;

c. Stage IIIc.

A11. Please provide the baseline characteristics for CheckMate 238 and CA 184-029 for the subgroup analyses requested in Question A10.

A12. Please provide mean RFS and accompanying 95% confidence intervals for nivolumab and ipilimumab at 12, 18 and 24 months of follow-up for CheckMate 238 and the equivalent data for ipilimumab and placebo in CA184-029.

A13. Please provide results for RFS at 12, 18 and 24 months of follow-up for the subgroup analysis based on geographic location (North America versus Western Europe versus Eastern Europe versus Asia versus Australia) for CheckMate 238.

A14. Please clarify if individual cases of recurrence of melanoma were assessed by an independent reviewer in CheckMate 238 in addition to the investigator assessment primary analysis. If so, please provide results for analyses of RFS at 12, 18 and 24 months of follow-up based on independent review.

Safety data

A15. Please provide trial level relative risks (RRs) and 95% confidence intervals for the safety data from CheckMate 238 and CA184-029 for the adverse events included in the economic model.

Study population

A16. Please clarify how many people in the nivolumab and ipilimumab groups in CheckMate 238 were recruited from sites in the UK.

Subsequent therapies

A17. Please provide the absolute numbers of patients and patients at risk, using data from the updated database lock of 19 December 2017 (24 months follow-up) for CheckMate 238 (or the latest available data) and the data from CA184-029 for the subsequent therapies received split by line of therapy (i.e. 1L, 2L, 3L+).

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please add the parametric curves derived from the meta-regression analyses in clarification questions A1, A2, A4 and A10 as options in the economic model.

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B2. **Priority question:** Please adjust the OS models fitted to the CA184-029 and CheckMate 238 trials (latest available data) for subsequent therapies, grouping by class of drug, and incorporate an interaction with the primary treatment group. Please add these to the economic model to allow modelling of alternative subsequent treatment strategies independently for each primary treatment group.

B3. **Priority question:** Please provide spline based models for each of the RFS meta-regression ITCs without rebasing curves at 12 weeks. Please apply at least one knot (placed at 12 weeks) but also consider adding further knots to provide a better fit. Please also adjust as per clarification question B2 and add these as options in the economic model.

B4. **Priority question:** Please add the Kaplan-Meier data for both RFS and OS from the updated database lock of 19 December 2017 (24 months follow-up) (or the latest available data) for CheckMate 238.

B5. Please provide a scenario analysis using the results of clarification question B8.

B6. Please apply a different approach for nivolumab treatment costs, as the one off cost applied in the first model cycle prevents discounting from being applied.

B7. Please provide the utility regression model coefficients and p-values for each step of the variable selection procedure.

B8. Assuming the OS benefit of immunotherapies in the adjuvant setting is equivalent to in the metastatic melanoma setting, please use only data from metastatic melanoma and adjuvant therapy immunotherapy studies (i.e. exclude the interferon studies and COMBI-AD, but include any studies of immunotherapies in metastatic melanoma) for the calculation of OS and provide the resulting HR for nivolumab.

B9. Please clarify what adjustments have been made in the primary analysis of RFS to generate the parametric survival modelling patient-level ITCs. For example, the definition of RFS in CA184-029 does not include new primary melanoma as an event, whereas this is included in the definition of RFS in CheckMate 238. In the analysis, have new primary melanoma events been excluded from CheckMate 238? If not, how many primary melanoma events were there in each arm of CheckMate 238.

B10. Please clarify what adjustments have been made in the analyses listed below to generate the parametric survival modelling patient-level ITCs based on:

a. Sensitivity analysis matching RFS definition on subsequent therapy censoring in CA184-029.

b. Sensitivity analysis matching CA184-029 on reviewer.

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Section C: Textual clarifications and additional points

C1. For CheckMate 238, please clarify the number of people from Asia who had a RFS event at 24 months of follow-up. In the last paragraph of section B.2.7 (page 39 of the company submission), the number of people from Asia in the nivolumab group experiencing a RFS event is reported to be [redacted] and [redacted]. Additionally, the number having a RFS event in the ipilimumab group is reported to be [redacted] and [redacted].

C2. Please clarify what outcome the statement "nivolumab is a well-tolerated treatment, with a safety profile generally comparable to routine surveillance ([redacted])" on page 80 of the company submission refers to.

C3. Please confirm whether the data presented in Table 17 on page 83 of the company submission are from the 19 December 2017 data cut.

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Health technology appraisal

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

Dear Dio,

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Yours sincerely

Eleanor Donegan
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

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Section A: Clarification on effectiveness data

A1. **Priority question:** Please carry out the indirect treatment comparisons (ITCs), both patient level data (PLD) meta-regression and Bucher methods, for recurrence-free survival (RFS) incorporating data from the updated database lock of 19 December 2017 (24 month follow-up) for CheckMate 238 and the data from CA184-029.

Table 1 presents the parameter estimates for the RFS meta-regression ITC model using the 24-month follow-up for CheckMate 238. Table 2 displays the model fit statistics for the meta-regression and indicates that the log-logistic curve is the preferred model based on statistical fit. To visually assess the goodness of fit for the models produced the following plots have been produced:

- Figure 1 presents the observed ipilimumab KM in CheckMate 238 versus each distribution from the meta-regression analysis
- Figure 2 presents the observed nivolumab KM in CheckMate 238 versus each distribution from the meta-regression analysis
- Figure 3 presents the observed KM for both nivolumab and ipilimumab in CheckMate 238 and the log-logistic curve (best fitting model) from the meta-regression analysis
- Figure 4 presents the observed ipilimumab KM in CA184-029 versus each distribution from the meta-regression analysis
- Figure 5 presents the observed placebo KM in CA184-029 versus each distribution from the meta-regression analysis
- Figure 6 presents the observed KM for both nivolumab and ipilimumab in CA184-029 and the log-logistic curve (best fitting model) from the meta-regression analysis

The log-logistic meta-regression model was then used to estimate the long-term survival estimates for each treatment using a match population (i.e. the covariate proportions in the group prognosis are consistent across all treatment groups), this is presented in Figure 7.

Table 1: Recurrence-free survival (24-month follow-up) meta-regression parameter estimates

Coefficient	Exp	GG	Gom	LL	LN	Wei
TRT: PBO (ref:ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TRT: Nivo (ref:ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage: IIIa (ref: IIIb)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage: IIIc (ref: IIIb)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV: (ref: IIIb)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex: Female (ref: male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age: >= 65 (ref: <65)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial: 029 (ref: 238)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape TRT: PBO (ref:ipi)			[redacted]	[redacted]		[redacted]
Shape TRT: Nivo (ref:ipi)			[redacted]	[redacted]		[redacted]
Sigma TRT: PBO (ref:ipi)		[redacted]				
Sigma TRT: Nivo (ref:ipi)		[redacted]				
Sdlog TRT: PBO (ref:ipi)					[redacted]	

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Coefficient	Exp	GG	Gom	LL	LN	Wei
Sdlog TRT: Nivo (ref:ipi)					[redacted]	
Shape			[redacted]	[redacted]		[redacted]
Rate	[redacted]		[redacted]			
Scale				[redacted]		[redacted]
Meanlog					[redacted]	
Sdlog					[redacted]	
Mu		[redacted]				
Sigma		[redacted]				
Q		[redacted]				

Key: Exp, exponential; GG, generalised gamma; Gom, Gompertz; Ipi, ipilimumab 10 mg; LL, log-logistic; LN, log-normal; Nivo, nivolumab; PBO, placebo; Wei, Weibull.
Notes: To interpret the Stage, sex and age coefficients for the exponential and Gompertz distributions a negative value indicates improved outcomes and a positive value indicates reduced outcomes relative to the reference category. For the generalised gamma, log-logistic, log-normal and Weibull distributions converse is true.

Table 2: Recurrence-free survival (24-month follow-up) meta-regression model fit statistics

Model	AIC	BIC
Exponential	12128.65	12177.02
Generalised Gamma	11827.33	11897.18
Gompertz	11879.27	11943.75
Log-logistic	**11819.06**	**11883.54**
Log-normal	11832.21	11896.69
Weibull	11845.56	11910.04

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 1: CheckMate 238 recurrence-free survival (24-month follow-up) – long-term survival extrapolation from the meta-regression model rebased at Week 12 – ipilimumab arm

Key: Ipi, ipilimumab 10 mg; KM, Kaplan–Meier.

Notes: KM from baseline is displayed, curves are fit from 12 weeks onwards.

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Figure 2: CheckMate 238 recurrence-free survival (24-month follow-up) – long-term survival extrapolation from the meta-regression model rebased at Week 12 – nivolumab arm

Key: KM, Kaplan–Meier; Nivo, nivolumab.

Notes: KM from baseline is displayed, curves are fit from 12 weeks onwards.

Figure 3: CheckMate 238 recurrence-free survival (24-month follow-up) – long-term survival extrapolation from log-logistic meta-regression model rebased at Week 12

Key: Ipi, ipilimumab 10 mg; KM, Kaplan–Meier; Nivo, nivolumab.
Notes: KM from baseline is displayed, log logistic curve is fit from 12 weeks onwards.

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Figure 4: CA184-029 recurrence-free survival – long-term survival extrapolation from the meta-regression model rebased at Week 12 – ipilimumab arm

Key: Ipi, ipilimumab 10 mg; KM, Kaplan–Meier.
Notes: KM from baseline is displayed, curves are fit from 12 weeks onwards.

Figure 5: CA184-029 recurrence-free survival – long-term survival extrapolation from the meta-regression model rebased at Week 12 – placebo arm

Key: KM, Kaplan–Meier; PBO, placebo.
Notes: KM from baseline is displayed, curves are fit from 12 weeks onwards.

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Figure 6: CA184-029 recurrence-free survival – long-term survival extrapolation from the log-logistic meta-regression model rebased at Week 12

Key: Ipi, ipilimumab 10 mg; KM, Kaplan–Meier; PBO, placebo.
Notes: KM from baseline is displayed, log logistic curves are fit from 12 weeks onwards.

Figure 7: Recurrence-free survival –long-term survival extrapolation from meta-regression model rebased at Week 12 split by treatment using matched population

Key: Ipi, ipilimumab 10 mg; ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab; PBO, placebo.

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The results of the Bucher RFS analyses using 24-month follow-up for CheckMate 238 are presented in Table 3. The results are consistent with those obtained using the 18-month data; demonstrating a consistent [redacted]. This suggests that following adjuvant treatment with nivolumab (compared to ipilimumab or placebo), fewer patients experience a recurrence, including distant recurrence, where the disease is generally considered incurable and the treatment goal is likely to be palliative rather than curative.

Table 3: Results of the recurrence free survival indirect treatment comparison using the Bucher method.

Covariate adjusted	Population	238 HR (95% CI) Nivo vs Ipi	029 HR (95% CI) PBO vs Ipi*	Bucher HR (95% CI) Nivo vs PBO
No	ITT	[redacted]	[redacted]	[redacted]
Yes	ITT	[redacted]	[redacted]	[redacted]
No	Stage IIIb/c	[redacted]	[redacted]	[redacted]
Yes	Stage IIIb/c	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; HR, hazard ratio; Ipi; ipilimumab; ITT, intention-to-treat; Nivo, nivolumab; PBO, placebo; TRT, treatment.

Note: * HRs presented are comparing placebo against ipilimumab, hence HR>1 means that ipilimumab performs better than placebo.

A2. **Priority question:** Please carry out the ITCs, both PLD meta-regression and Bucher methods, using CheckMate 238 and CA184-029 to generate an effect estimate for overall survival (OS) for the comparison of nivolumab versus placebo at 24 months or using the latest available data from CheckMate 238.

BMS are not able to fully address the ERG's request relating to the generation of effect estimates for overall survival using patient level data (PLD) from Checkmate 238 for the following reasons:

- Checkmate 238 is a randomised control trial (RCT) in an adjuvant setting, with RFS as the primary endpoint; since the aim of adjuvant treatment is to prevent disease recurrence following surgical resection. Although overall survival (OS) is clinically meaningful, this endpoint requires extended follow-up and is confounded by subsequent treatments. [redacted]

[redacted]

[redacted] This is standard for

adjuvant trials as evidenced by previous timelines for the release of OS data from the CA184-029 study.

[redacted] at this stage to perform the analyses requested by the ERG.

BMS [redacted]

[redacted]

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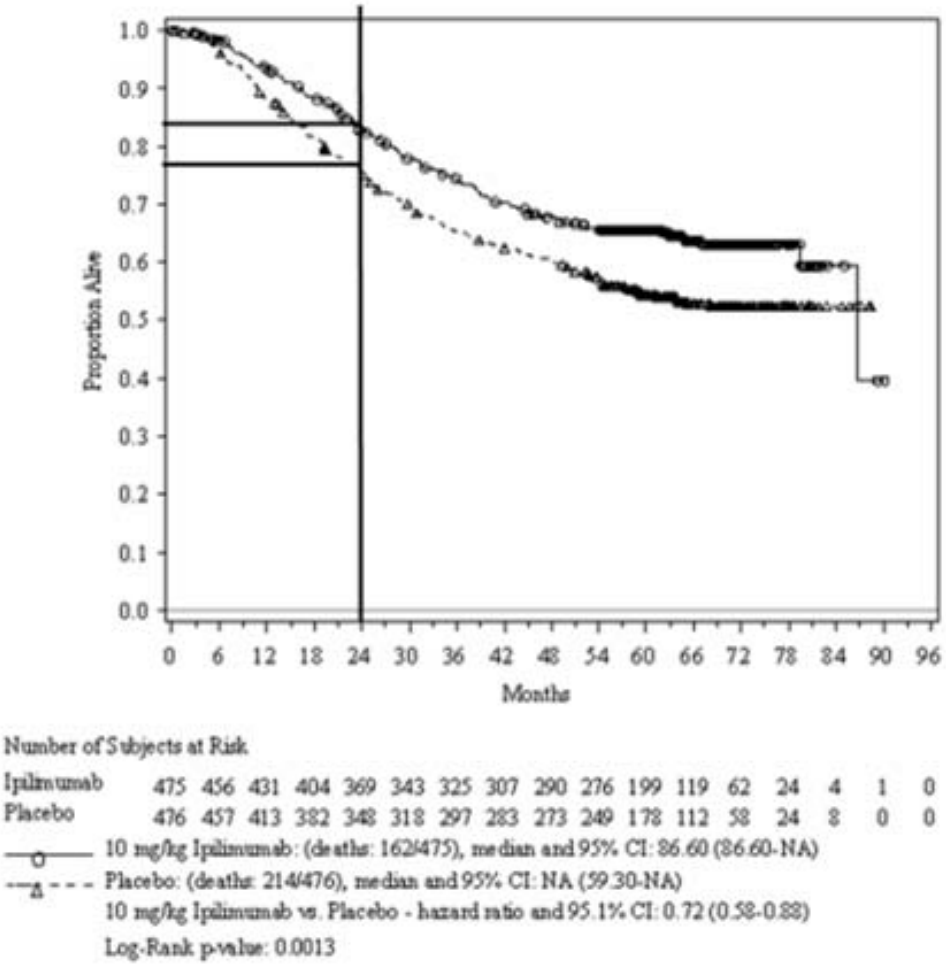
[redacted] when compared to the patients in study CA184029, despite inclusion of higher risk Stage IV patients in CA209-238 (18.7% of patients in the study), who were excluded in CA184-029.

Figure 9: CheckMate 029 OS - Eggermont et al 2016 overall survival



Although trial CheckMate-238 includes more advanced stage patients than CA184-029 (Stage IIIB/C and stage IV), the [redacted] treatment with nivolumab in the adjuvant setting increases the proportion of patients that remain disease free and are potentially cured of disease following resection. As such, a lower number of patients will go on to develop systemic melanoma which is associated with retained despite the potential for being retreated with immunotherapy agents in the advanced setting.

Bucher ITC [redacted]

[redacted]

CA184-029 gives HR_{OS} of 0.72 (95% CI: 0.58 – 0.88) for ipilimumab versus placebo.[1] Table 4 shows the Bucher analysis results.

[redacted]

Method	Population	[redacted]	029 HR (95% CI) PBO vs Ipi *	[redacted]
Bucher ITC	ITT	[redacted]	1.39 (1.14, 1.72)	[redacted]

Key: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; Nivo, nivolumab; PBO, placebo; TRT, treatment.

* HRs presented are comparing placebo against ipilimumab, hence HR>1 means that ipilimumab performs better than placebo.

[redacted]

A3. **Priority question:** Please confirm that the sensitivity analyses for RFS where the definition of RFS for CA184-029 was matched to CheckMate 238 in terms of censoring for subsequent therapy is based on censoring those in CA184-029 at the time of last disease assessment prior to receipt of subsequent therapy.

For RFS in 029 the meta-regression was only performed with the within trial sensitivity analysis in which patients were censored at their last disease assessment prior to the receipt of subsequent therapy. Note, the meta-regression was not performed multiple times with different RFS definitions. Figure 3 in the submission appendices presents the within 029 definitions for RFS which displayed little difference between the possible definitions.

A4. **Priority question:** Please carry out the ITCs, both PLD meta-regression and Bucher methods, incorporating data from the updated database lock of 19 December 2017 (24 month follow-up) for CheckMate 238 (or the latest available data) and the data from CA184-029 for the following outcomes:

a. recurrence-free survival (RFS) using the independent review data for both CheckMate 238 and CA184-029;

Checkmate 238 was an active controlled trial and since recurrence has a significant clinical implication (unless local) it was considered that independent assessment was not required. As such, only investigator- based assessment of RFS is available for this study, which is more clinically relevant and more closely resembles real world practice compared to independent assessment. For this reason, BMS are not able to process the request of

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additional analyses using the independent review of data from both Checkmate 238 and CA184-029. However, within the submission the potential impact of this choice is discussed in full and is anticipated to be minimal as outlined in Appendix D page 21.

b. RFS for CheckMate 238 and the subgroup of people who received up to 1 year of ipilimumab in CA184-029;

Although we recognise that there exists a difference in the duration of ipilimumab between the two trials, the impact of this is expected to be limited:

- The data shows similar RFS outcomes for Stage IIIb/IIIc patients across trials in the ipilimumab arm (see company submission Section B2.9 Figure 14 and 15);
- The median number of ipilimumab doses is four in both trials;[1, 2]
- Only a small proportion of patients in the CA184-029 trial had ipilimumab treatment beyond 1 year ([redacted]%). The ipilimumab median number of doses was 4 (interquartile range: 1-8)[1]
- Clinical opinion suggests that the difference in dosing would not impact effectiveness between the trials.[3]

The analysis of the subgroup of patients who received up to 1-year ipilimumab treatment would not be a fair comparison relative to the ipilimumab patients in CheckMate 238. Figure 10 presents the RFS KM's in CA184-029 for both the ITT population and the subgroup of patients who received up to 1 year's treatment split by treatment. The KM's indicate that in both the ipilimumab and placebo group the rate of recurrence in the subgroup population is faster than in the ITT population; the ipilimumab subgroup population is comparable to the placebo ITT population, where almost all of the placebo subgroup population have experienced an RFS event within a year. If the comparison were fair, then it would be expected that for the first year, the KM's would approximately overlap between the ITT population and the subgroup. This is not the case because patients included within the analysis are likely to have increased risk of relapse. It should also be noted that this comparison breaks randomisation and it is likely that patients who have received ipilimumab for more than one year would have been the patients who responded better to treatment and are able to tolerate the drug. Therefore presenting the ITC of RFS for CM238 patients and subgroup of patients that received ipilimumab for 1 year would produce biased estimates due to selection bias. 14

Figure 10: CA184-029 recurrence-free survival KM for the ITT population and subgroup of patients who received up to one year treatment split by treatment

Key: Ipi, ipilimumab 10 mg; ITT, intention-to-treat KM, Kaplan–Meier; PBO, placebo; TRT, treatment; yr, year.

A suggested alternative approach which is more methodologically robust since randomisation is maintained, would be to censor patients at one year if they are still receiving ipilimumab treatment (note, placebo patients would not be censored at this time). Although this approach incorporates all randomised patients, as patients who are well enough to continue receiving ipilimumab treatment would be censored informatively at one year, the analysis biases the results against ipilimumab.

Figure 11 presents the recurrence-free survival for the ITT population in CA184-029 and for the ITT population where patients are censored at one year if they were still receiving treatment (note, the placebo has been displayed for completeness and is not of interest for the censored analysis). The KM's overlap for each treatment for the initial year as the same group of patients are considered for this period. Following one year a slight increase in the rate of RFS events is observed in the ipilimumab arm in comparison to the ITT ipilimumab arm. Although this approach is still inherently biased as ipilimumab patients are informatively censored, it is less biased than the ERG's suggested analysis. The ITC analysis has therefore been performed for the ITT population, where ipilimumab patients in CA184-029 are censored at one year if still on treatment rather than using the subgroup of ipilimumab in CA184-029 patients who received treatment up to one year.

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Figure 11: CA184-029 recurrence-free survival KM for the ITT population and for the ITT population where patients are censored at one year if they remained on treatment

Key: Ipi, ipilimumab 10 mg; ITT, intention-to-treat KM, Kaplan–Meier; PBO, placebo; TRT, treatment; yr, year.

Table 5 presents the parameter estimates for the RFS meta-regression ITC model using the 24-month follow-up for CheckMate 238 where ipilimumab patients are censored at one year if still on treatment. Table 6 displays the model fit statistics for the meta-regression and indicates that the log-logistic curve is the preferred model based on statistical fit. This is also in line with the previous curve selection from the 18-month data which was based on statistical fit and clinical opinion suggesting that the curves looked pessimistic compared to clinical practice, therefore log-logistic also provides a more optimistic estimates (see company submission, Section B2.9, page 69).[4] To visually assess the goodness of fit for the models produced the following plots have been produced:

- Figure 12 presents the observed ipilimumab KM in CheckMate 238 versus each distribution from the meta-regression analysis
- Figure 13 presents the observed nivolumab KM in CheckMate 238 versus each distribution from the meta-regression analysis
- Figure 14 presents the observed KM for both nivolumab and ipilimumab in CheckMate 238 and the log-logistic curve (best fitting model) from the meta-regression analysis
- Figure 15 presents the observed ipilimumab KM in CA184-029 versus each distribution from the meta-regression analysis (censored at 1 year if still on treatment)
- Figure 16 presents the observed placebo KM in CA184-029 versus each distribution from the meta-regression analysis

- Figure 17 presents the observed KM for both nivolumab and ipilimumab in CA184-029 (censoring of patients at 1 year if still on treatment)and the log-logistic curve (best fitting model) from the meta-regression analysis

The log-logistic meta-regression model was then used to estimate the long-term survival estimates for each treatment using a matched population (i.e. the covariate proportions in the group prognosis are consistent across all treatment groups), this is presented in Figure 18.

Table 5: Recurrence-free survival (24-month follow-up; ipilimumab patients censored at 1 year if still on treatment) meta-regression parameter estimates

Coefficient	Exp	GG	Gom	LL	LN	Wei
TRT: PBO (ref:ipi)						
TRT: Nivo (ref:ipi)						
Stage: IIIa (ref: IIIb)						
Stage: IIIc (ref: IIIb)						
Stage IV: (ref: IIIb)						
Sex: Female (ref: male)						
Age: >= 65 (ref: <65)						
Trial: 029 (ref: 238)						
Shape TRT: PBO (ref:ipi)						
Shape TRT: Nivo (ref:ipi)						
Sigma TRT: PBO (ref:ipi)						
Sigma TRT: Nivo (ref:ipi)						
Sdlog TRT: PBO (ref:ipi)						
Sdlog TRT: Nivo (ref:ipi)						
Shape						
Rate						
Scale						
Meanlog						
Sdlog						
Mu						
Sigma						
Q						

Key: Exp, exponential; GG, generalised gamma; Gom, Gompertz; Ipi, ipilimumab 10 mg; LL, log-logistic; LN, log-normal; Nivo, nivolumab; PBO, placebo; Wei, Weibull.
Notes: To interpret the Stage, sex and age coefficients for the exponential and Gompertz distributions a negative value indicates improved outcomes and a positive value indicates reduced outcomes relative to the reference category. For the generalised gamma, log-logistic, log-normal and Weibull distributions converse is true.

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Table 6: Recurrence-free survival (24-month follow-up; ipilimumab patients censored at 1 year if still on treatment) meta-regression model fit statistics

Model	**AIC**	**BIC**
Exponential	11483.12	11531.48
Generalised Gamma	11214.88	11284.74
Gompertz	11264.82	11329.30
Log-logistic	**11205.19**	**11269.67**
Log-normal	11222.45	11286.93
Weibull	11228.91	11293.39
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.		

Figure 12: CheckMate 238 ipilimumab arm recurrence-free survival (24-month follow-up) rebased at Week 12– long-term survival extrapolation from the meta-regression model (ipilimumab arm in CA184-029 censored at 1 year if still on treatment)

Key: Ipi, ipilimumab 10 mg; KM, Kaplan–Meier.

Notes: KM from baseline is displayed, curves are fit from 12 weeks onwards

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Figure 13: CheckMate 238 nivolumab arm recurrence-free survival (24-month follow-up) rebased at Week 12 – long-term survival extrapolation from the meta-regression model (ipilimumab arm in CA184-029 censored at 1 year if still on treatment)

Key: KM, Kaplan–Meier; Nivo, nivolumab.

Notes: KM from baseline is displayed, curves are fit from 12 weeks onwards.

Figure 14: CheckMate 238 recurrence-free survival (24-month follow-up) – long-term survival extrapolation from log-logistic meta-regression model rebased at Week 12

Key: Ipi, ipilimumab 10 mg; KM, Kaplan–Meier; Nivo, nivolumab.
Notes: KM from baseline is displayed, log logistic curve is fit from 12 weeks onwards.

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Figure 15: CA184-029 ipilimumab arm recurrence-free survival rebased at Week 12 – long-term survival extrapolation from the meta-regression model (ipilimumab arm patients in CA184-029 censored at 1 year if still on treatment)

Key: Ipi, ipilimumab 10 mg; KM, Kaplan–Meier.

Notes: KM from baseline is displayed, curves are fit from 12 weeks onwards.

Figure 16: CA184-029 placebo arm recurrence-free survival rebased at Week 12 – long-term survival extrapolation from the meta-regression model (ipilimumab arm patients in CA184-029 censored at 1 year if still on treatment)

Key: KM, Kaplan–Meier; PBO, placebo.

Notes: KM from baseline is displayed, curves are fit from 12 weeks onwards.

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Figure 17: CA184-029 recurrence-free survival – long-term survival extrapolation from the log-logistic meta-regression model (ipilimumab arm in CA184-029 censored at 1 year if still on treatment) rebased at Week 12

Key: Ipi, ipilimumab 10 mg; KM, Kaplan–Meier; PBO, placebo.

Notes: KM from baseline is displayed, log logistic curves are fit from 12 weeks onwards.

Figure 18: Recurrence-free survival –long-term survival extrapolation from meta-regression model (patients in the ipilimumab arm in CA184-029 censored at 1 year if still on treatment) rebased at Week 12 split by treatment using matched population

Key: Ipi, ipilimumab 10 mg; ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab; PBO, placebo

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The results of the Bucher analyses using 24-month follow-up for CheckMate 238 and where ipilimumab patients are censored at 1 year in CA184-029 are presented in Table 7. Results remain consistent with the ITC included in the submission, with nivolumab demonstrating [redacted] despite the bias against ipilimumab for reasons discussed above.

Table 7: Results of the recurrence free survival indirect treatment comparison using the Bucher method (ipilimumab patients censored at 1 year if still receiving treatment).

Covariate adjusted	Population	238 HR RFS (95% CI) Nivo vs Ipi	029 HR RFS (95% CI) PBO vs Ipi*	Bucher HR RFS (95% CI) Nivo vs PBO
No	ITT	[redacted]	[redacted]	[redacted]
Yes	ITT	[redacted]	[redacted]	[redacted]
No	Stage IIIb/c	[redacted]	[redacted]	[redacted]
Yes	Stage IIIb/c	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; HR, hazard ratio; Ipi; ipilimumab; ITT, intention-to-treat; Nivo, nivolumab; PBO, placebo; TRT, treatment.

* HRs presented are comparing placebo against ipilimumab, hence HR>1 means that ipilimumab performs better than placebo.

c. RFS for CheckMate 238 using the subgroup of people PD-L1 status ≥ 5% and the whole CA184-029 study population;

PD-L1 is a transiently expressed protein on the cell surface of immune and tumour cells and can be up or down regulated by a variety of internal and external factors including prior treatment with other therapies. Over time for any given patient, expression levels may therefore vary with tumour alternating between high and low expression levels. Further, detection of PD-L1 varies according to the specificity of the detection kit. Additionally, expression can also vary across any tumour sample with areas of high expression neighbouring areas of no expression making accurate assessment problematic and open to a degree of interpretation.

There is also no consensus on the most appropriate cut off to identify low or high expressors – 1%, 5%, 10% and higher have all been used in different trials, or amongst physicians on the value of PD-L1 for treatment decisions with low rates of testing currently for metastatic melanoma. Indeed, due to the challenges associated with measuring and assessing PD-L1, clinicians are of the opinion that it would not be informative to present outcomes by PD-L1 status.[3] [redacted].[5]

Specifically to the CheckMate 238 trial, recruited patients were stratified according to PD-L1 expression at the 5% cut off, eliminating any bias in the study outcomes. Subgroup analyses of RFS according to PD-L1 status have been presented within the main submission document (Section B.2.6. page 31). Consistent with the primary analysis, in PD-L1 status ≥ 5% RFS HRs favoured nivolumab compared to ipilimumab ([redacted]), showing that benefit with nivolumab is observed irrespective of PD-L1 status (Figures 7 and 12 main submission document).

Although RFS rates are slightly higher for both Nivolumab and Ipilimumab in PD-L1 ≥ 5% patients, analyses of RFS across all predefined PD-L1 expression levels suggesting that nivolumab demonstrates improved RFS regardless of PD-L1 status in this patient population.

Figure 19 below presents the forest plot of RFS by different PD-L1 expression levels from CheckMate 238 using the 18-month datacut included in the main HTA submission. The subgroup analyses demonstrate the superiority of nivolumab versus ipilimumab regardless of PD-L1 expression level.

Figure 19 Forest plot of RFS by PD-L1 expression level, CheckMate 238, 18-month follow-up

Therefore, there is no indication that PD-L1 expression exerts an effect on the efficacy outcomes for CheckMate 238. This is consistent with the clinical evidence available for nivolumab monotherapy in metastatic setting for which the EMA concluded in no treatment effect being attributed due to PD-L1 expression.

PD-L1 data from CA184-029 study is not available since the trial was conducted some time ago when PD-L1 testing was not established and therefore the patients recruited were not therefore assessed for PD-L1 status. Therefore, the additional analysis requested by the ERG requiring the incorporation of a PD-L1 subgroup within the RFS ITC for CheckMate-238

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but comparing to the whole population of CA184-029 would be subject to inconsistency and introduce bias on the ITC.

In addition, the requested analyses deviate from the decision problem, which does not specify exploration of subgroups and most importantly are outside the anticipated marketing authorisation filed with the EMA for adjuvant melanoma. For the reasons outlined above, any analyses specific to PD-L1 status are unlikely to have a major impact in the cost-effectiveness of the technology. Therefore, BMS do not consider PD-L1 status ≥ 5% subgroup is relevant for the decision problem itself and ask that the RFS data is viewed in its totality for the purpose of this HTA submission regardless of PD-L1 status in line with the anticipated marketing authorisation.

d. RFS for CheckMate 238 using the subgroup of people PD-L1 status < 5% or indeterminate and the whole CA184-029 study population.

As in question A4c above, BMS do not consider that the PD-L1 status < 5% subgroup is relevant based on the clinical evidence available. Consistent with the primary analysis, in patients with PD-L1 status < 5% RFS HRs favoured nivolumab compared to ipilimumab [redacted] showing that benefit with nivolumab is observed irrespective of PD-L1 status. As such, and for the reasons outlined above, any analyses specific to PD-L1 status are unlikely to have a major impact in the cost-effectiveness of the technology.

A5. **Priority question:** Please provide the baseline characteristics for:

a. the subgroup of people who received up to 1 year of ipilimumab in CA184-029;

The baseline characteristics for the subgroup of people who received up to 1 year of ipilimumab in CA184-029 are presented in Table 8 alongside the all treated patients in the ipilimumab arm in the trial. The table shows that the baseline characteristics are broadly similar between the overall treated patients in the ipilimumab arm and the subgroup of patients received up to 1 year of ipilimumab in CA184-029.

Table 8: Characteristics Summary on Subgroup of Subjects who Received up to 1 year of Ipilimumab All Treated Subjects vs all Ipilimumab treated patients from CA184-029

b. the subgroup of people PD-L1 status ≥ 5% in CheckMate 238;

The baseline characteristics for the subgroup of patients with PD-L1 status >=5% in

	Ipilimumab (n=475)	[redacted]
Male, n (%)	296 (62)	
Age, median (range):	51 (20–84)	
Disease stage[a], n (%):		
Stage IIIA	98 (21)	
Stage IIIB	182 (38)	
Stage IIIC (1–3 LN+)	122 (26)	
Stage IIIC (≥4 LN+)	73 (15)	
AJCC 2002[b], n (%):		
Stage IIIA	98 (21)	
Stage IIIB	213 (45)	
Stage IIIC (1-3 LN+)	69 (15)	
Stage IIIC (≥4 LN+)	95 (20)	
Lymph node involvement, n (%):		
Microscopic	210 (44)	
Macroscopic	265 (56)	
Number of positive lymph nodes, n (%):		
1	217 (46)	
2–3	163 (34)	
≥4	95 (20)	
Ulceration, n (%)		
No	257 (54)	
Yes	197 (41)	
Unknown	21 (4)	

Key: AJCC, American Joint Committee on Cancer; EORTC, European Organisation for Research and Treatment of Cancer; LN, lymph node.
Notes: [a], As provided at randomisation; [b], As indicated on case report forms.
Source: Eggermont *et al.*, 2015.[6]

CheckMate 238 study for the nivolumab and ipilimumab arms are presented in Table 9. The table shows that, apart from slightly more males in the ipilimumab arm, the baseline characteristics are broadly similar between the two treatment arms in CheckMate 238.

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Table 9: Baseline Characteristics Summary on Subgroup of Subjects with PD-L1 >=5% (CRF) All Randomized Subjects

	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Median age (range):	[redacted]	[redacted]
Disease stage, n (%):		
IIIB	[redacted]	[redacted]
IIIC	[redacted]	[redacted]
IV	[redacted]	[redacted]
Other or NR	[redacted]	[redacted]
Type of lymph node involvement in Stage III, n (%):		
Microscopic	[redacted]	[redacted]
Macroscopic	[redacted]	[redacted]
NR	[redacted]	[redacted]
Tumour ulceration in Stage III, n (%):		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
NR	[redacted]	[redacted]
Metastasis in Stage IV, n (%):		
M1a	[redacted]	[redacted]
M1b	[redacted]	[redacted]
M1c with brain metastases	[redacted]	[redacted]
M1c without brain metastases	[redacted]	[redacted]
BRAF status, n (%):		
Mutation	[redacted]	[redacted]
No mutation	[redacted]	[redacted]
NR	[redacted]	[redacted]

Key: NR, not reported; PD-L1, programmed death receptor ligand-1.
Source: Weber *et al.*, 2017[2]; CheckMate 238 CSR[7]

c. the subgroup of people PD-L1 status < 5% or indeterminate in CheckMate 238.

The baseline characteristics for the subgroup of patients with PD-L1 status <5% in CheckMate 238 the nivolumab and ipilimumab arms are presented in Table 10. The table

shows that the baseline characteristics are broadly similar between the two treatment arms in CheckMate 238.

Table 10: Baseline Characteristics Summary on Subgroup of Subjects with PD-L1 <5% (CRF) All Randomized Subjects

	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Median age (range):	[redacted]	[redacted]
Disease stage, n (%):		
IIIB	[redacted]	[redacted]
IIIC	[redacted]	[redacted]
IV	[redacted]	[redacted]
Other or NR	[redacted]	[redacted]
Type of lymph node involvement in Stage III, n (%):		
Microscopic	[redacted]	[redacted]
Macroscopic	[redacted]	[redacted]
NR	[redacted]	[redacted]
Tumour ulceration in Stage III, n (%):		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
NR	[redacted]	[redacted]
Metastasis in Stage IV, n (%):		
M1a	[redacted]	[redacted]
M1b	[redacted]	[redacted]
M1c with brain metastases	[redacted]	[redacted]
M1c without brain metastases	[redacted]	[redacted]
BRAF status, n (%):		
Mutation	[redacted]	[redacted]
No mutation	[redacted]	[redacted]
NR	[redacted]	[redacted]

Key: NR, not reported; PD-L1, programmed death receptor ligand-1.
Source: Weber *et al.*, 2017[2]; CheckMate 238 CSR[7]

A6. **Priority question:** Please provide the absolute number of events and patients at risk, using data from the updated database lock of 19 December 2017 (24 month follow-up) for CheckMate 238 (or the latest available data) and the data from CA184-029 for the following outcomes:

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a. adverse events outcomes reported in the economic model;

b. adverse events outcomes reported in the economic model using the censoring of adverse of events data at 30 days after last treatment dose (rather than 70 days in CA184-029) for both CheckMate 238 and CA184-029;

c. adverse events outcomes reported in the economic model for CheckMate 238 and the subgroup of people in CA184-029 who received up to one year treatment of ipilimumab;

d. adverse events outcomes reported in the economic model for CheckMate 238 and the subgroup of people in CA184-029 who received up to one year treatment of ipilimumab with censoring of adverse events at 30 days after last treatment dose.

Please note, that the safety data was not updated in the 24 month datacut. Therefore, Table 11 below presents the adverse events (AEs) reported in the economic model using the CheckMate 238 (18 month follow-up data) and CA184-029. The AEs considered within the model are: immune-related (any grade), diarrhoea (Grade ≥2) and any other Grade ≥3 AE. Immune-related AEs taken from the trials were based on the PLD using the 'Body system' category and were defined as 'Immune system disorders'; diarrhoea incidence was based on the 'dictionary-derived term' excluding any already captured within the immune-related category.

The CheckMate 238 AEs were also reported based on censoring of AEs data at 30 days or 100 days after last treatment dose as opposed to the CA184-029 AEs reported based on censoring of AEs at 70 days after last treatment dose. CA184-029 AEs censoring at 30 days were calculated using the date of last dose received and start date of AE are presented in the table Table 11.

The AEs for the subgroup of patients who received up to one year of ipilimumab treatment in CA184-029 are also presented in Table 11.

Table 11: Adverse events from CheckMate 238 (18-month data) and CA184-029

	CheckMate 238 – 18-month data						CA184-029 (ITT)						CA184-029 (subgroup of patients up to 1-year ipilimumab treatment)		
	Nivolumab			Ipilimumab			Ipilimumab			Placebo			Ipilimumab		
Cut off after last treatment dose (days)	**All**	**30**	**100**	**All**	**30**	**100**	**All**	**30**	**70**	**All**	**30**	**70**	**All**	**30**	**70**
Total patients in analysis															
Immune-related disorders (any grade)															
Number of events															
Number of patients															
Number of patients hospitalised															
Hospital events															
Diarrhoea (Grade ≥2)															
Number of events															
Number of patients															
Number of patients hospitalised															
Hospital events															
Other adverse events (Grade ≥3)															
Number of events															
Number of patients															
Number of patients hospitalised															
Hospital events															

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A7. **Priority question:** Please provide the rationale for assuming that the relationship between RFS and OS are the same across different drug classes in the calculation of OS for nivolumab using the 'surrogacy relationship equation'.

In terms of the methodological steps followed, surrogacy is assessed in two steps; the patient-level and the trial-level associations. The patient-level association is given by the correlation between results for the surrogate and the true endpoint for individual patients and in this case indicates whether patients with prolonged RFS are also more likely to experience prolonged OS. The trial-level association is given by the correlation between treatment effects (i.e., hazard ratios [HRs]) on RFS and OS; this is the more relevant condition for surrogate validation. The accumulated experience so far suggests that patient-level association is nearly universally present, whereas the trial-level association is a much stricter condition and often absent.[8] The trial-level association may indeed vary across treatment classes and possibly across treatment settings, such as adjuvant versus palliative therapy or first versus subsequent lines. As a result, work is ongoing to assess the validity of RFS as a surrogate for OS also with immune checkpoint inhibitors. Such assessment requires several randomized trials with mature RFS and OS results, something unavailable at present.

The trial-level association between RFS and OS has been proven in the interferon era.[9] Interferon is a cytokine that induces immunomodulatory effects on host immune cells.[10] Immune checkpoint inhibitors "release the brake on the immune system" and promote antitumor immune mechanisms.[11, 12] Therefore, interferon and immune checkpoint inhibitors act via immune mechanisms. Given the paucity of data on adjuvant immune checkpoint inhibitors, thus precluding a formal pooling of trials for surrogacy assessment, an exercise was made using a single trial of adjuvant ipilimumab, the only one with mature results so far.[1] In this exercise, it was possible to derive a regression equation and to estimate the trial-level association between RFS and OS using geographic subunits of that trial (Coart et al., in preparation for publication).[13] The results showed a regression equation very similar to the one obtained in the meta-analysis of interferon.[9]

Therefore, the limited data available suggest that the trial-level correlation between RFS and OS observed with interferon-based adjuvant therapy can be used as a platform to conduct exploratory analyses of surrogacy in adjuvant trials with immune checkpoint inhibitors. In one such exercise, an attempt was made to forecast OS results for adjuvant nivolumab based on observed RFS results using the previous correlation between RFS and OS with interferon-based therapy .[13] The full details of this exercise are available as a supplement. In summary, the results have suggested that the future analysis of CheckMate 238 will [redacted] because the HR for OS thus forecasted had its 95% confidence interval [redacted]. BMS attach the report containing the analyses conducted updating the already published and well established surrogacy relationship for RFS to OS (Coart et al 2018).

A8. **Priority question:** Please provide further details on the origin of the 'surrogacy relationship equation' used to calculate the OS of nivolumab and details of the trials included in the calculation used in the economic base case to supplement the information provided in the Company Submission Document B pages 118 to 124.

Surrogacy relationship equation is used to estimate the hazard ratio for overall survival on the basis of the hazard ratio for relapse-free survival. This equation was estimated by Coart et al. (2018). Further details are provided in the confidential study report.[13]

As mentioned in the response to question A7, an exercise was made to forecast the OS results for nivolumab based on the observed RFS results for this agent and on the basis of a regression equation obtained from the same trials used in the interferon-era meta-analysis.[9] Initial RFS results for the nivolumab trial have been published (Weber et al., 2017)[2] and have been recently updated to include a minimum follow-up of 2 years.[14]

The exercise consisted in first deriving a new regression equation based on published (aggregate) data for the interferon trials, given that individual-patient data were not available. This new regression equation was very similar to the one derived by Suciu et al., thus allowing the next step in the exercise. For this next step, the updated HR for RFS (0.66) from the nivolumab trial was plotted on the X axis of the graph with the linear regression for the association between RFS and OS. That point on the X axis defines the origin of a vertical line that meets the regression line, and from this meeting point a horizontal line indicates on the Y axis the expected HR for OS from the use of nivolumab, assuming a stable relationship between RFS and OS as explained in the response to A7. [redacted]. [13]

A9. **Priority question:** Please provide mean, with accompanying 95% confidence interval, OS for nivolumab and ipilimumab at 12, 18 and 24 months of follow-up, together with the number of events and number of people at risk at each time point in the individual groups for CheckMate 238 and the equivalent data for ipilimumab and placebo in CA 184-029.

BMS is not able to address the ERG's request relating to the generation of effect estimates for overall survival using patient level data (PLD) from Checkmate 238 [redacted]

Staging

A10. Reclassifying patients using the Version 8 AJCC definitions of stage III and IV melanoma, please carry out the ITCs, both PLD meta-regression and Bucher methods, incorporating data from the updated database lock of 19 December 2017

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for CheckMate 238 (or the latest available data) and the data from CA 184-029 for the RFS for the following subgroups:

a. Stage IIIa;

b. Stage IIIb;

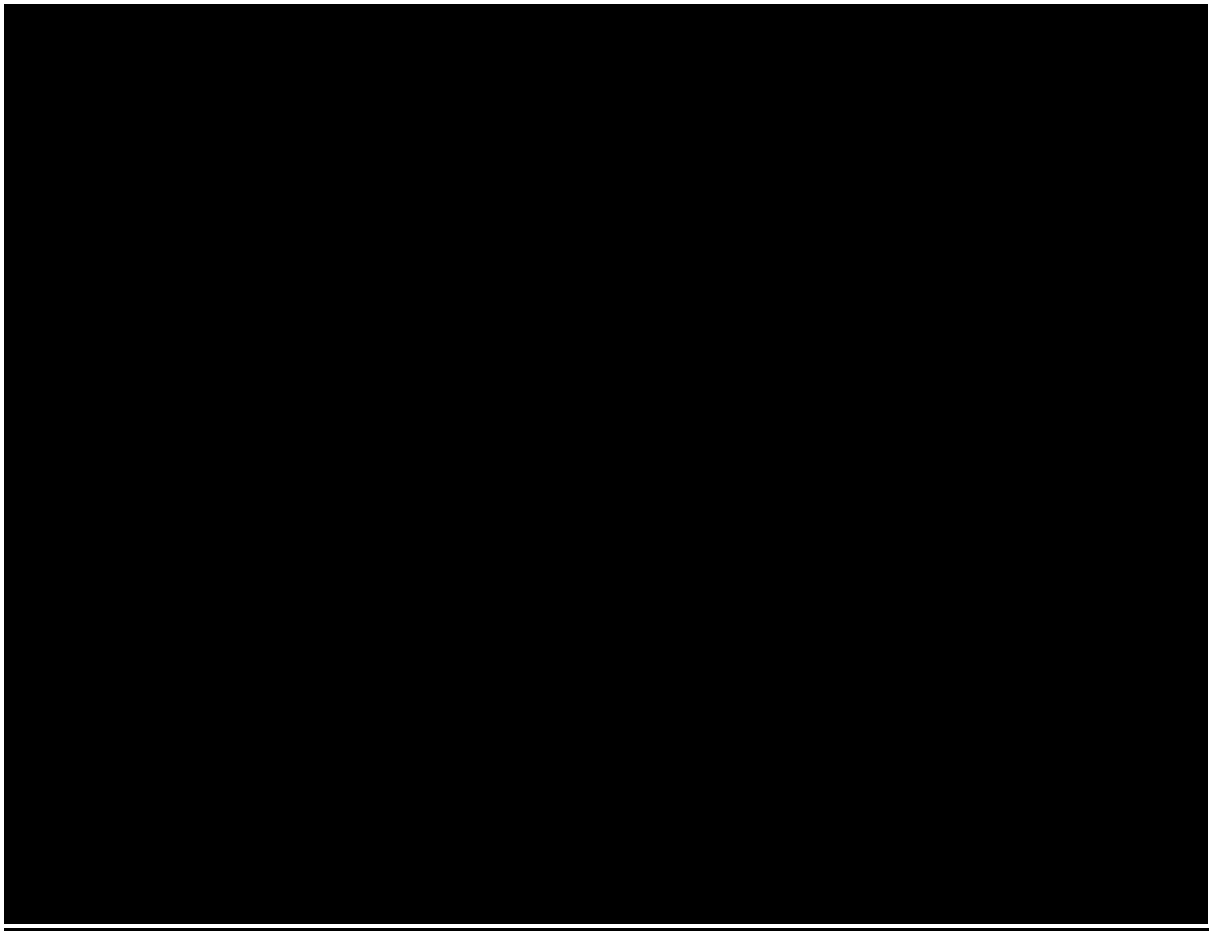
c. Stage IIIc.

The clinical data collected for CA209-238 is insufficient to restage all patients under AJCC 8th edition. Additionally, it is not possible to restage CA184-029 study patients (randomization performed according to AJCC 2002 classification) using AJCC 8th edition since it a study which was originally sponsored by the EORTC. Therefore, it is not possible to conduct the updated ITC analyses requested by the ERG in response to question A10.

CheckMate 238 patients were classified based on AJCC 7th edition which followed clinical practice at the time of RCT initiation, while the AJCC 8th edition was implemented starting January 1st 2018. With regards to reclassification using AJCC v8 edition, a subset of Checkmate 238 patients with non-ulcerated, micrometastatic disease who were defined as Stage IIIb (as per AJCC v7th edition) would now be considered Stage IIIa as per AJCC v8th edition (for schematic refer to Submission Appendix Figure 32).

BMS present a number of pre-defined subgroup analyses to address the change in AJCC staging. For patients with nonulcerated, micrometastatic disease (n=[redacted]), nivolumab had an HR of [redacted] vs. ipilimumab (see Figure 20). Many of these patients would have been considered Stage IIIb solely based on a mitotic rate ≥1/mm2, and in the AJCC 8th edition staging would be IIIa as mitotic rate is no longer a T staging criteria. However, among these patients, those who met with the criteria of 4 or more metastatic nodes or matted nodes would be excluded from the [redacted] patients as such patients would now considered stage IIIc/IIId.

Figure 20: Forest plot of Treatment on updated RFS in pre-defined subsets – all randomised subjects



Patients with non-ulcerated, micrometastatic disease who were defined as Stage IIIb subjects per AJCC 7th edition would be considered Stage IIIa subjects per AJCC 8th edition. For these subjects (N=[redacted]), the HR of nivolumab over ipilimumab was [redacted] based on June 2017 database lock with a minimum follow-up of 18 months. With a minimum follow-up of 24 months, one more subject in the ipilimumab group had an event and the HR of nivolumab over ipilimumab was [redacted] However, it should be noted that the subset of nivolumab patients with Stage IIIa disease was small (N=26) which is reflective of the wide 95% CIs.

The totality of the efficacy and safety data support the use of nivolumab monotherapy as adjuvant treatment in patients with completely resected Stage III and IV melanoma. It should also be noted that the change in classification system does not affect disease stage, therefore, patients present with lymph node involvement will still be classified with Stage III disease regardless of whether patients are classified using the 7th or 8th AJCC version.

Data presented within the submission are in line with the expected marketing authorisation *"OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection".* Therefore, the patient population defined by lymph node involvement and metastatic disease accurately reflects the patient population in study CA209-238 and will

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mitigate any confusion arising from the change in staging criteria between the AJCC 7th and 8th edition. BMS ask that evidence should be viewed in its totality regardless of disease substage to adequately inform the decision problem meeting in line with the anticipated marketing authorisation.

A11. Please provide the baseline characteristics for CheckMate 238 and CA184-029 for the subgroup analyses requested in Question A10.

As explained in our response to question A10 above, it is not possible to restage all patients from Checkmate 238 based on information collected in the trial. Therefore, BMS are not able to address question A11 as requested by the ERG.

A12. Please provide mean RFS and accompanying 95% confidence intervals for nivolumab and ipilimumab at 12, 18 and 24 months of follow-up for CheckMate 238 and the equivalent data for ipilimumab and placebo in CA184-029.

The restricted mean RFS and corresponding 95% confidence intervals are presented in Table 12 for the specified time points. CA184-029 analysis is based on ITT population with patients able to receive a maximum of 3 years ipilimumab treatment. It should be noted that due to the immaturity of the RFS data in CheckMate 238 a restricted mean analysis does not provide an accurate estimate compared to the true mean RFS over the life time horizon.

Table 12: Mean RFS for CheckMate 238 (24-month data) and CA184-029

Follow-up	CheckMate 238 RFS mean (95% CI) - months		CA184-029 RFS mean (95% CI) - months	
	Nivolumab	Ipilimumab	Ipilimumab	Placebo
0-12 months	[redacted]	[redacted]	[redacted]	[redacted]
0-18 months	[redacted]	[redacted]	[redacted]	[redacted]
0-24 months	[redacted]	[redacted]	[redacted]	[redacted]
Key: CI, confidence interval; RFS, recurrence-free survival				

A13. Please provide results for RFS at 12, 18 and 24 months of follow-up for the subgroup analysis based on geographic location (North America versus Western Europe versus Eastern Europe versus Asia versus Australia) for CheckMate 238.

Table 13 presents RFS for CheckMate 238 by geographic location. The results appear to be reasonably consistent across different geographic locations and treatment groups; RFS is observed to be slightly worse for both treatments in the Asian subgroup. However, it should be noted that the patient numbers are small therefore results should be interpreted with caution. Any further statistical analysis to detect differences between treatments would be underpowered and have therefore not been performed.

Table 13: Recurrence-free survival CheckMate 238 by geographic location

	Nivolumab Survival Rate (95% CI)	Ipilimumab Survival Rate (95% CI)
Population ITT		
6-Month		
12-Month		
18-Month		
24-Month		
30-Month		
North America		
6-Month		
12-Month		
18-Month		
24-Month		
Western Europe		
6-Month		
12-Month		
18-Month		
24-Month		
Eastern Europe		
6-Month		
12-Month		
18-Month		
24-Month		
Asia		
6-Month		
12-Month		
18-Month		
24-Month		
Australia		
6-Month		
12-Month		
18-Month		
24-Month		

Key: CI, confidence interval; ITT, intension-to-treat; N, number of patients;

A14. Please clarify if individual cases of recurrence of melanoma were assessed by an independent reviewer in CheckMate 238 in addition to the investigator assessment primary analysis. If so, please provide results for analyses of RFS at 12, 18 and 24 months of follow-up based on independent review.

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As per response to question A4a, Checkmate 238 was an active controlled trial. Since recurrence (unless local) has a significant clinical implications it was considered that an independent Review Committee (IRC) was not required for this study. Therefore, only investigator for based assessment of RFS is available in this study, which is clinically more relevant and better reflects real world practice.

Safety data

A15. Please provide trial level relative risks (RRs) and 95% confidence intervals for the safety data from CheckMate 238 and CA184-029 for the adverse events included in the economic model.

The relative risks and 95% confidence intervals for the AEs included in the economic model are presented in Table 14.

Table 14: Trial level safety data relative risks

	Immune-related (Any grade)	Diarrhoea (grade ≥2)	Other AEs (grade ≥3)
CheckMate 238 (18-month data)			
Nivolumab	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]	[redacted]	[redacted]
CheckMate 238 (24-month data)			
Nivolumab	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]	[redacted]	[redacted]
CA184-029			
Ipilimumab	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]	[redacted]	[redacted]
Key: AEs, adverse events; RR, relative risk			

Study population

A16. Please clarify how many people in the nivolumab and ipilimumab groups in CheckMate 238 were recruited from sites in the UK.

Overall [redacted] patients were enrolled into the trial from the UK, of which [redacted] met the study inclusion criteria and were subsequently randomised to receive nivolumab (n=[redacted]), and ipilimumab (n=[redacted]).

Subsequent therapies

A17. Please provide the absolute numbers of patients and patients at risk, using data from the updated database lock of 19 December 2017 (24 months follow-up) for

CheckMate 238 (or the latest available data) and the data from CA184-029 for the subsequent therapies received split by line of therapy (i.e. 1L, 2L, 3L+).

BMS are not able to provide an updated analysis using the 24 month dataset within the time allotted for response. However, during the clarification TC the ERG clarified that further information around the subsequent treatments presented in Tables 17 and 48 of the main submission reporting subsequent treatments categorised by treatment line (1L, 2L+) would provide sufficient additional clarity to address this request.

BMS clarify that Table 17 of the HTA submission includes information on treatment summaries made available to the EMA based on 24 month dataset. Given the level of assumptions required for this analysis, the 24 month dataset not currently available for analyses within the time frame because of complexity of how subsequent treatment data were stored and coded and hence considerable more time (compared to other trial data such as RFS) is required to clean and organise subsequent treatment data in the format required by the ERG..

Due to the limitations outlined above regarding the 24 month dataset, BMS have reproduced the analyses using the 18 month dataset which is available for further processing, to provide patient numbers, records of subsequent treatments and exposure categorized by 1L and 2L+ which matches the approach used within the economic model for CA184-029 and CheckMate 238 (Table 15 and Table 16, respectively).

Given the immaturity of subsequent treatment data from CheckMate 238 and considering the information collected, re-categorisation including 3L+ is not possible and would result in information which is increasingly granular and misleading in particular around treatment sequencing. Additionally due to the complexity of the collection of subsequent treatments in CA184-029 it is not possible to perform this analysis within the time frame. In clinical practice, most treatments in the metastatic setting are given with an indication in first-line or in second line, followed by palliative care in third line as patients may not be fit for subsequent active treatment at that stage. Therefore the breakdown of treatments split by first-line and second-line plus should be sufficient to see the patterns within the trials.

A number of criteria listed below were used to analyse the data in the 18month follow up dataset and generate model inputs for 1L and 2L+ subsequent treatments used in the model (please refer to company submission Section B.3.5 page 159.

Post recurrence

- To determine whether a record was post recurrence, the start date of subsequent therapy was used.

Missing start date

- Records with missing subsequent treatment (5 records in total) start date were excluded as it was not possible to determine whether the treatment started post recurrence.

Duplicates

- Duplicate records were removed – duplicates were identified by matching patient ID, treatment, treatment start date and treatment end date. Where a record matched

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patient ID, treatment and treatment start date, the record with missing end date or earliest end date were excluded.

Imputing end dates

- For the remaining records with missing end dates an end date was imputed. Note that it was not always a patient's last record that had missing end date.
    - For records where the next subsequent treatment is known to be used within combination with the treatment (D+T, Nivo+Ipi or Vem+Cob), if the records started within 14 days of each other the treatments were assumed to be used in combination (14 days is the cycle length for nivo and is the shortest cycle length of considered treatments).
        - It was assumed that if one of these records had an end date that would be used for the combination end date. E.g. if dabrafenib had a missing end date and trametinib ended 15th Jan 2017 both records will be assumed to end 15th Jan 2017 (this would then be considered a combination therapy as the end dates for the two records match [see next section]).
        - Where this was not possible the record was assumed to end on the day prior to when the patient starts their next subsequent therapy after that.
    - Where the next subsequent treatment is not known to be used within combination or the second part of the combination was received after 14 days, the record was assumed to end on the day prior to the receipt of the next subsequent therapy. E.g. if nivolumab started 10th July 2016 and had a missing end date and ipilimumab started 20th September 2016 and ended 13th Feb 2017. The ipilimumab record would remain unchanged and the nivolumab record would be assumed to end 19th September 2016.
    - If the treatment was the last subsequent therapy received and the end date was missing the patient is assumed to have received treatment until the last known date they were alive.

Combination therapies and overlapping records

- As data were typically recorded one treatment per record (there are one or two records which contain multiple treatments) combination therapies were identified for records which had matching start or end date (other records that overlapped were not considered as combination therapies).
    - 3Combination therapies could include any combination of treatments (not just D+T, Nivo+Ipi or Vem+Cob), however overlapping records of the same treatment were considered separately.
    - If records on the same treatment overlapped, the start time of the earlier record was adjusted to end on the day before the next record. If the record with the earlier start date ended later than the next record. The end date of the second record was adjusted to match that end date. This gives two records which don't overlap regardless of whether the first record completely overlaps the second.

Table 15: Subsequent treatments split by line – CA184-029

Treatment	10 MG/KG IPILIMUMAB				PLACEBO			
	1L		2L+		1L		2L+	
	Patients	Records	Patients	Records	Patients	Records	Patients	Records
Cisplatin								
Dabrafenib								
Dabrafenib + trametinib								
Dacarbazine (DETICENE)								
Interferon								
Interleukin								
Ipilimumab								
Ipilimumab plus nivolumab								
Nivolumab								
Other								
Other palliative chemotherapy								
Paclitaxel (Taxol)								
Pembrolizumab								
TEMOZOLOMIDE (Temodal)								
Talimogene laherparepvec								
Unassigned								
Vemurafenib								
Vemurafenib plus cobimetinib								
Total								

Key: 1L, first-line; 2L+, second-line plus

Notes: *Includes high-dose, low-dose, PEGylated and unspecified interferon. **Includes encorafenib, fotemustine, carboplatin, cobimetinib, cysplatine, lomustine and rituximab

Table 16: Subsequent treatments split by line – CheckMate 238 (18-month cut off)

Treatment	Ipilimumab 10 mg/kg				Nivolumab 3 mg/kg			
	1L		2L+		1L		2L+	
	Patients	Records	Patients	Records	Patients	Records	Patients	Records
Cisplatin								
Cobimetinib+vemurafenib								
Dabrafenib								
Dabrafenib+trametinib								
Dacarbazine								
Interleukin 2								
Ipilimumab								
Ipilimumab+nivolumab								
Interferon								

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Treatment	Ipilimumab 10 mg/kg				Nivolumab 3 mg/kg			
	1L		2L+		1L		2L+	
	Patients	Records	Patients	Records	Patients	Records	Patients	Records
Nivolumab	[redacted]							
Other palliative Chemotherapy								
Other/unassigned								
Paclitaxel								
Pembrolizumab								
Talimogene laherparepvec								
Temozolomide								
Vemurafenib								
Total								

Key: 1L, first-line; 2L+, second-line plus
Notes: *Includes alpha 2B and beta.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please add the parametric curves derived from the meta-regression analyses in clarification questions A1, A2, A4 and A10 as options in the economic model.

A1 request: RFS ITC meta-regression – using 24-month data for CheckMate 238

The parametric curves derived from the patient level data (PLD) meta-regression ITC using the CheckMate 238 24 months follow up (December data base lock) have been added to the model (Columns LJ-MA in "Curve parameters" sheet) and can be selected as an option (cell E214 in "Controls" sheet).

In addition to the parametric curves, patient characteristics used within corrected group prognosis (CGP) have been updated in the model using the 24-month data (Cells W11:X26 in "CGP" sheet). Please note, one patient who was classified as Stage IIIC in the 18-month data cut is now classified as Stage IIIB and another patient who was not reported is now classified as Stage IIIB. The differences in base line characteristics between the 18-month data and 24-month data are presented in Table 17.

Table 17: Baseline differences between 18-month and 24-month data sets

	18- month data cut		24-month data cut	
	Nivolumab (n=453)	Ipilimumab (n=453)	Nivolumab	Ipilimumab
Stage IIIB	163	148	[redacted]	
Stage IIIC	204	218		
Unknown Stage	2	0		
Ulceration present	153	135		
Lymph node involvement: microscopic	125	134		

RFS KM data from the 24-month cut off in CheckMate 238 is used for the nivolumab arm for the first 12 weeks. Figure 21 shows the final curves using the log logistic distribution and estimated survival of our matched population of interest (i.e. Stage IIIA – Stage IV NED) using the CGP method and Table 18 presents the model results when using the 24-month data from CheckMate 238 in the RFS ITC PLD meta-regression.

Figure 21: ITC RFS final curve using matched population

Key: IPD, individual patient data; ITC, indirect treatment comparison; RFS, recurrence-free survival

Table 18: Model cost-effectiveness results using the ITC from CheckMate 238 24-month data cut

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.96	[redacted]	[redacted]	[redacted]	[redacted]	£8,882
Key: LYG, life year gain; QALYs, quality adjusted life-years							

A2 request: OS ITC using 24-month data for CheckMate 238

As discussed in response to question A2, [redacted]

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[redacted] the parametric curves for inclusion in the economic model as requested by the ERG.

Therefore, the [redacted] for has not been included within the economic model, instead, scenarios have been implemented [redacted] and standard Bucher method presented in A2.

- The CheckMate 238 [redacted]
- Using a standard Bucher method with CA184-029 gives a [redacted]

A series of scenarios have been included in the model using the analysis in order to estimate the impact on the ICER. Results of these scenarios are presented in

[redacted]

Scenario	Description	ICER (with PAS)
Current base case	PSM – RFS using PLD meta-regression. [redacted]	£8,769

Scenario	Description	ICER (with PAS)
Keeping routine surveillance OS projections and new [redacted]	PSM – RFS using PLD meta-regression. [redacted]	£13,629
Keeping nivolumab [redacted]	PSM – RFS using PLD meta-regression. [redacted]	£14,805
Matching nivolumab OS [redacted] month data) and new Bucher HR for placebo versus nivolumab	PSM – RFS using PLD meta-regression. [redacted]	£18,483
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; [redacted]; PAS, patient access scheme; PLD, patient-level data; PSM, partitioned survival model; RFS, recurrence-free survival.		

These scenarios explore possible model results [redacted] from CheckMate 238. The analyses assumes that the [redacted] Given the immature OS data from CheckMate 238 and consequently highly uncertain HR for nivolumab versus ipilimumab based on CheckMate 238, results of these scenarios should be taken with caution:

[redacted]

- The CheckMate [redacted] With longer follow up we would [redacted] to ipilimumab in other settings. For example, evidence from CheckMate 067 suggests that nivolumab has a greater OS benefit compared to ipilimumab with an HR_{PFS} of 0.55 translating to an HR_{OS} of 0.63, noting that patients in the trial went on to receive further treatments upon progression including retreatment with immunotherapies.[15] This shows that early treatment with nivolumab is likely to provide greater benefit in OS compared to ipilimumab. These data also show that the difference between OS of nivolumab and ipilimumab increases over time with no difference for the first 5 months; after 12 months, the difference between nivolumab and ipilimumab OS is approximately 10%, whereas at 36 months the difference has increased to 18%.[15]

Due to the early stage of the disease and benefits of treatment upon recurrence, the OS data in the CheckMate 238 trial are likely to take a long time to mature as was observed in CA184-029 study. However, [redacted] there is strong evidence from

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CA184-029 that ipilimumab adjuvant therapy has an OS benefit over no treatment and the ICER remains significantly below £30,000 threshold making this an extremely cost-effective intervention in the NHS.

A4 request:

RFS ITC meta-regression 24-month data (using independent review data):

As discussed in response to A4a, independent review data for CheckMate 238 is not available and therefore this analysis has not been included within the economic model.

RFS ITC meta-regression 24-month data (and subgroup of patients who received up to 1 year of ipilimumab in CA184-029)

As discussed in response to question A4b the patients who received more than one year of ipilimumab treatment in CA184-029 have been censored at 1-year for this analysis. The parametric curves derived from the PLD meta-regression using the 24 months follow up (December data base lock) have been added to the model (Columns MC-MT in “Curve parameters” sheet) and can be selected as an option (cell E214 in “Controls” sheet).

Figure 22 shows the final curves using the log logistic distribution and estimated survival of our matched population of interest (i.e. Stage IIIA – Stage IV NED) using the CGP method and Table 20 presents the model results when using the 24-month data from CheckMate 238 in the RFS ITC PLD meta-regression. ICER remains below the £10,000 threshold despite the biased analysis against ipilimumab.

Figure 22: ITC RFS final curve using matched population (censored 029 ipilimumab patients who had more than 1 -year treatment)

Key: IPD, individual patient data; ITC, indirect treatment comparison; RFS, recurrence-free survival

Table 20: Model cost-effectiveness results using the ITC from 24-month data cut (censored 029 ipilimumab patients who had more than 1 -year treatment)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.68	[redacted]	[redacted]	[redacted]	[redacted]	£9,066
Key: LYG, life year gain; QALYs, quality adjusted life-years							

RFS ITC meta-regression 24-month data (subgroup PD-L1 ≥5%)

As discussed in response to question A4 c. considering the PD-L1 subgroup of patients in Checkmate 238 separately is not appropriate due to a number of limitations relating to PD-L1 testing and data availability which are discussed extensively in the response to A4c above. The ERG's request on generating parametric survival curves based on PD-L1 status deviates from the decision problem itself and the anticipated marketing authorisation for adjuvant melanoma. Additionally, comparing PD-L1 subgroup from CheckMate 238 with the ITT population in CA184-029 is not an appropriate or fair analysis. Therefore, this analysis has not been included within the submission.

RFS ITC meta-regression 24-month data (subgroup PD-L1 <5% or indeterminate)

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As discussed in response to question A4 d. considering the PD-L1 subgroup of patients in Checkmate 238 separately is not appropriate due to a number of limitations already discussed. Therefore, this analysis has not been included within the submission.

A10 request: RFS ITC meta-regression 24-month data (Reclassifying patients to AJCC v8 definitions of Stage III and IV)

As discussed in response to question A10, the clinical data collected for CA209-238 is insufficient to restage all patients under AJCC 8th edition. Additionally, it is not possible to restage CA184-029 study patients (randomization performed according to AJCC 2002 v6 classification) using AJCC v8. Therefore, this request cannot be processed at this stage.

However, it should be noted that the change in classification does not affect the disease stage itself since patients present with lymph node involvement will still be classified with Stage III disease regardless of whether patients classified using the 7th or 8th AJCC version. Data presented within the submission are in line with the expected marketing authorisation *"OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection".* Patient population defined by lymph node involvement and metastatic disease accurately reflects the patient population in study CA209-238 and will mitigate any confusion arising from the change in staging criteria between the AJCC 7th and 8th edition.

B2. **Priority question:** Please adjust the OS models fitted to the CA184-029 and CheckMate 238 trials (latest available data) for subsequent therapies, grouping by class of drug, and incorporate an interaction with the primary treatment group. Please add these to the economic model to allow modelling of alternative subsequent treatment strategies independently for each primary treatment group.

As discussed in response to question [redacted] and therefore this analysis has not been conducted and included in the economic model. An alternative option is included within the economic model labelled 'Markov option 2' (cell J70 in "Controls" sheet) which the user has the flexibility to manually change the proportion of patients who received different types of first-line subsequent treatments after a distant recurrence which will impact the post-recurrence survival and subsequent treatment cost. These can be changed by selecting the subsequent treatment data source to be 'Manual input' (cell J61 in "Controls" sheet) and changing the % input cells in the "Subsequent TX" sheet.

B3. **Priority question:** Please provide spline based models for each of the RFS meta-regression ITCs without rebasing curves at 12 weeks. Please apply at least one knot (placed at 12 weeks) but also consider adding further knots to provide a better fit.

Please also adjust as per clarification question B2 and add these as options in the economic model.

Spline modelling has been explored using the RFS data from CheckMate 238 (24-month data) and CA184-029 without re-basing curves at 12 weeks for the RFS meta-regression as per ERG's request. Spline models were fitted using the "flexsurv" package in the statistical package, R. The approach used is in line with Royston and Palmer (2002)[16] and uses the functional form "Hazard".[17] Default knots are given as a Weibull, log-logistic or log-normal model if the functional form "hazard", "odds" or "normal" is selected, respectively. The knots are then chosen as equally-spaced quantities of the log uncensored survival times, otherwise knot positions can be specified.

RFS ITC meta-regression (24-month data)

A knot was placed at 12 weeks to coincide with the first assessment in the trials and other knot positions were explored; 24 weeks to coincide with the second assessment in the trials (a smaller change in hazard is also observed here), and 48 weeks, as this was the knot suggested by R by default when no knot positions were specified. Two hazard functional forms were also explored; the first assumed proportional hazards between the treatments and the second allows the treatment effects to be independent. Table 21 presents the goodness of fit statistics of the four models considered. The AIC indicate that the treatment independent hazard model with the 2nd knot at 24 weeks fits the data better and therefore this model was incorporated into the economic model (New model sheet "Splines").

Table 21: Spline model selection – RFS ITC (24-month DBL for CheckMate 238)

Spline model	2nd knot position	AIC
Proportional hazard	One knot only	15309.29
Independent treatment	One knot only	15280.14
Proportional hazard	24 weeks	15223.28
Independent treatment	**24 weeks**	**15222.14**
Proportional hazard	48 weeks	15249.36
Independent treatment	48 weeks	15237.41
Key: AIC, Akaike information criterion		

Table 22 presents the coefficients for the spline model using two knots, 12 weeks and 24 weeks and independent treatment hazards.

Table 22: Spline based model coefficients (2 knots, independent hazard) - RFS ITC (24-month DBL for CheckMate 238)

Parameter	Coefficient
gamma0	[redacted]
gamma1	[redacted]
gamma2	[redacted]
gamma3	[redacted]
TRT: PBO	[redacted]
TRT: Nivo	[redacted]
Stage: STAGE IIIA	[redacted]
Stage: STAGE IIIC	[redacted]
Stage: STAGE IV	[redacted]
SEX: F	[redacted]
AGE_cat: >= 65	[redacted]
Trial: 029	[redacted]
gamma1 (TRTPBO)	[redacted]
gamma1 (TRTNivo)	[redacted]

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Parameter	Coefficient
gamma2 (TRTPBO)	[redacted]
gamma2 (TRTNivo)	[redacted]
gamma3 (TRTPBO)	[redacted]
gamma3 (TRTNivo)	[redacted]
Key: F, female; PBO, placebo; TRT, treatment	

Figure 23 and Figure 29 present the spline models fit to the trial data for nivolumab in CheckMate 238 and placebo in CA184-029, respectively. The spline model appears to fit the nivolumab data slightly better than the parametric curve but gives a worse fit for the placebo data. Figure 25 presents the final spline curves once the patient characteristics are used to reflect the modelled population (i.e. Stage IIIA – IV NED).

Figure 23: CheckMate 238 RFS ITC PLD meta-regression spline model (2 knots hazard) - Nivolumab

[redacted]

Key: ITC, indirect treatment comparison; KM, Kaplan-Meier; PLD, patient level data; RFS, recurrence-free survival

Figure 24: CA184-029 RFS ITC PLD meta-regression spline model (2 knots hazard) – Placebo

Key: ITC, indirect treatment comparison; KM, Kaplan-Meier; PBO, placebo; PLD, patient level data; RFS, recurrence-free survival

Figure 25: RFS – ITC PLD meta-regression spline model (2 knots hazard) – Model population

Key: ITC, indirect treatment comparison; PLD, patient level data; RFS, recurrence-free survival

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Table 23 presents the cost-effectiveness results using the spline based models for the RFS curves.

Table 23: Model cost-effectiveness results using the ITC from 24-month data cut spline model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.87	[redacted]	[redacted]	[redacted]	[redacted]	£7,540
Key: LYG, life year gain; QALYs, quality adjusted life-years							

RFS ITC meta-regression 24-month data (and subgroup of patients who received up to 1 year of ipilimumab in CA184-029)

As per the previous spline model analysis, a knot was placed at 12 weeks to coincide with the first assessment in the trials and 24 weeks and 48 weeks knot positions were explored. Two hazard functional forms were also explored; the first assumed proportional hazards between the treatments and the second allows the treatment effects to be independent. Table 21 presents the goodness of fit statistics of the four models considered. The AIC indicate that the treatment independent hazard model with the 2nd knot at 24 weeks fits the data better and therefore this model was incorporated into the economic model.

Table 24: Spline model selection – RFS ITC (24-month DBL for CheckMate 238 and subgroup of patients who received up to 1 year of ipilimumab in CA184-029)

Spline model	2nd knot position	AIC
Proportional hazard	One knot only	**14696.19**
Independent treatment	One knot only	**14666.45**
Proportional hazard	24 weeks	14612.96
Independent treatment	**24 weeks**	**14611.20**
Proportional hazard	48 weeks	14638.25
Independent treatment	48 weeks	14625.89
Key: AIC, Akaike information criterion		

Table 22 presents the coefficients for the spline model using two knots, 12 weeks and 24 weeks and independent treatment hazards.

Table 25: Spline based model coefficients (2 knots, independent hazard) - RFS ITC (24-month DBL for CheckMate 238 and subgroup of patients who received up to 1 year of ipilimumab in CA184-029)

Parameter	Coefficient
gamma0	[redacted]
gamma1	[redacted]
gamma2	[redacted]
gamma3	[redacted]
TRT: PBO	[redacted]
TRT: Nivo	[redacted]
Stage: STAGE IIIA	[redacted]

Stage: STAGE IIIC	[redacted]	
Stage: STAGE IV	[redacted]	
SEX: F	[redacted]	
AGE_cat: >= 65	[redacted]	
Trial: 029	[redacted]	
gamma1 (TRTPBO)	[redacted]	
gamma1 (TRTNivo)	[redacted]	
gamma2 (TRTPBO)	[redacted]	
gamma2 (TRTNivo)	[redacted]	
gamma3 (TRTPBO)	[redacted]	
gamma3 (TRTNivo)	[redacted]	
Key: F, female; PBO, placebo; TRT, treatment		

Figure 23 and Figure 27Figure 29 present the spline models fit to the trial data for nivolumab in CheckMate 238 and placebo in CA184-029, respectively. Figure 28 Figure 25 presents the final spline curves once the patient characteristics reflect the modelled population (i.e. Stage IIIA – IV NED).

Figure 26: CheckMate 238 RFS ITC PLD meta-regression spline model (2 knots hazard) - Nivolumab

[redacted]

Key: ITC, indirect treatment comparison; KM, Kaplan-Meier; PLD, patient level data; RFS, recurrence-free survival

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Figure 27: CA184-029 RFS ITC PLD meta-regression spline model (2 knots hazard) – Placebo

Key: ITC, indirect treatment comparison; KM, Kaplan-Meier; PBO, placebo; PLD, patient level data; RFS, recurrence-free survival

Figure 28: RFS – ITC PLD meta-regression spline model (2 knots hazard) – Model population

Key: ITC, indirect treatment comparison; PLD, patient level data; RFS, recurrence-free survival

Table 23 presents the cost-effectiveness results using the spline based models for the RFS curves. Nivolumab remains highly cost-effective versus BCS using spline models.

Table 26: Model cost-effectiveness results using the ITC from 24-month data cut spline model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.87	[redacted]	[redacted]	[redacted]	[redacted]	£7,801
Key: LYG, life year gain; QALYs, quality adjusted life-years							

B4. **Priority question:** Please add the Kaplan-Meier data for both RFS and OS from the updated database lock of 19 December 2017 (24 months follow-up) (or the latest available data) for CheckMate 238.

The 24-month RFS KM data from CheckMate 238 presented in HTA submission has been added to the economic model (Figure 29).

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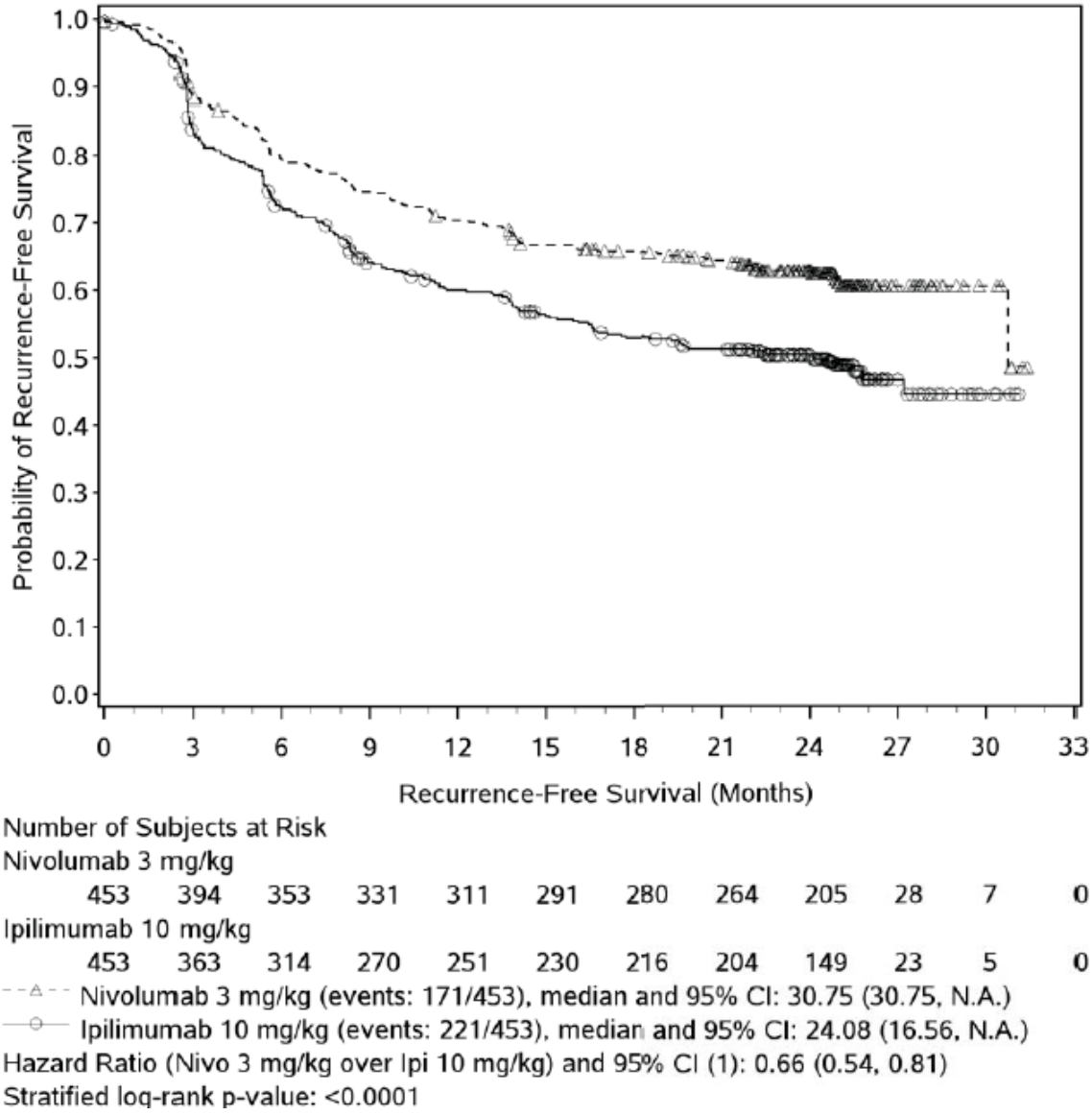
Figure 29: RFS KM CheckMate 238 – 24 month data



B5. Please provide a scenario analysis using the results of clarification question B8.

Due to this analysis being unavailable (see response to B8.) this scenario has not been added to the economic model.

B6. Please apply a different approach for nivolumab treatment costs, as the one off cost applied in the first model cycle prevents discounting from being applied.

Nivolumab treatment cost is currently applied as one-off cost in cycle 0 where the treatment duration is for a maximum of 1 year. Applying the treatment cost per cycle (28 days) would not change the results of the economic model as the discounting is currently applied to

integer years by rounding down the exact year in the model (e.g. 0.75 year in model is rounded to year 0 for discounting purposes) and therefore no discount of costs/efficacy is applied in the first year.

In order to test the impact of applying discounting to the exact model time for the nivolumab treatment cost a scenario has been added to the model which applies the treatment and administration cost of nivolumab per 28-day cycle and the discounting is applied using the exact year per cycle (i.e. no rounding). This change in discounting application also changes the other discounted costs and benefits accumulated over the time-horizon therefore impacting the ICER before the nivolumab treatment cost scenario is applied; by changing the discounting approach to exact year the ICER increases from £8,769 per QALY in the current base case to £8,970 per QALY.

Table 27 presents the results of applying the treatment costs per cycle with discounting applied using exact year per cycle. In cycle 0 all patients receive treatment, in cycle 1 the cost of treatment applied in the model applies to the patients who had the 2nd and 3rd dose of treatment (due to model cycle length being 4 weeks and nivolumab treatment cycle length being 2 weeks). Similarly, for the other cycles up to cycle 13, the cost of treatment includes the number of patients who received the previous two doses of nivolumab based on observed trial data (See Section B3.3 Table 28 in company submission).

Table 27: Model cost-effectiveness results- treatment cost scenario

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.87	[redacted]	[redacted]	[redacted]	[redacted]	£8,791
Key: LYG, life year gain; QALYs, quality adjusted life-years							

B7. Please provide the utility regression model coefficients and p-values for each step of the variable selection procedure.

Table 28 presents the model coefficients and respective p-values for each step in the forward selection for the observed utility data. This corresponds to the following models:

- Null Model: Intercept + Baseline utility
- Step 1: Intercept + Baseline utility + Recurrence
- Step 2: Intercept + Baseline utility + Recurrence + Disease stage
- Step 3: Intercept + Baseline utility + Recurrence + Disease stage + Treatment
- Step 4 (final model): Intercept + Baseline utility + Recurrence + Disease stage + Treatment +interaction (Recurrence and Treatment)

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Table 28: Model coefficients and p-values from the forward selection– observed model

Coefficient	Null model		Step 1		Step 2		Step 3		Step 4 (final)	
	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value
Intercept	0.368	<0.001	0.378	<0.001	0.393	<0.001	0.400	<0.001	0.403	<0.001
Baseline utility	0.549	<0.001	0.548	<0.001	0.547	<0.001	0.547	<0.001	0.547	<0.001
Recurrence: post-recurrence (ref: pre-recurrence)	NA	NA	-0.063	<0.001	-0.062	<0.001	-0.061	<0.001	-0.089	<0.001
Disease Stage: IIIc (ref: IIIb)	NA	NA	NA	NA	-0.019	0.034	-0.019	0.038	-0.019	0.036
Disease Stage: IV (ref: IIIb)	NA	NA	NA	NA	-0.030	0.011	-0.029	0.012	-0.030	0.010
Treatment: Ipi (ref: Nivo)	NA	NA	NA	NA	NA	NA	-0.014	0.076	-0.021	0.009
Interaction: post-recurrence*Ipi	NA	NA	NA	NA	NA	NA	NA	NA	0.049	0.000
Key: Ipi, ipilimumab 10 mg; Nivo, nivolumab.										

Table 29 presents the model coefficients and respective p-values for each step in the forward selection for the mapped utility data. This corresponds to the following models:

- Null Model: Intercept + Baseline utility
- Step 1: Intercept + Baseline utility + Recurrence
- Step 2: Intercept + Baseline utility + Recurrence + Treatment
- Step 3: Intercept + Baseline utility + Recurrence + Treatment + Interaction (Recurrence and Treatment)
- Step 4: Intercept + Baseline utility + Recurrence + Treatment + Interaction (Recurrence and Treatment) + Trial
- Step 5: Intercept + Baseline utility + Recurrence + Disease stage + Treatment + Interaction (Recurrence and Treatment) + Trial + Sex

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Table 29: Model coefficients and p-values from the forward selection– observed model

Coefficient	Null model		Step 1		Step 2		Step 3		Step 4		Step 5 (final)	
	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value
Intercept	0.289	<0.001	0.297	<0.001	0.300	<0.001	0.301	<0.001	0.325	<0.001	0.322	<0.001
Baseline utility	0.639	<0.001	0.639	<0.001	0.639	<0.001	0.640	<0.001	0.640	<0.001	0.637	<0.001
Recurrence: post-recurrence (ref: pre-recurrence)	NA	NA	-0.052	<0.001	-0.053	<0.001	-0.084	<0.001	-0.084	<0.001	-0.084	<0.001
Treatment: Ipi (ref: Nivo)	NA	NA	NA	NA	-0.015	0.009	-0.020	0.001	-0.033	<0.001	-0.033	<0.001
Treatment: PBO (ref: Nivo)	NA	NA	NA	NA	0.015	0.021	0.014	0.032	-0.009	0.347	-0.009	0.338
Interaction: post-recurrence* Ipi	NA	NA	NA	NA	NA	NA	0.048	<0.001	0.047	<0.001	0.047	<0.001
Interaction: post-recurrence* PBO	NA	NA	NA	NA	NA	NA	0.023	0.024	0.023	0.024	0.023	0.023
Trial: 238 (ref: 029)	NA	NA	NA	NA	NA	NA	NA	NA	-0.023	0.001	-0.023	0.001
Sex: male (ref: female)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.009	0.053

Key: Ipi, ipilimumab 10 mg; Nivo, nivolumab; PBO, placebo.

B8. Assuming the OS benefit of immunotherapies in the adjuvant setting is equivalent to in the metastatic melanoma setting, please use only data from metastatic melanoma and adjuvant therapy immunotherapy studies (i.e. exclude the interferon studies and COMBI-AD, but include any studies of immunotherapies in metastatic melanoma) for the calculation of OS and provide the resulting HR for nivolumab.

BMS would like to take the opportunity to highlight a number of issues relating to this analysis (please refer to the surrogacy report for further information).

The surrogacy relationship as is remains the most robust method for estimating OS to inform the economic model for the following reasons:

- The body of evidence in surrogacy relationship between RFS and OS is established in an adjuvant setting. Metastatic melanoma setting was not studied in the current surrogacy relationship work and as such inclusion of these studies would be methodologically flawed.
- RFS is often a primary outcome in the adjuvant treatment studies whereas metastatic treatment studies use PFS. Bridging and assuming equivalency between RFS and PFS across treatment setting would require another set of assumption and further methodological research.
- The correlation equation was created using aggregate data from multiple trials. Excluding interferon trials and COMBI-AD would lead to a study size of 1 - CA184-029 trial only.

As mentioned in the response to question A7, the relationship between a surrogate and a final endpoint appears to be context-dependent. Likewise, the relationship between a final endpoint, such as OS, and two different tentative surrogates, such as RFS and PFS, are likely different. There is empirical evidence that RFS (or its analogous, disease-free survival [DFS]) and PFS behave differently in their trial-level association with OS (see, for example, Oba et al., 2013[18] and Paoletti et al., 2013[19], who show that in gastric cancer, DFS is a valid surrogate for OS, whereas PFS has a correlation with OS that precludes its validity as a surrogate).

Given the above, pooling trials in the adjuvant and palliative settings does not appear an appropriate strategy from a methodological point of view. Likewise, it is possible that including a trial of targeted rather than immunotherapy (namely, COMBI-AD) is not appropriate, despite the fact that it comes from the same clinical setting as the trials with immune checkpoint inhibitors. As an alternative, we have repeated the exercise described in the response to question A8, now using the regression equation (Coart et al., 2018)[13] derived from the ipilimumab trial (Eggermont et al., 2016).[1] The results is shown in Figure 30, in which each “bubble” represents a set of centres in that clinical trial defined by geographic location. The (diagonal) regression line describes the association between the RFS HR and the OS HR. On the X axis, the solid vertical line represents the HR from the nivolumab trial, whereas the two dashed lines represent the upper and lower limit of the 95% confidence interval for this HR (Weber et al., 2017).[2] The three points on the X axis define the origin of three vertical lines that meet the regression line, and from these meeting points three horizontal lines indicate on the Y axis the expected HR for OS from the use of

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nivolumab (solid line), a “best-case” scenario (the lower dashed line) and a “worst-case” scenario (the upper dashed line). In all cases, the predicted HR for OS would be [redacted]. It should be noted that this graph does not show prediction limits for the regression line or 95% confidence limits for the predicted OS HR. Such limits were not computed and would likely be non-informative, given the limited sample size from the single trial used for deriving the regression line.

It should also be noted that the key aim of adjuvant therapy is to potentially cure patients with the lowest burden of disease such as micrometastatic disease after complete surgical resection. This is in contrast to the metastatic setting where the treatment goal is to prolong survival.

Figure 30: Treatment effects on RFS versus treatment effects on OS

Key: HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival

B9. Please clarify what adjustments have been made in the primary analysis of RFS to generate the parametric survival modelling patient-level ITCs. For example, the definition of RFS in CA184-029 does not include new primary melanoma as an event, whereas this is included in the definition of RFS in CheckMate 238. In the analysis, have new primary melanoma events been excluded from CheckMate 238? If not, how many primary melanoma events were there in each arm of CheckMate 238.

Checkmate-238 RFS definition:

The primary endpoint of RFS is determined based on the disease recurrence date provided by the investigator and is defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma, or death (whatever the cause), whichever occurs first. (Note: a subject who dies without reported recurrence will be considered to have recurred on the date of death.) For subjects who remain alive and whose disease has not recurred, RFS will be censored on the date of last evaluable disease assessment. For those subjects who remained alive and had no recorded post-randomization tumour assessment, RFS will be censored on the day of randomization. New primary melanoma events have not been excluded from the analysis and have been recorded as event at the date of first recurrence as per the censoring rules outlined in the latest CA209-238 statistical analysis protocol. Overall, [redacted] patients had new primary melanoma, [redacted] in the nivolumab and [redacted] in the ipilimumab arm, due to the low numbers of patients who experienced new primary melanoma the inclusion of new primary melanoma is unlikely to impact results, as such, no further adjustment was made for new primary melanoma. Table 30 shows the RFS event or censor descriptions from the trial.

CA184-029 RFS definition:

The primary endpoint of RFS is determined based on the disease recurrence date provided by the IRC and is defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis) or death (whatever the cause), whichever occurs first. (Note: a subject who dies without reported recurrence will be considered to have recurred on the date of death.). For subjects who remain alive and whose disease has not recurred, RFS will be censored on the date of last evaluable disease assessment. In the within trial RFS sensitivity analysis used within the ITC meta-regression patients were censored at the time of their last disease assessment if they received subsequent therapy prior to recurrence. Table 31 shows the RFS event or censor descriptions in the trial.

Table 30: CheckMate 238 RFS event or censor description 24-month data cut

Event or censor	RFS event description	All patients (n=906)	Nivo patients (n=453)	Ipi patients (n=453)
Event	[redacted]	[redacted]	[redacted]	[redacted]
Event	[redacted]	[redacted]	[redacted]	[redacted]
Event	[redacted]	[redacted]	[redacted]	[redacted]
Event	[redacted]	[redacted]	[redacted]	[redacted]

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Event or censor	RFS event description	All patients (n=906)	Nivo patients (n=453)	Ipi patients (n=453)
Event	[redacted]	[redacted]	[redacted]	[redacted]
Event	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]

Table 31: CA184-029 RFS event and censor description

Event or censor	RFS event description	All patients (n=951)	Ipi patients (n=475)	Placebo patients (n=476)
Event	[redacted]	[redacted]	[redacted]	[redacted]
Event	[redacted]	[redacted]	[redacted]	[redacted]
Event	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]
Censor	[redacted]	[redacted]	[redacted]	[redacted]

B10. Please clarify what adjustments have been made in the analyses listed below to generate the parametric survival modelling patient-level ITCs based on:

a. Sensitivity analysis matching RFS definition on subsequent therapy censoring in CA184-029.

The within trial sensitivity analysis for CA184-029 which censored patients at the receipt of subsequent therapy is detailed in B9. This definition of RFS in CA184-029 was used in the ITC analyses. No further adjustment for the differences in RFS definition were considered for the ITC analysis.

b. Sensitivity analysis matching CA184-029 on reviewer.

The investigator reviewed within trial sensitivity analysis for CA184-029 was not used for the ITC analysis within the model. Figure 3 in the submission Appendices presents the KM for this analysis in comparison to the primary RFS definition within CA184-029 and the

sensitivity analysis which matches on subsequent therapy censoring. Each of the KM's presented were very similar and therefore the analysis which matched the reviewer in to CheckMate 238 was not considered for ITC analysis.

Section C: Textual clarifications and additional points

C1. For CheckMate 238, please clarify the number of people from [redacted] who had a RFS event at 24 months of follow-up. In the last paragraph of section B.2.7 (page 39 of the company submission), the number of people from [redacted] in the nivolumab group experiencing a RFS event is reported to be [redacted] and [redacted]. Additionally, the number having a RFS event in the ipilimumab group is reported to be[redacted] and [redacted].

The difference in the two sets of numbers correspond to the two different subgroups of Asian race and Asian region. In the subgroup of patients with race identified as Asian there were [redacted] patients in the nivolumab group and [redacted] patients in the ipilimumab. In the subgroup of patients in the Asian region there were [redacted] patients in the nivolumab group and [redacted] patients in the ipilimumab group.

C2. Please clarify what outcome the statement "nivolumab is a well-tolerated treatment, with a safety profile generally comparable to routine surveillance ([redacted]on page 80 of the company submission refers to.

This outcome refers to the comparison of all cause grade 3-4 AEs between nivolumab and placebo. The odds ratio (OR) is calculated using a Bucher comparison of the within trial ORs of any AE grade 3-4 using AEs censored at 100 days in CheckMate 238 and 70 days in CA184-029. Please note that the reported OR in the company submission is incorrect though the interpretation of the result has not changed. The revised OR is presented below:

- OR nivolumab vs ipilimumab (CheckMate 238 18-month): [redacted]
- OR placebo vs ipilimumab (CA184-029): [redacted]
- OR nivolumab vs placebo (Bucher comparison): [redacted]

C3. Please confirm whether the data presented in Table 17 on page 83 of the company submission are from the 19 December 2017 data cut.

The data presented in Table 17 are from the 19 December 2017 data cut and were obtained from the summary information presented to the EMA.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Nivolumab for adjuvant treatment of resected stage III and IV melanoma ID1316

Thank you for agreeing to give us your organisation's 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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Association of Skin Cancer Specialist Nurses (BASCSN)**

3. Job title or position	**Specialist Skin Cancer Nurses – BASCSN Board Members**
4. Are you (please tick all that apply):	☐ 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):
5a. Brief description of the organisation (including who funds it).	**An association of specialist skin cancer nurses. Funding from conference profit and some external non-promotional grants from pharmaceutical companies**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The main aim of the treatment is to reduce the risk of patients who have been diagnosed with high risk primary melanoma developing metastatic melanoma .

or prevent progression or disability.)	
7. 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.)	A significant reduction in the number of patients developing metastatic disease when compared to patients having standard of care which is currently no treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are currently no effective adjuvant treatments for melanoma at this earlier stage. The sooner this treatment is available in an adjuvant setting, the better for NHS patients diagnosed with Stage III/IV resected disease
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Current standard of care is observation with additional scanning for patients at high risk of developing metastases
• Are any clinical guidelines used in the treatment of the	British association of dermatologists NICE Improving outcomes guidance.

condition, and if so, which?	
• 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.)	There are some differences of opinion about the best method of surveillance but the majority of HCP have a consistent opinion
• What impact would the technology have on the current pathway of care?	There would be more patients having active, adjuvant treatment. But hopefully in the future, fewer people will be having treatment for metastatic disease.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not current standard of care. Hopefully will be
• How does healthcare resource use differ between the technology and current care?	More patients will be having adjuvant treatment and therefore increased pressure on outpatient clinics and treatment units
• In what clinical setting should the technology be	Specialist centres

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Extra clinic space and likely more staff. Initial training of staff in new technology
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with a previous diagnosis of high risk melanoma would be most suitable to receive the treatment
The use of the technology	
13. 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.)	As current standard of care is observation there will be more clinic visits and investigations for the patient with subsequent knock on effect of additional clinic visits, blood tests and increased capacity needed for SACT units etc Some side effects may occasionally require occasional admission.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes Yes
15. 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?	Yes
16. 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	Yes , reduction in number of patients developing metastatic disease and therefore overall survival improved leading to reduction in need for treatment for stage IV disease and consequential support services

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Nivolumab as an adjuvant agent will fit in well to the exisiting clinical pathway for this disease, providing patient opportunity where none existed previously at this stage. This will provide a 'step-change' in the management of malignant melanoma.
• Does the use of the technology address any particular unmet need of the patient population?	Currently no adjuvant treatment available
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This treatment is generally well tolerated with the majority of patients being able to carry out all activities of daily living including going to work. While there are possible adverse effects from this treatment, these are now well identified and can be managed effectively. Overall there are likely to be significant health benefits to those individuals affected by this disease.
Sources of evidence	
18. 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?	
• 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
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. How do data on real-world experience compare with the trial data?	Unable to comment at this time as not used outside clinical trial
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Substantial improvement in relapse free survival and overall survival
- Generally well tolerated
- Out patient treatment
- Quality of life usually maintained
- Reduction in number of patients needing treatment for metastatic disease

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nivolumab for adjuvant treatment of resected stage III and IV melanoma ID1316

Thank you for agreeing to give us your organisation's 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 submission

- 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	

2. Name of organisation	MELANOMA UK
3. Job title or position	CORPORATE SPONSORSHIP
4a. Brief description of the organisation (including who funds it). How many members does it have?	Melanoma UK is a patient support and advocacy group, set up in 2007, The group was set up in memory of Jon Herron, a young man from Larne in Northern Ireland who sadly passed away in May 2008. Initially the aim was to fund raise and raise awareness of melanoma. The group started off as Factor 50 and became Melanoma UK in 2013. Our aim is to give patients and their families much needed support during the very difficult times faced upon diagnosis. We aim to get them access to the best care available and support them throughout the journey. Patients, families, carers and clinicians are at the heart of our work. We are passionate about our work and will work tirelessly to get results.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no
5. How did you gather information about the experiences of patients and carers to include in your submission?	Melanoma UK not only provide face-to-face opportunities to meet and discuss how patients and carers deal with their condition, we now have a lot of our interaction taking place online, through blogs, internet forums and websites. Through the launch of the Melanoma UK Patient Registry we are also able to capture real time information on patient experience dealing with melanoma. These various platforms provide patients and carers a safe space to post their hopes for the short-, medium- and long-term future and share their fears with others. Melanoma UK try to help people to understand their condition. We are a very hands on patient support group.
Living with the condition	
6. What is it like to live with the condition? What do carers	As a carer I felt overwhelmed, helpless and uncertain every minute of the day. Knowing that my niece faced physical and emotional challenges bought on a wide range of feelings.

experience when caring for someone with the condition?	**These included, fear, shock, desperation and isolation because I was uncertain of her future. I didn't know what support was available for me as a carer and didnt like to ask becuse this was her journey not mine.**
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	
8. Is there an unmet need for patients with this condition?	**The principle unmet need of patients dealing with melanoma is the lack of adequate treatments - limited options**
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	- **could ill improve their overall condition** - **ease of use** - **shorter time spent at hospital getting treatment** - **Hope**

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	**- might worsen their condition** **- difficulty in use (injection rather than tablets)** **- where the technology has to be used (hospital rather than at home)** **- severity of side effects**
Patient population	
11. 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.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**NO - Melanoma is a disease that affects young, old, black, white.....melanoma does not discriminate so neither should the treatment available.**

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission:

- **This treatment is vital for our patients. It gives them hope and confidence that this disease will not recur**
- **Patients and carers are at the center of everything we do and this treatment could potentially improve their life**
- **There is more need for transformational drugs/treatments for melanoma sufferers**
- xxx
- xxx

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission in August 2018 for the 1st meeting on the NICE appraisal of adjuvant nivolumab in stage III and resected stage IV malignant melanoma

1. NHS England notes that the median duration of follow-up in the adjuvant nivolumab study is short and that very few patients are at risk after 24 months. The dataset is thus very immature in terms of observing what the long term difference might be for recurrence-free survival. NHS England notes that the next analysis of the adjuvant nivolumab trial will be in Q4/2019.
2. NHS England observes that there is currently no evidence of any difference in overall survival [redacted].
3. Although nivolumab given for advanced disease does probably cure a modest proportion of patients, the majority of patients relapse and die of their metastatic melanoma. There are precedents from other malignancies in which non-curative systemic therapy in the advanced disease setting nevertheless increases the cure rate as adjuvant treatment in early disease post-surgery eg breast cancer, colorectal cancer, non small cell lung cancer. NHS England would therefore consider it likely for adjuvant nivolumab to have a long term survival benefit in melanoma (as adjuvant ipilumumab has already shown).
4. NHS England notes the great heterogeneity in the indirect analyses to connect the adjuvant nivolumab vs ipilimumab trial with the adjuvant ipilimumab vs placebo study. There are many reasons for this heterogeneity: type of melanoma (cutaneous vs mucosal), different staging systems in operation (although stage III melanoma has not changed very much from the older system to the recent one), duration of treatment with ipilimumab, differing censoring rules, different time periods in which the studies were conducted and at times when treatments were changing very quickly and finally very different durations of follow up. This considerable heterogeneity between these 2 trials makes the conclusions of any cost effectiveness analysis more uncertain.
5. Nevertheless, a direct comparison has been done between adjuvant anti-PD-L1 immunotherapy in the form of pembrolizumab and placebo (NEJM 2018; 378: 1789-1801). With a median duration of follow up of 15 months, the study shows a difference in 1 year recurrence free survival of 75% with pembrolizumab vs 61% for placebo. This indication is coming to Committee A next month.
6. The subsequent treatments used in the economic model relate to the times that the adjuvant nivolumab vs ipilimumab and the adjuvant ipilimumab vs placebo trials were done. Treatments were changing quickly during the earlier adjuvant trial and the treatments used then cannot all be taken as being in current practice. The great difference in follow up durations also plays a part in determining which treatments have been used and therefore appearing in the economic model.
7. Later relapses on adjuvant nivolumab (eg beyond 2 years after completing treatment) will be managed similarly to those relapsing on routine surveillance ie with dabrafenib and trametinib if BRAF positive and with consideration of nivolumab monotherapy/pembrolizumab monotherapy/nivolumab plus ipilimumab combination therapy. However, there will be some differences in management in those that relapse early (eg <2 years after completing adjuvant nivolumab) with less initial nivolumab

monotherapy/pembrolizumab monotherapy and greater consideration of ipilimumab monotherapy as well as nivolumab and ipilimumab combination therapy in some cases.

8. The other subsequent treatments used in the economic model bear little resemblance to what is likely to happen in current practice. Interferon is not used at all. Both chemotherapy and talimogene are rarely employed.
9. NHS England notes the importance of subsequent treatment costs in the economic model and is therefore concerned that the ones used by the company do not reflect what is likely to be used in practice in England.
10. NHS England observes that no administration costs for adjuvant therapies appear to have been included in the economic model. This is incorrect. The NHS England chemotherapy delivery tariff in 2017/18 for nivolumab is coded as SB13Z and should be £299 per cycle (ie every 2 weeks). If these costs have been omitted, then the cost of administering nivolumab for a full 1 year of treatment would be just over £7.5K.

[redacted]

Chair NHS England Chemotherapy Clinical Reference Group and CDF National Clinical Lead for the Cancer Drug Fund

August 2018

NICE National Institute for Health and Care Excellence

Clinical expert statement

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Louise Fearfield**
2. Name of organisation	**British Association of Dermatologists**

3. Job title or position	**Consultant Dermatologist**
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.)	To prevent disease progression in the first instance Increase overall survival
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.)	Time to relapse No relapse
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes –
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Surgery is the mainstay of treatment Rarely : Radiotherapy Interferon is not generally used (as it is not effective and is not well tolerated) although has been given in the adjuvant setting in the past
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE melanoma guidelines [NG14]
• 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.)	Generally well defined
• What impact would the technology have on the current pathway of care?	It should reduce the number of surgical procedures required as patients may go onto adjuvant therapy instead of surgery that is currently taking place It has been shown to increase disease free survival and it it increases overall survival then it will impact on reduction of progression to unresectable stage IV disease. This will potentially increase the number of patients needing longer term follow-up
11. Will the technology be used (or is it already used) in	Yes but as adjuvant therapy – it will also only be given for up to a year At present Nivolumab is used for unresectable stage IV melanoma

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Hospitals are already set up to give this treatment
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist melanoma clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None as it is already in use
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase	So far it has been shown to significantly increase recurrence free survival (Weber et al NEJM 2017; 377:1824-1835)

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	The trial found no change in quality of life scores compared to baseline
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
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	No difference to how it is used now except that Nivolumab has recently moved to a 4 week dosing schedule rather than every two weeks and I don't know whether this will be adopted?

treatments needed, additional clinical requirements, factors 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?	Probably as per trial – 1 year of treatment and stop if adverse events
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	Yes as there is no adjuvant therapy outside of trials at present that has been shown to significantly increase

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?	disease free survival
• 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?	Yes 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?	Ipilumumab is currently licenced by the FDA in 2015 for adjuvant therapy for resected stage III melanoma but there is a high toxicity rate associated with this drug (42% grade 3 or 4 immune adverse related events NEJM 2016;375:1845-55, Lancet Oncol 2017;18:393-403 and 45.9% Weber et al NEJM 2017;377:1824-1835) There were only 14.4 % Grade 3 or 4 adverse events in the adjuvant Nivolumab group as per trial (Weber et al NEJM; 377:1824-1835). It is much better tolerated but not without it's side effects

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the UK was involved in the trial that is pivotal to this NICE appraisal (Weber et al NEJM 2017;377:1824-1835)
• 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?	Recurrence free survival Overall survival although this will require longer follow- up
• 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?	Not aware of any
20. Are you aware of any	No

relevant evidence that might not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Compare well
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.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Has been shown to significantly increase disease free survival
- No effective adjuvant therapy available in the UK at present
- Better tolerated and lower toxicity profile than some other alternatives (Interferon)
- May reduce the need for potentially morbid surgical procedures
- Already in use in the metastatic setting so health professionals are used to using it, dealing with side effects

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.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**James Larkin**
2. Name of organisation	**Royal Marsden NHS Foundation Trust**

3. Job title or position	**Consultant Medical Oncologist**
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.)	Reduction of recurrence of Stage 3/Stage 4 NEDmelanoma
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.)	Variable but as per other adjuvant drug use in oncology
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Observation
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE
• 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.)	Yes but some variation in imaging follow up
• What impact would the technology have on the current pathway of care?	Main issue is resource implications of this IV therapy
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

• How does healthcare resource use differ between the technology and current care?	Above: large impact for pharmacy, IV services, clinician time
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Mainly resources as above.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the	Yes

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?	No
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	Nivolumab is already widely used

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?	No as per CM 238 trial
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?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes

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?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes no effective adjuvant treatment for melanoma until this
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?	Manageable side effects in general and lots of experience with drug for Stage 4 melanoma and in other tumour types
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?	Significant improvement in RFS with acceptable toxicity
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Whether RFS will predict OS is unknown currently but adjuvant ipilimumab has both RFS and OS benefits (but is much more toxic than nivo)
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the	No published RWD I'm aware of

trial data?	
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.	
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your statement. • Well tolerated • Significant RFS benefit • Significant resource implications • •	

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.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for adjuvant treatment of resected stage III and IV melanoma

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by MELANOMA UK and consequently I will not be submitting a personal statement.

Name: .DIANE CANNON.....

Signed: .....

Date: ...15.08.2018.....

Nivolumab for adjuvant treatment of resected stage III and IV melanoma

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 17/156/02

BMJ Technology Assessment Group

Title: Nivolumab for adjuvant treatment of resected stage III and IV melanoma

Produced by: BMJ Technology Assessment Group (BMJ-TAG)

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Date completed: 19/07/2018

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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.

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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.

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Contributions of authors:

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All authors read and commented on draft versions of the ERG report.

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TABLE OF ABBREVIATIONS

Abbreviation	In full
AE	Adverse event
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
AUC	Area under the curve
BIC	Bayesian Information Criterion
CE	Cost effectiveness
CEAC	Cost-effectiveness acceptability curve
CGP	Corrected group prognosis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	Cytotoxic T-lymphocyte-associated protein
DIC	Deviance Information Criterion
DMFS	Distant metastasis-free survival
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EoL	End-of-life
ERG	Evidence Review Group
GM-CSF	Granulocyte colony-stimulating factor
GP100	Glycoprotein 100
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health-state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
IVRS	Interactive voice response system
KM	Kaplan–Meier
LY	Life-year
MAE	Mean absolute error
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office of National Statistics
OS	Overall survival

OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PET	Positron emission tomography
PD-1	Programmed death receptor-1
PD-L1	Programmed death receptor ligand-1
PH	Proportional hazards
PLD	Patient level data
PR	Post recurrence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRS	Post-recurrence survival
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
RF	Recurrence-free
RFS	Recurrence-free survival
RMSE	Root-mean-squared error
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
T-VEC	Talimogene laherparepvec
UV	Ultra-violet

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of nivolumab (Opdivo®; Bristol-Myers Squibb) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of adjuvant nivolumab in the treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

The company provided a reasonable overview of the disease area and current service provision. Briefly, melanoma is an aggressive type of skin cancer that refers to a malignant tumour of melanocytes, the melanin-producing cells found mostly in the skin. The staging system most commonly used for describing the extent to which the melanoma has spread is the American Joint Committee on Cancer (AJCC) system which has recently been updated to the 8th edition. In the UK, adjuvant therapy for melanoma is not common clinical practice after surgical resection, instead patients are managed through routine surveillance; at present there are no active therapies approved by NICE for use in the adjuvant melanoma setting.

In June 2018, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the use of adjuvant nivolumab, and a change in the marketing authorisation was recommended for the use of nivolumab in this new indication for the treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Clinical effectiveness data in the company submission (CS) for adjuvant nivolumab are derived from the CheckMate 238 randomised controlled trial (RCT) designed to evaluate the efficacy and safety of nivolumab versus ipilimumab. In addition, clinical effectiveness data on ipilimumab versus placebo from study CA184-029 were included to inform the economic model inputs and to enable an indirect treatment comparison (ITC) to be conducted between nivolumab and routine surveillance (using placebo as a surrogate for routine surveillance).

Patients enrolled in CheckMate 238 were aged 18 years or over and were required to have had complete surgical resection of Stage IIIB, IIIC or IV melanoma, according to the 2009 classification of the American Joint Committee on Cancer (AJCC) 7th edition. The patients eligible for inclusion in CA184-029 were required to be at least 18 years of age and to have undergone a complete regional lymph node dissection and have histologically confirmed melanoma metastatic to lymph nodes only. In terms of staging, the patients enrolled in CA184-029 had Stage IIIA, IIIB or IIIC melanoma defined according to the AJCC 6th edition.

The Evidence Review Group (ERG) and its clinical experts considers the population in CheckMate 238 and CA184-029 to be relevant to the decision problem. In addition, the ERG considers the intervention and outcomes from CheckMate 238 to be consistent with those specified in the final scope issued by NICE. As mentioned, above, an ITC was required to enable the comparison of nivolumab with routine surveillance that was requested in NICE final scope. As a result of the requirement for the ITC, the ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment as the data for these outcomes in CheckMate 238 and CA184-029 unsuitable for combining in an ITC.

1.2 Summary of clinical effectiveness evidence submitted by the company and the ERG critique

The company conducted a global level SLR and refined the results to address the decision problem specified in the NICE final scope. The ERG considers the company's searches were adequate to identify the key RCT evidence, although the ERG notes that foreign language publications were omitted. In terms of methodological practice for study inclusion and data extraction, the ERG considers the company to have used robust and standard methods.

The company's SLR identified one RCT that provided evidence on the clinical effectiveness of adjuvant nivolumab in patients with resected Stage III or IV melanoma with lymph node involvement or metastatic disease. CheckMate 238 compared nivolumab versus ipilimumab and so an ITC was required to provide estimates of the effectiveness of nivolumab versus routine surveillance, as requested by the NICE final scope. One study, CA184-029, was identified as suitable for inclusion in the ITC to provide a link between nivolumab and routine surveillance, which investigated ipilimumab compared to placebo (i.e. placebo being used as a surrogate for routine surveillance) in patients with completely resected Stage III melanoma.

CheckMate 238 is an international double-blind phase III RCT that was assessed to be of high methodological quality by both the company and the ERG. The results of CheckMate 238 in the CS were reported using two different data-cuts, one with a minimum of 18-months follow-up and the other following a minimum of 24-months follow-up. The ERG focuses its report and critique on the later data-cut and notes that follow-up in CheckMate 238 is still ongoing with [redacted]

Following a minimum of 24 months follow-up, nivolumab demonstrated a statistically significant improvement in RFS (HR 0.66; 95% CI: 0.54 to 0.81) and DMFS (HR: 0.76; 95% CI: 0.59 to 0.98) compared to ipilimumab. The company supplied results from [redacted]

[redacted]The company did not report any numerical data for HRQL in the clinical effectiveness review section of the CS although they reported that, "*HRQL scores were maintained after treatment in both groups with respect to the score on the EORTC QLQ-C30 Global Health Status or on any of the individual scales, as well as to scores on the EQ-5D utility index and the EQ-5D visual analogue scale (VAS)*". The ERG thus concludes that there were no significant differences in HRQL with nivolumab compared to ipilimumab.

There were no subgroup analyses specified in the NICE final scope, although the company presented a series of subgroup analysis results in the CS. Of particular note, the ERG considers the results of CheckMate 238 to suggest a trend toward a greater RFS benefit with adjuvant nivolumab compared to ipilimumab in those patients with PD-L1 ≥ 5% although the ERG acknowledges that treatment with nivolumab was favoured in both the PD-L1 ≥ 5% and PD-L1 < 5% subgroups. In terms of the subgroup data by geographic location in CheckMate 238, the ERG considers the results suggest that the [redacted].

The AJCC was recently updated to the 8th edition whereas at the time of recruitment in CheckMate 238 the AJCC 7th edition was used in clinical practice. This change in AJCC staging definitions since the commencement of CheckMate 238 means that a subset of the [redacted] patients who were defined as Stage IIIb using the AJCC 7th edition would now be considered Stage IIIa as per AJCC 8th edition (N=[redacted]) and a further subset would now be classified as stage IIIc/IIId (N = not reported in the CS). The company conducted subgroup analyses for RFS based on the AJCC 7th edition classification of patients and also for the patients reclassified as Stage IIIa using AJCC 8th edition. The ERG notes that there was a consistent trend favouring nivolumab although statistical significance was not reached for most of the subgroups. The ERG also notes that many of the subgroups were small (N < 100 per treatment arm) and that they were not powered to detect statistically significant differences in treatment effects.

AEs were reported in nearly all of the patients in both the nivolumab and ipilimumab treatment groups of CheckMate 238, although they were of lesser severity with nivolumab compared to ipilimumab (Grade 3–4 AEs reported by 25.4% of nivolumab patients compared to 55.2% of ipilimumab patients). In addition, the AEs were more frequently deemed to be treatment-related with ipilimumab (95.8%) compared to nivolumab (85.2%) and to lead to treatment discontinuation (ipilimumab 41.7% compared to nivolumab 7.7%). The ERG's clinical experts reported that the AE results from CheckMate 238 are as expected and that they are consistent with the results seen for these drugs in the metastatic melanoma treatment setting.

CA184-029, the study used in the ITC, was a multinational, randomised, double-blind, phase III study of adjuvant ipilimumab in patients with Stage III cutaneous melanoma who had undergone complete

regional lymph node surgical removal. The ERG's clinical experts reported that the baseline characteristics for CA184-029 appear broadly consistent with those of CheckMate 238, although the ERG notes that median age of patients in CA184-029 is slightly younger compared to CheckMate 238 and patients in CheckMate 238 included patients with a more advanced disease stage (Stage IV) that were excluded from CA184-029. In addition, approximately 20% of the patients in CA184-029 had Stage IIIa disease and Stage IIIa patients were excluded from CheckMate 238. The ERG notes that the company applied co-variate adjustments in the ITC analyses to adjust for these differences in Stage and age. There were also comparability issues in terms of the RFS definitions used in CheckMate 238 and CA184-029 although the ERG considers the resulting analyses conducted by the company mean that the only difference was that RFS was assessed by the investigator in CheckMate whereas in CA184-029 it was assessed by an independent panel. The ERG considers this difference in outcome assessment is likely result in a conservative estimate of the efficacy of ipilimumab versus placebo.

The ERG also noted that there was a difference in the maximum duration of ipilimumab treatment between CheckMate 238 and CA184-029; in CheckMate a maximum of one-years treatment was allowed whereas in CA184-029 ipilimumab treatment could continue for upto three-years and approximately [redacted] of patients continued ipilimumab treatment beyond one year. The company conducted additional analyses in their clarification response using data where ipilimumab patients who were treated beyond one-year were censored at one year which the ERG considers to be a more conservative estimate of the benefit of nivolumab compared to placebo as opposed to the over-optimistic results provided by the ITT ipilimumab population.

The ERG also noted that the subsequent therapies differed between CheckMate 238 and CA8184-029 and the ERG's clinical experts reported that the types of subsequent therapies given in CheckMate 238 were likely to be generally more consistent with the types used in UK clinical practice. The ERG notes that part of the reason for the differences in subsequent therapy is likely to be related to advances in clinical practice since CA184-029. The ERG also notes that due to the outcome censoring selected for the ITC analyses, these differences in subsequent therapies will have the largest impact in the analysis of OS.

In terms of the ITC, the company conducted analyses for RFS using patient level data (PLD) meta-regression and parametric survival models; and also conducted a Bucher adjusted indirect comparison. For the PLD ITC the company included covariates for Gender, age, stage and trial, with the rationale for including a trial covariate being, "it will account for all unobserved differences between trials, thus

maintaining randomisation". The ERG is unclear as to exactly what these differences addressed by the trial level covariate are as the company has described them as "unobserved". The resulting parametric curves from the log-logistic meta-regression model (that was deemed to be the best-fitting model) suggest that for the matched population (CheckMate 238 and CA184-029), nivolumab is associated with the longest RFS compared to both ipilimumab and placebo.

The Bucher ITC analyses for RFS using the full ITT populations of CheckMate 238 and CA182-029 were conducted with and without covariate adjustments for age, gender and stage. [redacted].

The CA184-029 data suggests that the ipilimumab censored at one-year population has a slightly shorter RFS compared to the ITT population beyond approximately 18 months; although this analysis is likely to be biased against ipilimumab as the censored patients are likely to be those who will have the best prognosis at 1 year. The HRs estimated by the Bucher ITC for nivolumab versus placebo were numerically [redacted] higher when the ipilimumab censored at one-year data were used rather than the full ipilimumab dataset, [redacted].

The ERG requested the company conduct a re-analysis of the clinical data from CheckMate 238 and CA184-029, re-staging patients into the new AJCC 8th edition disease stages for melanoma, and an analysis by baseline PD-L1 status, although the company reported that they were unable to conduct these analyses due to insufficient PLD being available from CA184-029. The ERG nevertheless considers them both to be potential subgroups of interest.

OS for nivolumab versus routine surveillance for use in the economic model was estimated using a surrogacy analysis. The ERG requested updated ITC analyses using the PLD and the Bucher ITC method using the OS for nivolumab [redacted].

The HR generated from the surrogacy analysis for OS of nivolumab vs ipilimumab was [redacted] However, the ERG has numerous concerns regarding the methodology and exploratory nature of the analysis. The ERG notes that the original surrogacy analysis cited by the company used PLD data from interferon studies to generate the surrogacy equation, whereas the method used in the CS was based on [redacted] with the original published PLD equation used in sensitivity analyses. The ERG also has concerns that the majority of studies used in the surrogacy analysis to inform the OS estimate in CheckMate 238 are based on interferon [redacted], which unlike nivolumab and ipilimumab, is not an immunotherapy and is also not routinely used in the adjuvant melanoma setting in the UK. The ERG is, therefore, concerned about the transferability of the RFS–OS relationship identified in interferon studies to immunotherapy and other adjuvant melanoma therapies. The ERG, therefore, considers the HR generated via the Bucher ITC to be the most reliable estimation at present for nivolumab versus routine surveillance based on [redacted]

1.3 Summary of cost effectiveness evidence submitted by the company

The company developed a *de novo* economic model to evaluate the cost-effectiveness of adjuvant nivolumab compared to routine surveillance in patients with fully resected melanoma. The economic model was based mostly on the CheckMate 238 trial, comparing nivolumab with ipilimumab, and CA184-029 trial, comparing ipilimumab with placebo. However, other sources of evidence were also used to supplement this data and provide alternative scenarios.

The company had access to PLD for both recurrence-free survival (RFS) and OS for the CA184-029 trial; however, they did not have mature PLD for OS from the CheckMate 238 trial; only for RFS. This meant that an ITC based on a meta-regression could only be performed on the RFS data. The primary analysis for RFS was done using a meta-regression to fit and adjust parametric survival curves for nivolumab and for routine surveillance. The Bucher method, using HRs, was also used as a scenario analysis.

For OS, the company utilised data from a published surrogacy relationship study between RFS and OS, which was derived using trials that assessed interferon in the adjuvant setting. The published relationship was estimated using PLD. However, the company used the HRs from the study and performed a regression analysis to predict the OS HRs from RFS HRs. The company used the HRs from this study as well as potentially more applicable HRs from the CA184-029 trial and the recently published COMBI-AD trial, comparing adjuvant dabrafenib in combination with trametinib against placebo in patient with melanoma.

This surrogate relationship allowed a HR for OS, comparing nivolumab to ipilimumab, to be predicted by inputting the CheckMate 238 RFS HR. This HR was then multiplied by the OS HR from the CA184-

029 trial to provide an estimate HR of nivolumab compared to placebo. This was applied to the placebo OS generalised gamma curve, determined to be the best fitting parametric curve for the CA184-029 OS data, and this was applied in the model as the estimated OS curve for nivolumab.

An alternative modelling approach was also provided by the company, which was based on a Markov structure. This model required transition probabilities to be estimated for transitions between the recurrence-free (RF) and post-recurrence (PR) health states; the RF and death health states; and the PR and death health states. The transitions from RF to both PR and death were derived by weighting the RFS models used in the PSM by the proportion of events that were recurrence events and deaths, respectively, in the CheckMate 238 trial. Transitions from PR to death were estimated in two different ways.

The first approach (Markov Option 1) was to estimate treatment specific HRs comparing PRS with OS using the CA184-029 trial data. These were then applied to the generalised gamma curve fitted to the OS data in the CA184-029 trial. An alternative approach (Markov Option 2) was done whereby the company fitted parametric survival curves to OS data from trials in a metastatic setting of the subsequent therapies received in the CheckMate 238 trial. A published fractional polynomial-based NMA of OS in a metastatic setting for these subsequent treatments was also used as a scenario analysis.

Long term OS was informed by registry data, which was used to fit parametric survival models. These were applied after 10 years in the model. General population mortality data was also used to ensure that the OS hazard in the extrapolated models did not become less than that of the general population. Long term RFS was also predicted after 10 years by applying a HR derived from data published in Agarwala *et al.* 2017; a study assessing adjuvant interferon for patients with melanoma.

Health-state utility values (HSUVs) were derived from EQ-5D-3L data collected in the CheckMate 238 trial. These HSUVs were derived from a regression analysis that included covariates for treatment, disease recurrence, disease stage and an interaction term for recurrence after ipilimumab treatment. The coefficients were used to estimate HSUVs for the RF and PR health-states for nivolumab treatment, which was assumed to be equivalent to HSUVs for the routine surveillance group given the lack of EQ-5D data in the CA184-029 trial.

The company also used EORTC-QLQ-C30 from the two trials to map to the EQ-5D using a published mapping algorithm, used the estimated HSUVs using this data to provide a scenario analysis. The company also identified additional published utility values that were also used to provide a scenario analysis to assess the impact of uncertainty.

Resource use was elicited from a survey of clinical experts and included outpatient visits to various health care professionals, diagnostic imaging and laboratory tests. Adverse event (AE) management was also modelled, using data from the CheckMate 238 and CA184-029 trials to inform the requirement for hospitalisation for immune-related AEs of any grade, diarrhoea grade 2 and above, and other AEs of grade 3 and above. End-of-life costs were also estimated using published evidence.

The incremental cost effectiveness ratio (ICER) from the company's originally submitted base case analysis was £8,769 per quality-adjusted life-year (QALY). The alternative base cases for Markov Option 1 and Option 2 were £8,831 per QALY and £17,947 per QALY. These results were based on the 18-month data cut of the CheckMate 238 trial for RFS. After clarification questions, the company provided analyses using the updated 24-month data cut from CheckMate 238 for RFS. This data resulted in ICERs of £8,882, £8,567 and £18,685 per QALY, respectively.

1.4 Summary of the ERG's critique of cost effectiveness evidence submitted

Although the ERG considers the company to have provided a large range of analyses to assess different alternative modelling approaches and data sources, the ERG considers there to be potentially serious uncertainty in the company's base case analysis as well as the alternative modelling approaches provided.

A key underlying problem throughout the company's analyses is the lack of OS data from the CheckMate 238 trial. This means that alternative sources of evidence and assumptions were required to estimate the potential benefits of nivolumab compared with routine surveillance in the adjuvant setting. The company's use of a surrogate relationship between RFS and OS is uncertain as the relationship was derived from predominantly interferon-based trials and was estimated using summary level data to predict a HR, assuming proportional hazards (PH). This may not be a plausible assumption and cannot be rigorously tested given the lack of long term OS data for nivolumab in the adjuvant setting. Further potentially unreliable assumptions of PH were also imposed for the long-term predictions of RFS after 10 years, as well as the estimation of PRS compared to OS used for an analysis using the Markov structure.

The alternative modelling approaches using the Markov structure avoid the need for the surrogate relationship, but add uncertainty from other sources in attempting to resolve the issue. As already stated, the estimation of PRS required in the Markov structure is uncertain due to the assumption of PH. The alternative source of evidence, using OS data in the metastatic setting is a potential way of resolving this issue; however, the data are taken from different populations that may not reflect exactly the population of patients that exist in the model at the point of disease recurrence.

A further issue relating to OS is that the subsequent treatments received in the CA184-029 trial have generally been superseded by more effective drugs such as immunotherapies in current UK clinical practice. Therefore, the more effective immunotherapies are likely to improve OS for patients after disease recurrence for those who receive routine surveillance and the relative benefit of adjuvant nivolumab may not be a great as the company's analyses suggest.

If the use of the OS data identified in the metastatic setting is robust and reliable, this approach potentially resolves the issue of subsequent treatments, or at least allows for the exploration of alternative estimates of PRS by varying the proportions of subsequent treatments in the model. The ERG conducted a scenario that used nivolumab as the subsequent therapy for all distant recurrence after routine surveillance and this increased the incremental cost-effectiveness ratio (ICER) substantially from £18,685 to £161,658 per QALY. Another scenario was conducted that also applied ipilimumab to all distant recurrence patients after adjuvant nivolumab. This ICER was also much greater than the company's base case at £34,925 per QALY; above the upper £30k per QALY threshold.

There were also some minor issues with excess resources use for imaging, whereby the majority of patients in the model were assumed to receive regular CT and PET scans of the chest and abdomen. Clinical experts suggested that it is unlikely for both to be given in UK clinical practice. The ERG assessed the impact of removing the PET scan costs from the model and this had a negligible effect on the results. A similar issue was noted with the use of both CT and MRI for the head. The ERG found the impact of this to be minimal also.

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

Clinical

- The data for nivolumab is based on evidence from an international phase III, double-blind, high-quality RCT (CheckMate 238), which is closely aligned with the NICE final scope requested population, intervention and outcomes.
- The company's statistical approach was generally appropriate and well described.
- The company conducted a comprehensive SLR to identify clinical effectiveness evidence of relevance to the decision problem in the NICE final scope.

- The company provided additional data and conducted a range of supplementary and subgroup analyses that allowed the ERG to assess the robustness of relative treatment effects of nivolumab versus ipilimumab.

- The company used two different ITC methods for estimating the clinical effectiveness of nivolumab versus routine surveillance for RFS (PLD meta-regression and Bucher ITC) and OS (Bucher ITC and surrogacy analysis).

Economic

- The economic model appeared to be well constructed with no errors identified by the ERG.

- The company attempted to provide a range of alternative analyses to assess the uncertainty in various parameters and data sources in the model.

- In particular, the use of both the partitioned survival structure and the Markov structure provided a useful alternatives ways of modelling survival given the lack of data available to inform OS for nivolumab.

1.5.2 Weaknesses and areas of uncertainty

Clinical

- There is no head-to-head clinical trial for the comparison of nivolumab with routine surveillance and so an ITC was conducted using ipilimumab as the common comparator and placebo as a surrogate for routine surveillance. The two trials used in the ITC (CheckMate 238 and CA184-029) are heterogenous due to differences in inclusion criteria, duration of ipilimumab therapy, and the use of subsequent therapies.

- The ERG notes the proportion of UK patients in CheckMate 238 was small although the subgroup analyses by geographical region suggest the Western Europe subgroup results are consistent with the whole ITT trial population. In addition, the ERG's clinical experts considered the baseline characteristics of patients in CheckMate 238 to be broadly consistent with that expected in the UK. The ERG however considers the absence of Stage IV patients from CA184-029, potentially limits the validity of the ITC results for the comparison of nivolumab with routine surveillance in this subgroup.

- The ERG has concerns around the potential impact and applicability to the UK population of the subsequent non-randomised therapies used in both CheckMate 238 and CA184-029; this particularly affects the estimates for the outcome of overall survival.

- The ERG considers the validity and generalisability of the results of the ITC to be questionable based on differences in the ipilimumab treatment duration between the CheckMate 238 and CA184-029 studies (upto 1 year in CheckMate 238 and upto 3 years in CA184-029). The ERG, therefore, considers the analysis provided by the company where ipilimumab patients continuing treatment beyond one-year are censored in CA184-029 to be a more robust analysis and results in a more conservative estimate of the benefit of nivolumab compared to placebo as opposed to the over-optimistic results provided by the use of the ITT ipilimumab CA184-029 population.

- The ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment although data were provided for these outcomes for nivolumab versus ipilimumab.

- The ERG is concerned about the use of non-standard methods for the surrogacy analysis which was reported to be a first-step 'statistical exercise' to estimate OS for nivolumab versus routine surveillance. In addition, the surrogacy relationship was based on predominantly interferon studies which is potentially unreliable when applied to data for an immunotherapy, and used trial-level data rather than the PLD which was used in the methods which the surrogacy analysis is based on (data with the original published PLD equation used in sensitivity analyses.).

- Data for nivolumab, and in particular for the outcome of OS, [redacted] and ongoing nature of the CheckMate 238 study. [redacted]

- The ERG is also concerned that the subsequent therapies in CA184-029 do not reflect clinical practice in the UK. Following routine surveillance, a larger proportion of patients are likely to receive more effective subsequent immunotherapies than in the CA184-029 trial, meaning that the OS estimate for nivolumab versus routine surveillance generated from the ITC is potentially underestimated.

Economic

- The key weakness in the company's economic analysis is the lack of mature PLD OS data to inform nivolumab. This prevented the use of an indirect comparison between the CheckMate 238 and CA184-029 trials, which could have been adjusted for, including adjustments for subsequent treatments, to provide a potentially more reliable analysis.

- The changing pathway in recent years has also made the OS data from the CA184-029 trial less applicable, given that more effective treatments are now available for use as subsequent treatments for advanced melanoma. Adding to this, the CA184-029 trial also used a different treatment duration for the ipilimumab group, making the ITC between the trials potentially unreliable. However, this was explored for RFS with the use of censored data.

- The use of a surrogate relationship to estimate OS from RFS, which the company describe as being derived in an exploratory analysis, is not reliable enough to be considered for the base case analysis. The alternative structures with alternative OS data sources for subsequent treatments demonstrate the extent of the potential uncertainty in OS estimates with ICER increasing substantially, meaning that the company's base case analysis cannot be confidently relied upon for decision making.

- The company apply multiple estimates of effect using HRs, where the assessment of PH has not been appropriately assessed, such as the estimation of PRS from OS and the long-term prediction of RFS from OS. The company also apply HRs to survival models that do not support the use of PH, which is methodologically flawed.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The ERG's preferred base case results are given in Table A, showing the impact of using the censored RFS ITC and changing the subsequent treatments. This base case used the company's alternative Markov Option 2 model as its foundation.

Table A. ERG base case ICER

Results per patient	Nivolumab	Routine surveillance	Incremental value
Company's alternative model (Markov Option 2)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	14.08	[redacted]
ICER			**£18,685**
RFS using censoring at one-year of treatment continuation			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	14.19	[redacted]
ICER (compared with company ICER)			**£18,960**
ICER with all changes incorporated			**£18,960**
Nivolumab as subsequent therapy for distant recurrence after routine surveillance			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	17.05	[redacted]
ICER (compared with company ICER)			**£161,658**
ICER with all changes incorporated			**£198,750**
Ipilimumab as subsequent therapy for distant recurrence after adjuvant nivolumab			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	17.05	[redacted]
ICER (compared with company ICER)			**£11,853**
ICER with all changes incorporated			**£36,135**
Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; LY, life-year; QALYs, quality-adjusted life years; RFS, recurrence-free survival.			

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section B.1.3 of the company submission (CS) provides an overview of the key aspects of melanoma, including its prevalence, associated risk factors, disease staging and the current treatment options. 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 be people with completely resected stage III or IV melanoma.[3]

Overall, the Evidence Review Group (ERG) considers the CS to present an appropriate overview of melanoma that is relevant to the decision problem and presents a synopsis of information from the CS below.

As outlined in the CS, with some supplementary information provided by the ERG:

- Melanoma is an aggressive type of skin cancer that refers to a malignant tumour of melanocytes, the melanin-producing cells found mostly in the skin.[4, 5]

- Melanoma may initially be asymptomatic, and often the first visible sign of disease is a mole that has changed in shape, colour, size or feel (cutaneous melanoma). Approximately 0.03% of the English population aged 18 or older were diagnosed with melanoma in 2014, resulting in an incidence of 13,744.[6, 7]

- Rates of melanoma have been steadily increasing since the 1990s; in the last decade, incidence rates increased by almost half (45%), making it the fifth most common cancer in the UK.[8] This increasing incidence is widely attributed to changing lifestyle factors, such as an increase in holidays taken in the sun and greater use of ultra-violet (UV) sunbeds, both of which increase people's exposure to UV light.[9, 10]

- Melanoma disproportionately affects younger people and, as a result, metastatic melanoma has the highest associated loss of economic productivity in Europe (estimated at €312,798 [approximately £272,316]/death in 2008) compared with other cancers, including brain cancer (€288,850 [approximately £251,468]/death).[11]

- As with other forms of cancer, melanoma is divided into stages describing the extent to which the cancer has spread. The staging system most commonly used for melanoma is the American Joint Committee on Cancer (AJCC) system based on Tumour (T), Node (N), and Metastasis (M) categories. This system has recently been updated to the 8th edition.[12] Importantly, patients

with Stage III disease have involvement of lymph nodes and could therefore be eligible for adjuvant nivolumab treatment. In addition, a small subset of patients with stage IV disease will have resectable disease and are also potentially eligible.

- In England, the majority of melanoma patients are diagnosed early (Stage I or II), with approximately 8% of patients diagnosed at Stage III or IV disease.[13] The Stage III or IV patients are initially treated with surgery, if possible, and it is estimated that surgery leads to completely resected disease in 80% of Stage III patients[14] and 8.6% of Stage IV patients.[15]

- The company estimated that a total of 1,481 patients in England will have melanoma with involvement of lymph nodes or metastatic disease and will have undergone complete resection and thus be eligible for treatment with nivolumab in the adjuvant setting (the ERG assume estimate refers to 2018 as it's unclear in the CS).

- Following surgical resection, adjuvant therapy for melanoma is not common clinical practice in the UK. Instead, patients are managed through routine surveillance; there are no active therapies approved by NICE for use in the adjuvant melanoma setting.

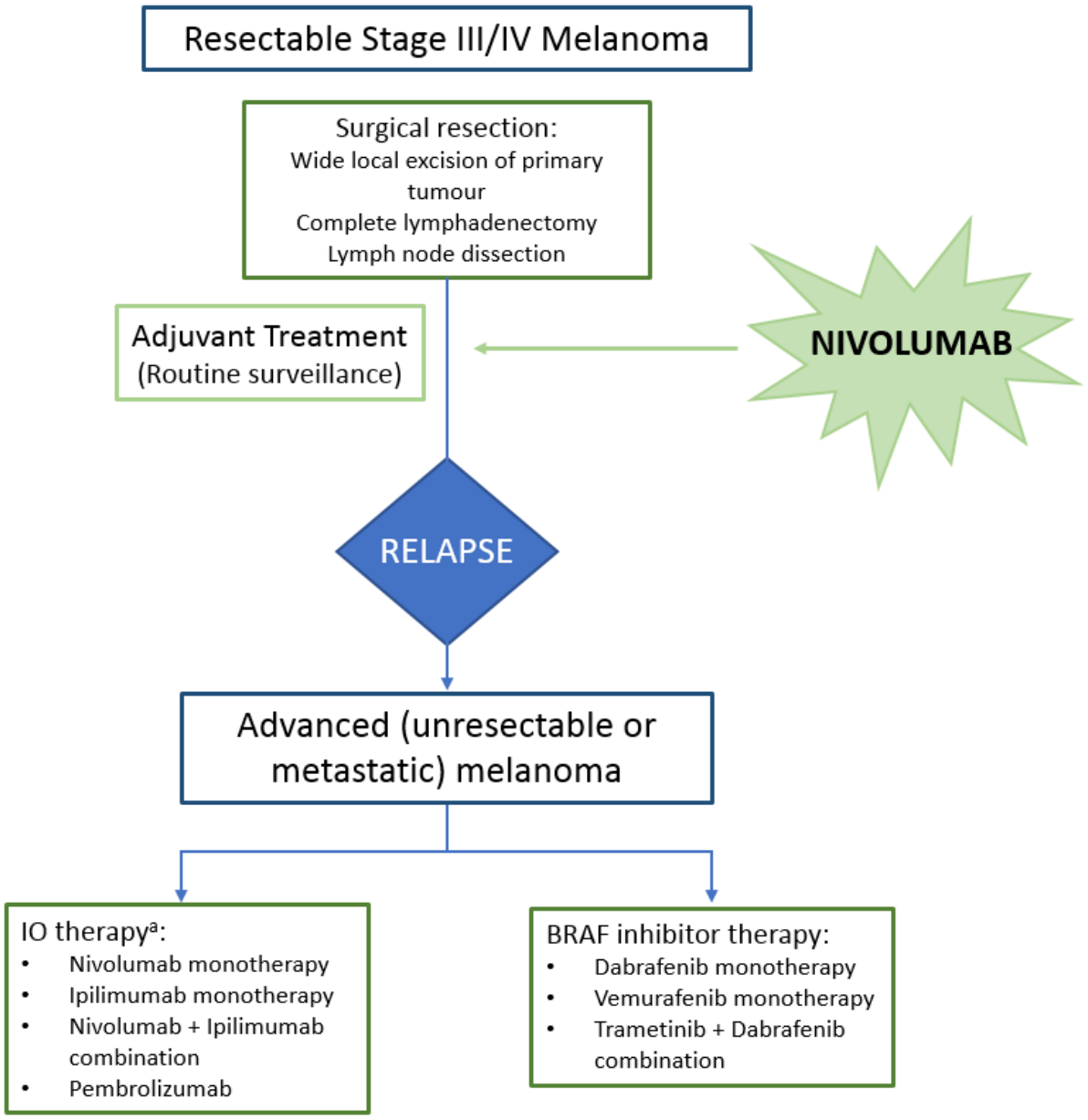
- Where the primary tumour has been successfully removed and patients have been declared disease free, the aim of adjuvant treatment is to prevent recurrence of disease. Despite surgical clearance of macroscopic disease, micro-metastatic disease is often present and either loco-regionally or distantly can result in later disease progression.

2.2 Critique of company's overview of current service provision

The CS provides a reasonable overview of current service provision for the management of people with completely surgically resectable Stage III or IV melanoma, including detail of where nivolumab will fit in the treatment pathway (Figure 1). The ERG notes that nivolumab acts by enhancing the ability of patient's own immune systems to recognise and destroy micrometastases or individual tumour cells at an early stage, and so helps to prevent further tumour growth and dissemination.

Nivolumab is the first checkpoint inhibitor agent licensed for use in the adjuvant setting for melanoma and there are currently no active therapies recommended by NICE for use in this adjuvant melanoma setting. Nivolumab, if recommended by NICE, will offer surgically resected stage III and IV patients an alternative to the routine surveillance currently provided and can therefore be considered a 'step-change' in the management of malignant melanoma (Figure 1).

Figure 1. Clinical pathway of care for malignant melanoma (reproduced from CS Document B, Figure 1)



Abbreviation: IO, immune-oncology.
Note: [a], regardless of BRAF status.
Source: Adapted from NICE melanoma pathway[16]

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the decision problem issued by the National Institute for Health and Care Excellence (NICE), together with the rationale for any deviation from the final scope[3] (Table 1).

Table 1. Summary of decision problem as outlined in the company's submission (reproduced from CS Document B Table 1, pages 7–8)

Characteristic	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with completely resected Stage III or IV melanoma	Adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.	Wording changed to reflect the anticipated licence.
Intervention	Nivolumab	Nivolumab	NA
Comparator(s)	Routine surveillance	Routine surveillance	NA
Outcomes	• Overall survival • Recurrence-free survival • Distant metastasis-free survival • Adverse effects of treatment • Health-related quality of life	• Overall survival • Recurrence-free survival • Distant metastasis-free survival • Adverse effects of treatment • Health-related quality of life	NA
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.	Adhering to the reference case, the cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year.	NA
	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.	Adhering to the reference case, a lifetime horizon is used.	NA
	Costs will be considered from an NHS and Personal Social Services perspective.	The reference case has been adhered to.	NA
	The availability of any PAS for the intervention or comparator technologies will be taken into account.	Adhering to the reference case, the PAS has been applied in all economic analysis for all BMS products.	Confidential PAS schemes that apply to relevant subsequent comparator therapies are not included in these analyses as BMS is not privy to such information.

Abbreviations: BMS, Bristol-Myers Squibb; NA, not applicable; NHS, National Health Service; PAS, patient access scheme.

3.1 Population

Clinical effectiveness data in the company submission (CS) for adjuvant nivolumab are derived from the CheckMate 238[1] randomised controlled trial (RCT) designed to evaluate the efficacy and safety of nivolumab versus ipilimumab. In addition, clinical effectiveness data on ipilimumab versus placebo from study CA184-029[2] were included to inform the economic model inputs and to enable an indirect treatment comparison (ITC) to be conducted between nivolumab and routine surveillance (using placebo as a surrogate for routine surveillance).

Patients eligible for inclusion in CheckMate 238 were required to be a minimum of 15 years old and to have had complete surgical resection of Stage IIIB, IIIC or IV melanoma, according to the 2009 classification of the American Joint Committee on Cancer (AJCC) 7th edition.[17] However, the Evidence Review Group (ERG) notes that only patients aged 18 or over were enrolled into the trial, which the company reported was due to difficulties in recruiting paediatric patients.

Patients eligible for inclusion in CA184-029[2] were required to be at least 18 years of age and to have undergone a complete regional lymph node dissection and had histologically confirmed melanoma metastatic to lymph nodes only. Patients therefore had to have either Stage IIIA, IIIB or IIIC melanoma, according to the AJCC 6th edition, with no in-transit metastasis. The ERG notes that the definitions of Stage IIIA, IIIB and IIIC were consistent between the AJCC 6th edition and AJCC 7th edition.

The final scope issued by NICE specifies the population of interest to be people with completely resected Stage III or IV melanoma. The ERG notes, based on the AJCC 7th edition, Stage IIIA patients were excluded from CheckMate 238 and Stage IV patients were excluded from CA184-029. However, the ERG also notes that the AJCC classification has recently been updated to the 8th edition[12] and the changes mean that some of the patients in both studies who were previously classified as Stage IIIB are likely to be Stage IIIA. There is therefore now clinical data for the full population, in terms of the AJCC 8th edition staging, for the population specified in the NICE final scope. The ERG considers that the population of CheckMate 238 is consistent with the anticipated marketing authorisation wording, that is, *"adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection"*.

In terms of the baseline characteristics of patients in CheckMate 238 and CA184-029, the ERG considers the demographics of the patients in both studies to adequately reflect the UK population likely to be eligible for adjuvant nivolumab, with the exception of lack of Stage IV patients in CA184-029. However, [redacted] of patients in CheckMate 238 were recruited from UK [redacted], although, in total, [redacted] of the trial population were from Western European countries.

In summary, the ERG considers the data presented within the submission from CheckMate 238 is likely to be representative of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection and who are therefore potentially eligible for adjuvant nivolumab therapy in England and Wales, and to be relevant to the decision problem that is the focus of this Single Technology Appraisal (STA). However, the ERG is concerned by the small proportion of UK patients in CheckMate 238 and the absence of Stage IV patients from CA184-029, which potentially limits the validity of the ITC results for the comparison of nivolumab with routine surveillance.

3.2 Intervention

The intervention that is the subject of this assessment is nivolumab (Opdivo®), a systemic immunotherapy treatment. Details on the mechanism of action, marketing authorisations and other key features of relevance relating to nivolumab are summarised in Table 2.

Table 2. Technology being appraised (reproduced from CS Document B Table 2, pages 9–10)

Detail	Description
UK approved name and brand name	Nivolumab (Opdivo®)
Mechanism of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to PD-1, an immune checkpoint receptor involved in T-cell differentiation and function, and blocks its interaction with its ligands, PD-L1 and PD-L2. Engagement of PD-1 with PD-L1 and PD-L2, which are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2. Malignant tumours may express PD-L1, making them susceptible to PD-1/PD-L1 therapeutic blockade. Within the adjuvant setting, nivolumab therefore acts by enhancing the ability of the patients own immune system to recognise and destroy micrometastases or individual tumour cells at an early Stage and prevent further tumour growth and dissemination. This approach, enabling the body's own immune system to target cancer, is novel in resected Stage III or IV melanoma and is viewed by physicians and patient interest groups as a 'step-change' in its management.
Marketing authorisation/CE mark status	An application was filed on [redacted] to the EMA to allow nivolumab to be used in the adjuvant setting. CHMP opinion is expected June 2018, with marketing authorisation expected [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication of interest within this submission is: "OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection" Nivolumab is also indicated in the UK and Europe for the following indications: As monotherapy or in combination with ipilimumab, for the treatment of advanced (unresectable or metastatic) melanoma in adults As monotherapy, for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults As monotherapy, for the treatment of advanced RCC after prior therapy in adults As monotherapy, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin

	As monotherapy, for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy As monotherapy, for the treatment of locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy Nivolumab monotherapy is anticipated to be licensed for adults with previously treated gastric or gastro-oesophageal junction cancer and is undergoing reimbursement for this indication. [redacted]
Method of administration and dosage	Intravenous infusion. The recommended dose of nivolumab for the treatment of adjuvant melanoma is weight based at 3mg/kg administered over 60 minutes every 2 weeks. Based on the pivotal CheckMate 238 trial, the maximum treatment duration is 12 months.[a]
Additional tests or investigations	No additional tests or investigations are needed.
List price and average cost of a course of treatment	£439.00 per 4ml vial; £1,097.00 per 10ml vial. Average cost of a course of treatment £53,771.[b]
Patient access scheme (if applicable)	A patient access scheme has been approved and comprises a [redacted] from the nivolumab list price. Applying this PAS to the list price, the cost per nivolumab dose is [redacted] with an average cost per course of treatment of [redacted][c]
Abbreviations: ASCT, autologous stem cell transplant; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; IV, intravenous; NSCLC, non-small cell lung cancer; PD-1, programmed death receptor-1; PD-L1, programmed death receptor ligand-1; PD-L2, programmed death receptor ligand-2, RCC, renal cell carcinoma. Notes: [a], some indications, not of interest to this submission, have a flat dose of 240mg every two weeks; [b], Average cost per dose = £2,739 x mean number of doses = [redacted] [c], Mean number of doses = [redacted]. Source: Nivolumab SmPC[18].	

The ERG notes that on the 28 June 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for Opdivo (nivolumab). The new indication is for the adjuvant treatment of melanoma and states that, *"Opdivo as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection".*[19]

The company presented data for nivolumab in the company submission (CS) from one randomised controlled trial (RCT) of nivolumab versus ipilimumab, CheckMate 238. The ERG notes that the dosing and treatment duration of nivolumab in CheckMate 238 are consistent with the anticipated marketing authorisation and the ERG considers the data provided by the company for the intervention are appropriate. The ERG and its clinical experts were not aware of any other studies of nivolumab as adjuvant therapy of relevance to this assessment.

The ERG considers it important to highlight that subsequent treatments used following disease recurrence in patients in CheckMate 238 differed between the two study arms and the impact of these differences is unclear in relation to the applicability of the results to the UK population. At the December 2017 data-cut 31.1% of patients from the nivolumab group and 41.1% from the ipilimumab group had received subsequent melanoma anti-cancer therapies (Table 6).[20] The subsequent therapy data presented by the company suggest an imbalance between the nivolumab and ipilimumab groups in

the mechanism of action of subsequent therapies. For example, patients randomised to nivolumab were [redacted] The ERG's clinical experts reported that they were unsure as to what treatments would routinely be used following disease progression in patients who have received adjuvant nivolumab as adjuvant therapy is not currently given in the UK. However, they considered that the subsequent therapies used in CheckMate 238 were reasonable and that the difference in subsequent immunotherapy use between the CheckMate 238 study arms could be explained by the drugs' mechanisms of actions (patients in ipilimumab arm most likely to receive pembrolizumab as subsequent immunotherapy whereas in nivolumab arm patients were most likely to receive ipilimumab on disease recurrence). The ERG's clinical experts did, however, report that the types of subsequent therapies given in CheckMate 238 were likely to be generally consistent with the types used in UK clinical practice.

In summary, the ERG considers the intervention to be in keeping with the NICE final scope and anticipated marketing authorisation for nivolumab, although the ERG has concerns around the potential impact and applicability to the UK population of the subsequent non-randomised therapies used in CheckMate 238.

3.3 Comparators

The comparator in CheckMate 238 was ipilimumab, which was not a comparator requested in the NICE final scope. The only comparator requested in the NICE final scope was routine surveillance. The company identified and included study CA184-029, an RCT of ipilimumab versus placebo to enable an ITC of nivolumab with routine surveillance (i.e. placebo). The company presented two different methods and sets of results in the CS for this comparison for the outcome of RFS as they had access to the patient level data (PLD) for both studies. The methods were a meta-regression analysis using the PLD from the two studies and an ITC using the Bucher method and trial level data from the two studies to validate the results from the PLD meta-regression. The ERG's clinical experts confirmed that the only relevant comparator is routine surveillance as there are no other approved adjuvant therapies for use in melanoma in England. The use of placebo as a surrogate for routine surveillance was also deemed to be acceptable by the ERG's clinical experts.

Treatment duration of ipilimumab differed between CheckMate 238 and CA184-029. In CheckMate 238, treatment with ipilimumab was limited to a maximum of one year, whereas in CA184-029 ipilimumab could be given for up to three years. The company reported that approximately [redacted] of patients in CA184-029 continued ipilimumab treatment beyond one year, which the ERG considers to be a substantial proportion of patients and therefore, during clarification, requested adjustments to the

company's ITC analyses to account for this discrepancy. A direct consequence of an over-estimation of the efficacy of ipilimumab compared with placebo would be an over-estimation of the difference in recurrence-free survival (RFS) between nivolumab and placebo (routine surveillance). The company provided additional analyses of RFS in their clarification response in which patients receiving ipilimumab beyond one year were censored at one year.

Patients from CA184-029 censored at one year are likely to be those that are healthier than patients who stop receiving ipilimumab. The ERG considers that an analysis where these patients are censored is likely to underestimate RFS in the ipilimumab group compared with placebo. The subsequent ITC would, therefore, potentially underestimate the difference in RFS between nivolumab and routine surveillance. The ERG considers this analysis to be a 'worst case' scenario based on the current data available. By contrast, the ERG considers the original analysis provided in the CS to be a 'best case' scenario. The ERG therefore does not consider either analysis to be ideal for addressing the comparison of nivolumab versus routine surveillance, although the ERG acknowledges that they are likely to be the best available estimates based on the current data available to the company.

The company also provided the results of an ITC analysis using only the Bucher method for the outcome of overall survival (OS) in their clarification response. The ERG considers that, like the CheckMate 238 trial level analysis, this analysis is likely to be confounded by subsequent therapies received post-randomised study treatment discontinuation. The subsequent therapies in CA184-029 included interferon, which is no longer routinely used in the treatment of melanoma in England, therefore raising further concerns over the generalisability and applicability of the ITC results for this outcome.

In summary, the ERG considers the comparator included in the CS to be in line with the comparator specified in the NICE final scope, although the ERG notes that an ITC has been required to enable the comparison of nivolumab versus routine surveillance. The ERG considers the validity and generalisability of the results of the ITC to be questionable based on differences in the study populations, ipilimumab treatment duration and subsequent therapies between the CheckMate 238 and CA184-029 studies.

3.4 Outcomes

The company presents no direct evidence for nivolumab versus routine surveillance. The company did, however, present clinical effectiveness data on nivolumab for all outcomes specified in the NICE final scope albeit from the CheckMate 238 study and therefore compared directly to ipilimumab rather than routine surveillance:

- OS;

- RFS;
- distant metastasis-free survival (DMFS);
- adverse effects (AEs) of treatment; and
- health-related quality of life (HRQoL).

In addition, results from ITC PLD meta-regression analyses and ITC Bucher Method analyses were provided in the CS for the outcome of RFS. However, although the ERG considers the outcome definition and use of intention to treat (ITT) data to be appropriate, the ERG has concerns over the comparability of the trials used to inform the ITC.

The company also presented data from an ITC using only the Bucher method for the comparison of nivolumab versus routine surveillance for the outcome of OS, as PLD were not available for this outcome. The ERG considers it important [redacted] also that the ERG has reservations over the comparability of the trials used to inform the ITC including concerns that there is heterogeneity in the subsequent therapies between the two studies informing the ITC.

The ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment.

Based on advice from clinical experts, the ERG considers that the outcomes presented in the submission are clinically relevant to the decision problem, although there is an absence of direct head-to-head or suitable evidence for indirect comparisons for several of the outcomes requested in the NICE final scope and some of the data for nivolumab are immature due to the short follow-up and ongoing nature of the CheckMate 238 study.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to identify efficacy and safety evidence from randomised controlled trials (RCTs) of adjuvant nivolumab and routine surveillance in patients with non-metastatic Stage III and Stage IV melanoma who had undergone complete surgical resection. The Evidence Review Group (ERG) notes that the SLR used by the company was conducted at a global level and had a wider scope than the National Institute for Health and Care Excellence (NICE) final scope for this appraisal. However, the company narrowed down the results appropriately in keeping with the NICE final scope.

The ERG provides a brief critique of the SLR process, which was detailed in Appendix D of the company's submission (CS), to support the ERG's opinion that no relevant evidence was overlooked.

4.1.1 Searches

The company carried out their searches between 28 September 2017 and 12 October 2017. The company conducted electronic database searches of MEDLINE®, EMBASE® and The Cochrane Central Register of Controlled Trials (CENTRAL). The ERG notes that no details on the start date of searches in the electronic databases were reported and so it is unclear if they were searched from inception. In addition, it is unclear what platforms were used or whether Medline In Process was searched (the omission of this may mean newer records that have not yet been indexed may have been overlooked).

The electronic database search strategies combined search terms for melanoma with drug therapy terms that, in addition to terms for nivolumab, included other drugs (ipilimumab, pembrolizumab, trametinib, dabrafenib and interferons). This was due to the global nature of the SLR and drugs that were considered irrelevant to the UK setting were excluded later in the SLR process. The ERG notes that randomised controlled trial (RCT) filters were applied in MEDLINE and EMBASE and the search results from all three databases were limited to English language publications. The ERG is unsure as to whether the English language publication limit may have introduced bias into the results, although the ERG is not aware of any potentially relevant missing studies from the CS. In addition, the ERG is unsure whether the restriction to RCTs and thus exclusion of non-RCT data may have resulted in the exclusion of potentially relevant non-RCT outcome data. Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts or undertake its own searches to validate the company's findings.

In addition to the electronic database searches, the company reported that the annual proceedings of selected conferences, as follows, were hand-searched for the last two years to identify any relevant on-going research:

- American Society of Clinical Oncology (ASCO);
- European Association of Dermato-Oncology;
- European Society of Medical Oncology (ESMO);
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR);
- International Society for Quality of Life Research;
- Society for Melanoma Research; and
- Society for Immunotherapy of Cancer.

In summary, the company conducted a search of the key electronic databases, including MEDLINE, EMBASE and The Cochrane Library, for RCT evidence relevant to decision problem and the context of the decision problem. The ERG and its clinical experts consider that the company is likely to have identified all English language RCT evidence relevant to the decision problem that is the focus of this STA. However, the ERG cannot be certain that all recent publications of relevance were identified due to the date of searches (searches were conducted over six months ago), possible omission of MEDLINE In-Process, and exclusion of non-RCT and foreign language publications.

4.1.2 Inclusion criteria

The inclusion criteria supplied by the company for the SLR in Appendix D of the CS (reproduced in Table 3) related to the global level SLR rather than for the focused SLR required by the NICE final scope. Nonetheless, the ERG considers the global level SLR inclusion criteria were broader than required by the NICE final scope, except for the restrictions to English language publications and RCT evidence as discussed in Section 4.1.1.

Table 3. Eligibility criteria (reproduced from CS Appendix D Table 4, pages 9-10)

Criteria	Description
Population	Adults (aged 18 years and older) with: •Non-metastatic Stage III melanoma[a] •Non-metastatic Stage IV melanoma
Interventions	Eligible interventions include adjuvant treatment (given after surgery) with one of the following:[b] •Nivolumab •Ipilimumab

	•Pembrolizumab •Dabrafenib in combination with trametinib •All interferon alphas (including 2a, 2b, pegylated 2a or 2b, and high and low doses)
Comparators	Eligible comparators include the following: •Any treatment listed as an eligible intervention •Placebo •Standard of care •Watchful waiting
Outcomes	Studies must report at least one of the following outcomes at a time point of 12 months or after: •Overall survival •Recurrence-free survival or disease-free survival •Distant metastatic-free survival •Adverse events Grade 3/4 •Overall discontinuations •Discontinuations due to adverse events •Global quality of life as measured by EORTC QLQ C-3
Study design	Only randomised controlled trials will be included
Language	Only studies published in English will be included
Abbreviations: EORTC QLQ C-3, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-3. [a,b] Footnotes missing in CS	

4.1.3 Critique of data extraction

The company reported a robust approach to study selection that involved two reviewers independently reviewing abstracts and full texts and the appropriate use of a third independent reviewer to resolve any disagreements at the full text screening stage. Two reviewers also independently completed the data extraction for the included studies.

The company provided a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the review in Appendix D of the CS, although this relates to the global level SLR. It is not clear to the ERG how the 24 RCTs identified for inclusion in the global level SLR were narrowed down to the final two RCTs included in the CS. However, from reviewing the titles of the 24 included RCTs, the ERG agrees with the company's selection of only CheckMate 238 and study CA184-029 for inclusion in the CS for this review.

In summary, there was only one publication relating to one study of nivolumab of relevance to the decision problem (CheckMate 238), and this compared nivolumab versus ipilimumab. To enable an indirect treatment comparison (ITC) of nivolumab with routine surveillance (the comparator required by the NICE final scope), a further 4 publications for 1 study (CA184-029), which compared ipilimumab versus placebo (routine surveillance), were also included. The suitability of Study CA184-029 and the company's ITC are discussed further in Section 4.4.

4.1.4 Quality assessment

The company provided a quality assessment of CheckMate 238 using criteria suggested in the NICE template for company submission of evidence to the Single Technology Appraisal (STA) process (Table 4). The ERG independently validated the company's assessment and agrees with the company's assessment of CheckMate 238 as being of high methodological quality (low risk of selection, reporting and attrition biases). The ERG notes that there was a difference between the nivolumab and ipilimumab treatment arms in reasons for study drug discontinuation, with more patients withdrawing due to disease progression with nivolumab (nivolumab 121 patients and ipilimumab 101 patients) and toxicity with ipilimumab (ipilimumab 208 patients and nivolumab 41 patients). However, the ERG also notes that this is unlikely to have had an undue effect on the results, in particular for recurrence-free survival (RFS) or distant metastasis-free survival (DMFS), where censoring was based on the date of last evaluable disease assessment for patients who did not have local or distant disease recurrence. Finally, the ERG notes that there was no independent assessment for the primary outcome of RFS, instead only investigator assessment was used. The ERG considers that given the double-blind nature of the study, the investigator assessment of RFS is likely to have had limited impact on biasing the results in any particular direction.

Table 4. Quality assessment of CheckMate 238 (reproduced from CS Document B Table 7, page 26)

Question	Response
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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
Source: Weber *et al.* 2017[1]	

4.1.5 Evidence synthesis

Pairwise evidence synthesis was not required as only one RCT of relevance was identified (CheckMate 238), however, an ITC was used to generate estimates of efficacy for the comparison of nivolumab versus routine surveillance as CheckMate 238 compared nivolumab versus ipilimumab. Details and critique of the ITC are provided in Section 4.4.

4.1.6 Summary statement

In summary the company conducted a global level SLR and refined the results to address the decision problem specified in the NICE final scope. The ERG considers the company's searches were adequate to identify the key RCT evidence, although the ERG notes that foreign language publications were omitted. In terms of methodological practice for study inclusion and data extraction, the ERG considers the company to have used robust and standard methods.

The company's SLR identified one RCT that provided evidence on the clinical effectiveness of adjuvant nivolumab in patients with resected Stage III or IV melanoma with lymph node involvement or metastatic disease. CheckMate 238 compared nivolumab versus ipilimumab and so an ITC was required to provide estimates of the effectiveness of nivolumab versus routine surveillance, as requested by the NICE final scope. One study, CA184-029, was identified as suitable for inclusion in the ITC to provide a link between nivolumab and routine surveillance, which investigated ipilimumab compared to placebo (i.e., placebo being used as a surrogate for routine surveillance) in patients with completely resected Stage III melanoma.[21] CA184-029 and the ITC are discussed further in Section 4.4. CheckMate 238 was assessed to be of high methodological quality by both the company and the ERG, and the study methodology is discussed in detail in Section 4.2.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Clinical effectiveness evidence presented in the CS for nivolumab is based on CheckMate 238, an international double-blind phase III RCT. The primary objective of CheckMate 238 was to compare RFS assessed by investigator, in patients treated with nivolumab versus ipilimumab following complete surgical resection of Stage III or Stage IV melanoma. Table 5 provides a summary of the key methodological features of CheckMate 238 which are discussed further in Sections 4.2.1 to 4.2.4.

Table 5. Summary of methodology, CheckMate 238 (reproduced from CS Document B Table 4, pages 19–21)

Characteristic	CheckMate 238
Location	130 centres in 25 countries including Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Finland, France, Greece, Hungary, Ireland, Italy, Japan, Korea, the Netherlands, Norway, Poland, Romania, South Africa, Spain, Sweden, Switzerland, Taiwan, the UK and the US.
Trial design	A multinational, randomised, double-blind, active-controlled, Phase III trial. Patients were randomised in a 1:1 ratio through an IVRS using a permuted block design, with stratification by PD-L1 status (positive vs negative/indeterminate) and AJCC Stage at screening (Stage IIIB/C vs Stage IV M1a-M1b vs Stage IV M1c).
Eligibility criteria for participants	Men and women aged ≥15 years were included if they met the following criteria: •Stage IIIB, IIIC or IV melanoma as per AJCC 7th edition (as detailed in Appendix L) •Histologically confirmed melanoma with metastases to regional lymph nodes or distant metastases that had been surgically resected •ECOG score of 0 or 1

	•Complete regional lymphadenectomy or resection required within 12 weeks before randomisation •Disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomisation with complete set of radiographic images available before randomisation •PD-L1 expression classification •Prior CNS metastases must be without evidence of recurrence for at least 4 weeks after treatment. Patients must be off immunosuppressive doses of systemic steroids for at least 14 days prior and must have returned to neurological baseline post-operatively. •Prior surgery that requires general anaesthesia must be completed at least 4 weeks before study drug administration. •WBCs ≥2,000/µl, neutrophils ≥1,500/µl, platelets ≥100x10^3/µl, haemoglobin ≥9.0g/dl, serum creatinine ≤1.5xULN or creatinine clearance >40ml/minute, AST and ALT ≤3xULN, total bilirubin ≤1.5xULN •Negative pregnancy test in women of childbearing potential and women must not be breastfeeding •Agreement to follow instructions for methods of contraception •Signed written informed consent Patients were excluded from the study if they met any of the following criteria: •Ocular or uveal melanoma •Carcinomatosis meningitis •History of autoimmune disease •Previous non-melanoma cancer without complete remission for more than 3 years •Systemic use of glucocorticoids •Previous systemic therapy for melanoma •Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the patient to receive protocol therapy •Any positive test for hepatitis B or C virus •Known history of testing positive for HIV or AIDS •History of Grade ≥3 allergy to human monoclonal antibodies
Settings and locations where the data were collected	An independent DMC was set up to provide independent oversight of safety, efficacy and study conduct. The DMC reviewed RFS data at the planned interim analyses. Data were collected locally by fully trained investigators. Site monitoring and pre-specified data validation checks were regularly conducted to ensure data quality.
Trial drugs	Nivolumab 3mg/kg Q2W. Ipilimumab 10mg/kg Q3W for four doses then Q12W. Treatment was administered for 1 year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent.
Permitted and disallowed concomitant medication	The following medications were prohibited during the treatment and follow-up phases: •Immunosuppressive agents •Immunosuppressive doses of systemic corticosteroids •Any concurrent systemic anti-neoplastic therapy for the treatment of melanoma or a new malignancy Patients were permitted the use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). Physiological replacement doses of systemic corticosteroids were permitted even if >10mg daily prednisone. A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions was permitted. Intravitreal injections of VEGF inhibitors were permitted if used according to the approved ocular indication, such as macular degeneration.
Primary outcomes (including scoring methods and timings of assessments)	RFS, defined as the time from randomisation until the date of the first recurrence (local, regional or distant metastasis), new primary melanoma, or death from any cause (whichever occurred first). Patients were assessed for recurrence every 12 weeks for the first 2 years after randomisation, and every 6 months thereafter until 5 years had elapsed. Assessments included a physical examination, CT and MRI scan.

Other outcomes used in the economic model/specified in the scope	DMFS, determined based on the first date of distant metastasis provided by the investigator and was defined as the time between the date of randomisation and the date of first distant metastasis or death, whatever the cause.[a] AEs according to the CTCAE v4.0. Immune-mediated AEs were determined on the basis of a prespecified list of terms from the MedDRA. HRQL according to the EORTC QLQ-C30 and the EQ-5D. HRQL was assessed at baseline, Weeks 5, 7, 11, 17, 25, 37 and 49, and then at two follow-up visits.
Abbreviations: AEs, adverse events; AJCC, American Joint Committee on Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DMC, data monitoring committee; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30; HRQL, health-related quality of life; IVRS, interactive voice response system; MRI, magnetic resonance imaging; RFS, recurrence-free survival; VEGF, vascular endothelial growth factor; WBC, white blood cell.	

4.2.1 Trial conduct

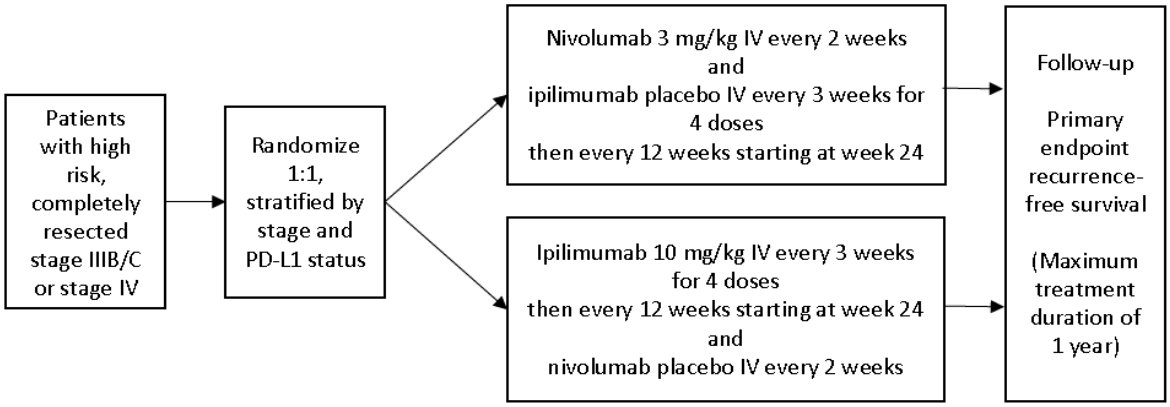
CheckMate 238 was an international randomised, double-blind, phase III trial of nivolumab compared with ipilimumab as adjuvant therapy in patients with completely resected Stage IIIB, IIIC or IV melanoma.[1] The company reported that CheckMate 238 was conducted at 130 centres in 25 countries, including 9 sites in England and Wales.

Patients were enrolled in CheckMate 238 between 30 March 2015 and 30 November 2015 and were required to be a minimum of 15 years old and to have Stage IIIB, IIIC or IV melanoma, according to the 2009 classification of the American Joint Committee on Cancer (AJCC) 7th edition.[1] However, as discussed in Section 3.1, only patients aged 18 or over were actually enrolled into the trial and the AJCC classification has recently been updated to the 8th edition[12] which means some Stage IIIA patients were enrolled.

Patients in CheckMate 238 were randomised 1:1 to nivolumab or ipilimumab study arms using an interactive voice response system (IVRS). The randomisation was stratified according to disease stage and programmed death receptor ligand-1 (PD-L1) status. The company focused their report in the CS on the 18-month follow-up data-cut of May 2017, although some results using 24-month follow-up data from December 2017 were also provided. The ERG reports only the latter data-cut, although in some instances the December 2017 data were not provided in the CS and so the May 2017 data-cut is used by the ERG where necessary. The Consolidated Standards of Reporting Trials (CONSORT) diagram provided in Appendix D of the CS indicates that, at the interim data-cut in May 2017, a total of 906 patients had undergone randomisation resulting in 453 patients in each of the nivolumab and ipilimumab groups. As discussed in Section 4.1.4, there was an imbalance in the reasons for discontinuation from study drug between the two study arms. Based on the May 2017 data-cut, 275 patients in the nivolumab arm had discontinued study drug with the most common reasons for discontinuation being disease recurrence (121 patients) and study drug toxicity (41 patients). In the ipilimumab arm, 331 patients discontinued with the most common reason being study drug toxicity (208 patients) and the second most common reason was disease recurrence (101 patients).

The interventions in CheckMate 238 comprised an active drug (nivolumab or ipilimumab) as well as a placebo for the alternative drug (ipilimumab placebo or nivolumab placebo) as depicted in Figure 2. Study drug treatment was continued up to a maximum of one year.

Figure 2. Study design schematic, CheckMate 238 (reproduced from CS Document B, Figure 2)



Abbreviations: IV, intravenous; PD-L1, programmed death receptor ligand-1.
Source: Weber *et al.* 2017[1]

The primary endpoint in CheckMate 238 was investigator assessed RFS and was defined as the time from randomisation until the date of the first recurrence (local, regional or distant metastasis), new primary melanoma, or death from any cause.[1] The company reported that they considered RFS to be the most relevant endpoint in the adjuvant setting, as they consider the aim of adjuvant treatment is to prevent systemic disease progression. The company also reported that they considered assessment by investigator to be more clinically relevant and more closely resembling of real world practice compared to independent assessment. The company acknowledged that OS is also clinically meaningful, but argued that in the adjuvant setting it would require extended follow-up and is confounded by subsequent treatments; it was therefore chosen as a secondary endpoint rather than the primary endpoint in CheckMate 238. Other secondary endpoints included safety, RFS according to tumour PD-L1 expression, and health-related quality of life (HRQoL). OS data were not presented in the CS, which the company claimed was due to immaturity of follow-up at the time of database lock. [redacted] DMFS was also reported in the CS and was an exploratory endpoint in CheckMate 238.

Follow-up assessments for recurrence in CheckMate 238 were scheduled to take place every 12 weeks for the first 2 years after randomisation and then every 6 months for the following 3 years. The ERG notes that, based on the 15 May 2017 data-cut, all 905 treated patients had discontinued or completed the 12-month study drug period with 393 and 379 patients in the nivolumab and ipilimumab arms respectively, remaining under ongoing study follow-up. The median number of study drug doses received was 24 (range: 1–26) in the nivolumab group and 4 (range: 1–7) in the ipilimumab group, and

although the difference in dosing regimens means a difference in median study drug doses is to be expected, the ipilimumab group still received fewer doses compared to the nivolumab group when treatment duration is also taken into consideration: The median treatment duration was [redacted] for the nivolumab group and [redacted] for the ipilimumab group.[22] The protocol stipulated that patients could receive up to one year of treatment, and 60.8% of patients in the nivolumab group achieved the full one year treatment, whereas only 26.9% of those in the ipilimumab group achieved the full one year of treatment. The ERG's clinical experts reported that this low completion rate for ipilimumab was not unexpected given its toxicity profile and the reasons for study drug discontinuation also reflect the toxic nature of ipilimumab.

The company provided details of the subsequent anti-cancer therapies patients had received following randomised study drug discontinuation, although this was based on the December 2017 data-cut (i.e. after a minimum of 24 months' follow-up). At the December 2017 data-cut, a total of [redacted] patients ([redacted]) from the nivolumab group and [redacted] patients ([redacted]) from the ipilimumab group had received subsequent melanoma anti-cancer therapies (Table 6).[20] The company provided a further breakdown of the anti-cancer therapies used at first-line and second-line for patients with disease recurrence during the clarification question stage, although unfortunately this was based on the 18-month follow-up data from the May 2017 data-cut. The ERG therefore considers the data presented in Table 6 to be of most relevance to the decision problem. The subsequent therapy data indicate an imbalance between the nivolumab and ipilimumab groups in the mechanism of action of subsequent therapies as well as differences in the specific immunotherapy used, where subsequent immunotherapies were used. For example, patients randomised to nivolumab were [redacted]

The ERG's clinical experts reported that they were unsure as to what treatments would routinely be used following disease progression in patients who have received adjuvant nivolumab, as adjuvant therapy is not currently given in the UK. However, they considered that the subsequent therapies used in CheckMate 238 were reasonable and that the difference in subsequent immunotherapy use between the CheckMate 238 study arms could be explained by the drugs mechanisms of actions: pembrolizumab and nivolumab both act as programmed death-1 (PD-1) receptor inhibitors whereas ipilimumab is a cytotoxic T-lymphocyte-associated protein (CTLA)-4 receptor inhibitor (patients in the ipilimumab arm were most likely to receive pembrolizumab as subsequent immunotherapy whereas in the nivolumab arm patients were most likely to receive ipilimumab on disease recurrence). The ERG's clinical experts reported that patients who were BRAF positive would receive BRAF plus MEK or less commonly single agent BRAF inhibitor treatment but with regards BRAF-negative patients and immunotherapies

it was less clear. One of the ERG's clinical experts reported that nivolumab may be more likely to be given if recurrence occurred more than six months after the last nivolumab dose and ipilimumab is less favoured due to its worse adverse event (AE) profile. The ERG's clinical experts did, however, report that the types of subsequent therapies given in CheckMate 238 were likely to be generally consistent with the types used in UK clinical practice although BRAF + MEK combination is now used more frequently than single agent BRAF.

Table 6. Subsequent therapy, ITT population, CheckMate 238, 24-months' follow-up (reproduced from CS Document B Table 17, page 83)

N (%)	Nivolumab (n=453)	Ipilimumab (n=453)
Any	141 (31.1)	186 (41.1)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

4.2.2 Baseline characteristics

The baseline characteristics for each trial arm in CheckMate 238 appear to be well balanced between the two trial arms (Table 7). The ERG notes from the CS that patients had a median age of 55 years, and the majority of patients were white (95%) and male (58%). The company response to clarification suggests that approximately 50% of randomised patients in CheckMate 238 were from Western Europe sites and less than 10% of the randomised patients were from UK sites (n=68).

With regards to disease Stage in relation to the AJCC 7th edition, most patients had Stage IIIC disease (47%), and the remaining patients had Stage IIIB disease (34%) or Stage IV disease (19%). PD-L1 expression <5% was identified in 62% of patients, and 45% of patients were BRAF-wildtype positive. The ERG's clinical experts reported that the baseline characteristics of patients in CheckMate 238 were broadly in keeping with the expected equivalent population in England. The ERG notes the change in

AJCC staging criteria and that the impact of this on the generalisability and applicability of the results of CheckMate 238 is unclear (as discussed in Section 3.1). The ERG and its clinical experts also consider the low number of patients from UK sites to potentially limit the applicability and generalisability of the results of CheckMate 238 to the UK, although again the impact of potential differences in melanoma risk, pathology and disease course between countries on the efficacy of nivolumab is unknown.

Table 7. Baseline characteristics, all randomised patients, CheckMate 238 (reproduced from CS Document B Table 5, page 22)

	Nivolumab (n=453)	Ipilimumab (n=453)
Median age (range):	56 (19–83)	54 (18–86)
Disease Stage, n (%):		
IIIB	163 (36.0)	148 (32.7)
IIIC	204 (45.0)	218 (48.1)
IV	82 (18.1)	87 (19.2)
Other or NR	4 (1.0)	0
Type of lymph node involvement in Stage III, n (%):		
Microscopic	125/369 (33.9)	134/366 (36.6)
Macroscopic	219/369 (59.3)	214/366 (58.5)
NR	25/369 (6.8)	18/336 (4.9)
Tumour ulceration in Stage III, n (%):		
Yes	153/369 (41.5)	135/366 (36.9)
No	201/369 (54.5)	216/366 (59.0)
NR	15/369 (4.1)	15/366 (4.1)
Metastasis in Stage IV, n (%):		
M1a	50/82 (61.0)	51/87 (58.6)
M1b	12/82 (14.6)	15/87 (17.2)
M1c with brain metastases	[redacted]	[redacted]
M1c without brain metastases	[redacted]	[redacted]
PD-L1 expression, n (%):		
<5%	275 (60.7)	286 (63.1)
≥5%	152 (33.6)	154 (34.0)
NR	26 (5.7)	13 (2.9)
BRAF status, n (%):		
Mutation	187 (41.3)	194 (42.8)
No mutation	197 (43.5)	214 (47.2)
NR	69 (15.2)	45 (9.9)

Abbreviations: NR, not reported; PD-L1, programmed death receptor ligand-1.
Source: Weber *et al.*, 2017[1]; CheckMate 238 CSR[22]

4.2.3 Description and critique of statistical approach used

The hypothesis tested in CheckMate 238 was that, "*treatment with nivolumab will improve RFS compared to ipilimumab in patients with Stage IIIB, IIIC or IV melanoma*".

According to the CS, statistical analysis plans (SAPs) were developed and approved prior to study initiation. Time-to-event distributions were estimated using Kaplan–Meier (KM) techniques for RFS and DMFS. Comparison between treatment groups was performed using a log-rank test stratified by disease Stage and PD-L1 status at randomisation. Cox proportional hazards (PH) models, again stratified by disease stage and PD-L1 status at randomisation, were used to calculate the hazard ratio (HR) and confidence intervals (CIs) for RFS.

A sample of 800 patients was planned for a final analysis of RFS that was time-driven (rather than event-driven) at a minimum of 36 months of follow-up for all patients. The company reported that the initial power calculation was based on 507 recurrence events (for the primary analysis of RFS) and that this was revised to 450 for the final analysis. The 450 events were expected to provide 85% power to detect a HR for disease recurrence or death of 0.75 (under the 0.83 cut-off for significance) with an overall two-sided type I error rate of 0.05. The CS reported that at the data-cut off for the interim analysis in May 2017, 360 (80%) events had taken place.

The primary efficacy analyses were conducted on the intention-to-treat (ITT) population, defined as all randomised patients.[1] Safety analyses were conducted on all treated patients, which included all randomised patients who received at least one dose of study drug. Results presented within the CS were based on a clinical data cut-off of 15 May 2017, where there was a median follow-up of 19.5 months and a minimum follow-up of 18 months.[1] An updated analysis was requested by the European Medicines Agency (EMA), and the database lock for this updated analysis was 19 December 2017, where all patients had a minimum follow-up of 24 months.[20] The company provided the results of this updated analysis for RFS and DMFS in the CS although they weren't used in the economic model or ITC. In response to clarification questions, the company updated the ITC and economic model with these data.

In terms of censoring for RFS and DMFS, the company reported that where recurrence or distant metastases events had not occurred, patients were censored on the date of their last evaluable disease assessment or on the day of randomisation if they had not received any post-randomisation disease assessments. Patients who received subsequent anti-cancer therapy or reported second non-melanoma primary cancer without prior recurrence were also censored on the date of their last evaluable disease assessment.

The ERG notes that limited details on the statistical approaches used for analysing the HRQoL and AE data were provided in the CS. In addition, both data and the SAP detail were omitted for the outcome of OS, although some detail and outcome data were subsequently provided in the company's clarification questions response. The company reported that [redacted]

[redacted] The company highlighted that they consider this to be standard for adjuvant trials citing the timelines for the release of OS data from the CA184-029 study. The company also reported that [redacted]

Subgroup data were not requested by the NICE final scope, although RFS by PD-L1 status was a secondary outcome in CheckMate 238, and the company reported the results of the analysis along with other pre-specified subgroup analyses. The results and subgroup analyses reported in the CS are discussed further in Section 4.3.5.

In summary, the ERG considers the company's statistical approach for the trial level data analysis of CheckMate 238 appropriate although detail for outcomes other than RFS and DMFS was lacking. The ERG also notes the immaturity of the data presented in the CS for all outcomes, although especially for OS where median survival has not yet been reached. The ERG's critique on the statistical analysis relating to the ITC is provided in Section 4.4.

4.2.4 Summary statement

In summary, CheckMate 238, an international randomised, double-blind, phase III trial of nivolumab compared with ipilimumab as adjuvant therapy in patients with completely resected Stage IIIB, IIIC or IV melanoma provided the clinical effectiveness evidence for adjuvant nivolumab in the CS.[1] CheckMate 238 was conducted at 130 centres in 25 countries, including 9 sites in England and Wales. The ERG considers CheckMate 238 addressed the population, intervention and outcomes requested in the NICE final scope although it was for the comparison of nivolumab versus ipilimumab and not the required comparison of nivolumab versus routine surveillance. However, the company also conducted an ITC to enable estimates of nivolumab versus routine surveillance to be presented in the CS (discussed in Section 4.4).

A total of 906 patients were randomised in CheckMate 238, resulting in 453 patients in each of the nivolumab and ipilimumab groups; study drug treatment in both groups was continued up to a maximum of one year. The ERG notes that the median treatment duration was [redacted] for the nivolumab group compared to [redacted] for the ipilimumab group.[22] Based on a May 2017 data-cut, 275 patients in the nivolumab arm had discontinued study drug with the most common reason for discontinuation being disease recurrence (121 patients). In contrast, in the ipilimumab arm, 331 patients had discontinued by the May 2017 data-cut with the most common reason being study drug toxicity (208 patients). The ERG's clinical experts reported that these differences in reasons for study drug discontinuations were not unexpected given the known toxicity profile of ipilimumab.

The baseline characteristics for each trial arm in CheckMate 238 appear to be well balanced and the company response to clarification suggests that approximately [redacted] randomised patients in CheckMate 238 were from Western Europe sites although less than [redacted] the randomised patients were from UK sites. The ERG's clinical experts reported that the baseline characteristics of patients in CheckMate 238 were generally in keeping with those expected of the equivalent patients in the UK although the ERG notes that only Stage IIIB, IIIC or IV melanoma patients were enrolled in CheckMate 238 when defined using the AJCC 7th edition.[1] However, the AJCC classification has recently been updated to the 8th edition[12] which means some Stage IIIA patients were also enrolled.

At the December 2017 data-cut, a total of 141 patients (31.1%) from the nivolumab group and 186 patients (41.1%) from the ipilimumab group had received subsequent melanoma anti-cancer therapies. The ERG's clinical experts reported that they were unsure as to what treatments would routinely be used following disease progression in patients who have received adjuvant nivolumab, as adjuvant therapy is not currently given in the UK. However, they considered that the subsequent therapies used in CheckMate 238 were reasonable. For the outcomes of RFS and DMFS, patients who received

subsequent anti-cancer therapy or reported second non-melanoma primary cancer without prior recurrence were censored on the date of their last evaluable disease assessment. However, the ERG notes that the impact of subsequent therapies affects the outcome of OS.

The ERG considers the company's statistical approach appropriate and reasonably well described for the primary outcome of RFS. However, the ERG considers it important to highlight the immaturity of the some of the data presented in the CS, especially OS where median survival has not yet been reached; [redacted]

4.3 Clinical effectiveness results

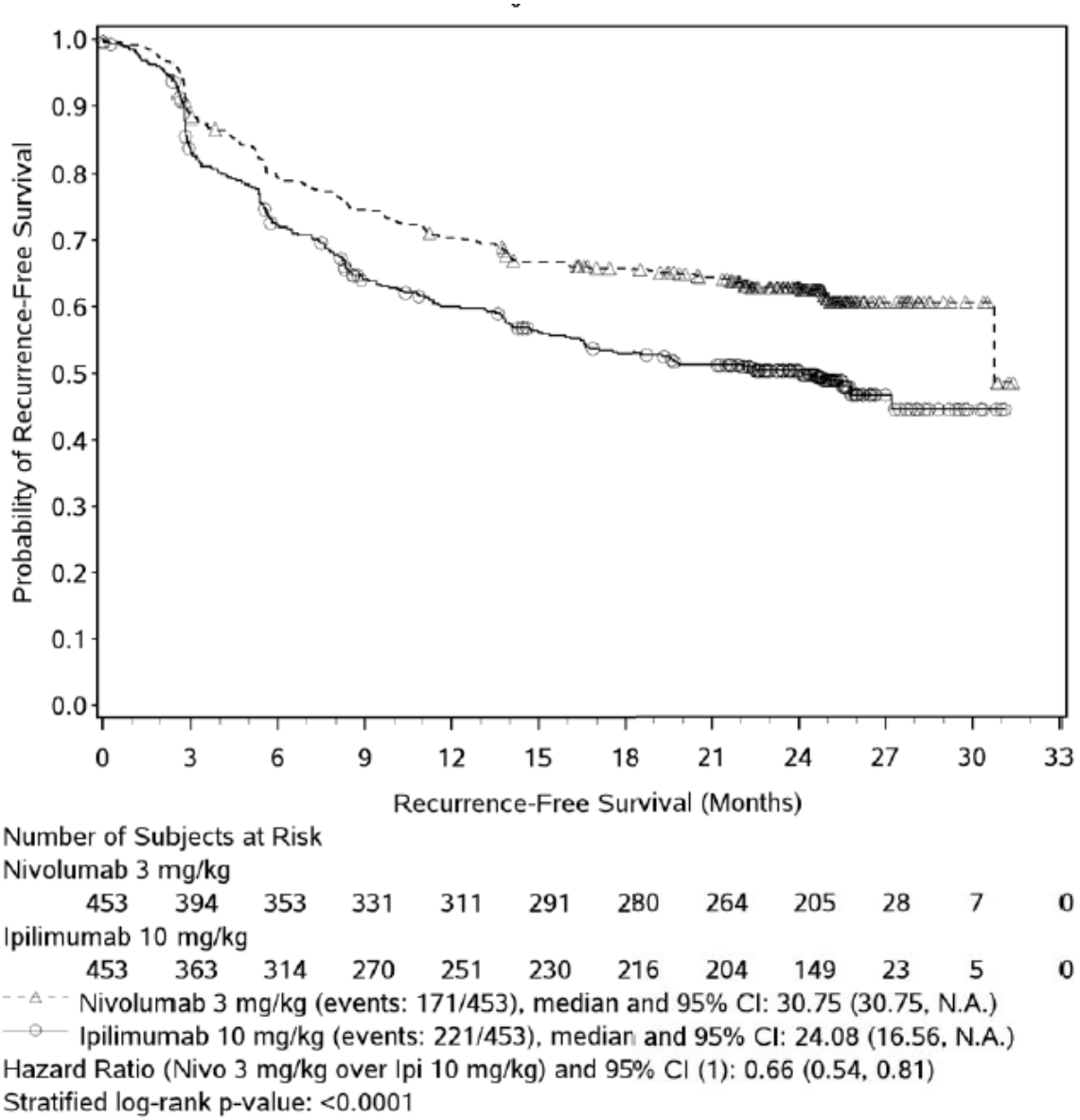
4.3.1 Recurrence-free survival (RFS)

RFS was the primary outcome in CheckMate 238 and data from an 18-month follow-up data cut (15 May 2017) and a 24-month follow-up (19 December 2017) were provided in the CS. The ERG presents only the later data-cut but acknowledges the results of the 18-month data-cut are in keeping with the 24-month results.

Following a minimum of 24 months' follow-up, nivolumab demonstrated a statistically significant improvement in RFS compared to ipilimumab (HR 0.66; 95% CI: 0.54 to 0.81; $p<0.0001$ [Figure 3]). Investigator-assessed disease recurrence or death was reported in 171 (37.7%) and 221 (48.8%) patients treated with nivolumab and ipilimumab, respectively.

Median RFS was reached at 30.8 months (95% CI: 30.8 to NA) in the nivolumab arm, and 24.1 months (95% CI: 16.6 to NA) in the ipilimumab arm. The company and the ERG consider it important to highlight that although median RFS has been reached, the data are still immature, with heavy censoring in the KM curve (Figure 3).

Figure 3. KM curve for RFS, ITT population, CheckMate 238, 24-month follow-up (reproduced from CS Document B, Figure 4)



Abbreviations: CI, confidence interval; ITT, intention-to-treat; KM, Kaplan–Meier; RFS, recurrence-free survival.
Source: BMS Data on File, 2018[20]

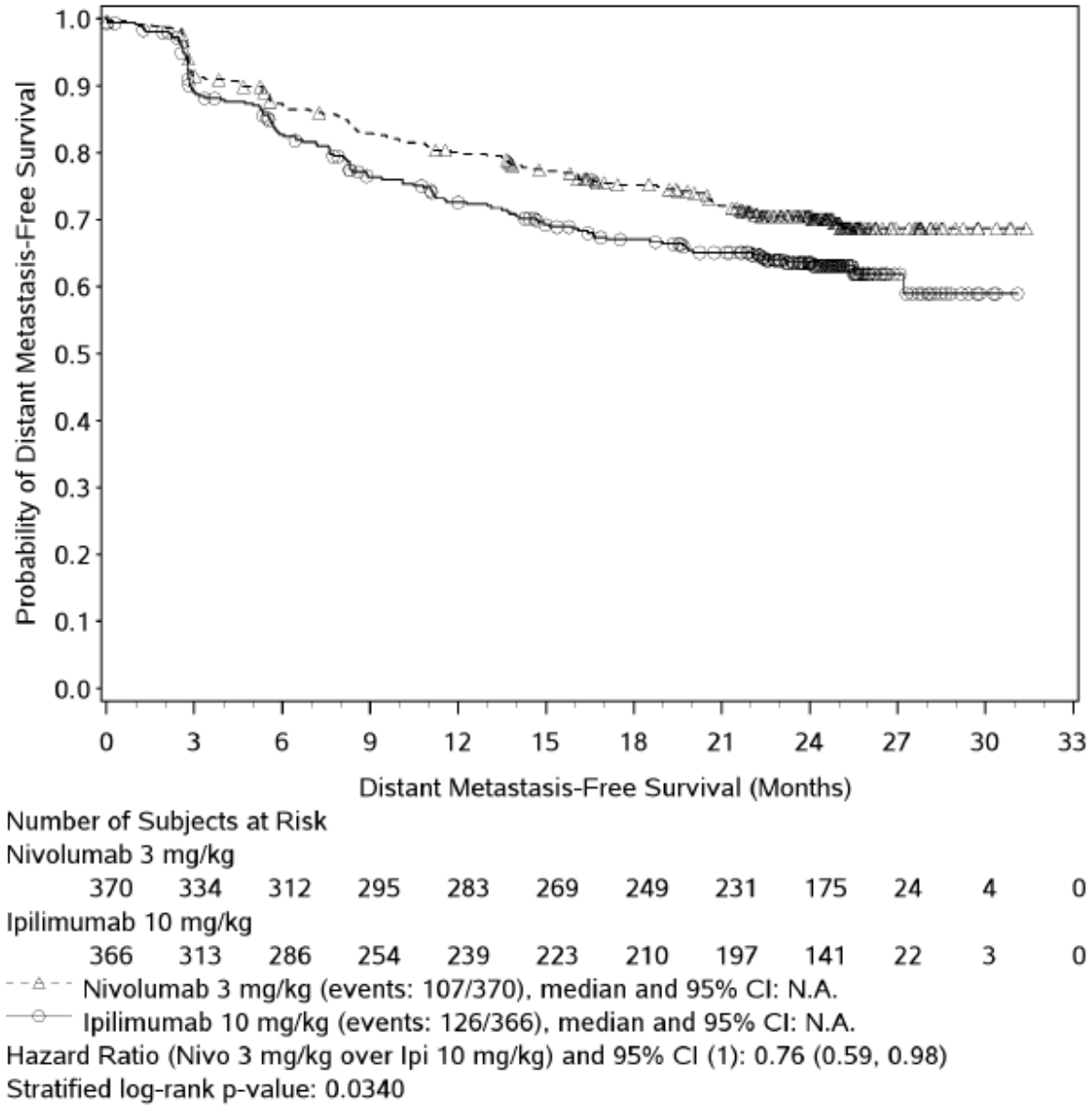
The company also reported the 12-, 18- and 24-month RFS rates for each treatment group. The rates for the nivolumab group were 70.4% (95% CI: [redacted] 65.8% (95% CI: [redacted] and 62.6% (95% CI: [redacted]), respectively. For ipilimumab, the respective rates were 60.0% (95% CI: [redacted], 53.0% (95% CI: [redacted]), 50.2% (95% CI: [redacted].

4.3.2 Distant metastasis-free survival (exploratory outcome)

In the CS, 18-month and 24-month follow-up data were presented for the exploratory outcome of DMFS in CheckMate 238. The median DMFS was not reached in either treatment group in the 19 December 2017 data-cut, in which there was a minimum of 24 months' follow-up. There was, however, a

statistically significant difference between the treatment groups with a significantly longer DMFS observed in the nivolumab group compared to in the ipilimumab group (HR: 0.76; 95% CI: 0.59 to 0.98 [Figure 4]). DMFS rates were also consistently higher in the nivolumab group than in the ipilimumab group at 12 months (80.1% versus 72.7%, respectively), 18 months (75.2% versus 67.1%, respectively) and 24 months (70.5% versus 63.7%, respectively).[22]

Figure 4. KM curve for DMFS, ITT population, CheckMate 238, 24-month follow-up (reproduced from CS Document B, Figure 11)



Abbreviations: CI, confidence interval; DMFS, distant metastasis-free survival; ITT, intent-to-treat; KM, Kaplan–Meier; N.A, not applicable.
Source: BMS Data on File, 2018[20]

4.3.3 Overall survival

In the company's response to clarification questions, [redacted]

[redacted]

Figure 5. CheckMate 238 [redacted]


[redacted]

4.3.4 Health-related quality of life (secondary outcome)

The HRQoL results for CheckMate 238 reported in the CS were based on the minimum of 18-months' follow-up data (i.e. 15 May 2017 data-cut) and comprised data gathered using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EQ-5D® questionnaire. The questionnaires were administered at baseline, during the treatment period and at two follow-up visits, the first at 30 days after the last study drug dose and

the second approximately 84 days after the first follow-up visit. The questionnaire completion rates during the treatment period exceeded 80% and, although it dropped during the follow-up period, it was still generally above 70%.

The company did not report any numerical data for HRQL in the clinical effectiveness review section of the CS although they reported that "*HRQL scores were maintained after treatment in both groups with respect to the score on the EORTC QLQ-C30 Global Health Status or on any of the individual scales, as well as to scores on the EQ-5D utility index and the EQ-5D visual analogue scale (VAS)*".[1] The company also reported in the CS that Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) mean summary scale scores demonstrated "*no clinically meaningful deterioration or improvement*" at any time point for either treatment group. The ERG therefore concludes that there were no significant differences in HRQL with nivolumab compared to ipilimumab in CheckMate 238.

4.3.5 Subgroup analyses of RFS

4.3.5.1 PD-L1 status

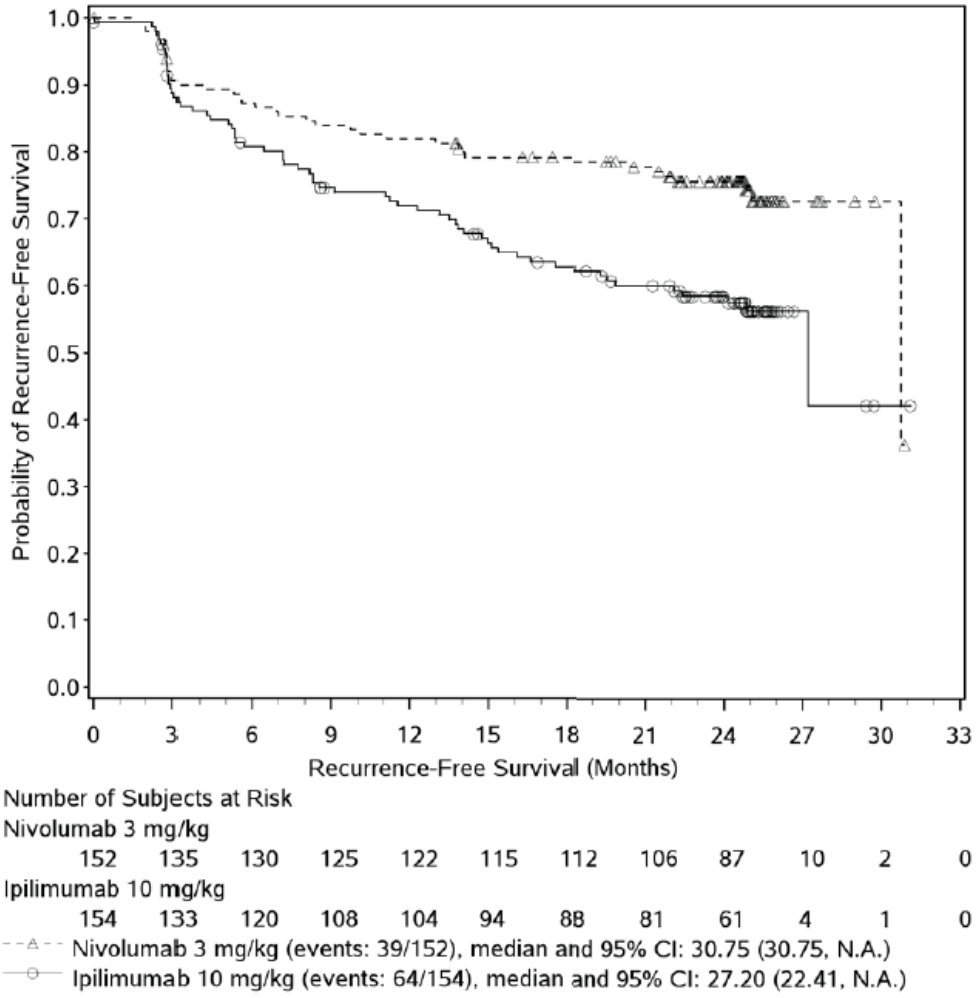
Subgroup analyses of RFS according to tumour PD-L1 expression was a pre-specified secondary endpoint in CheckMate 238 and patients were stratified at baseline for PD-L1 ≥ 5% and PD-L1 < 5%. The ERG notes that it can be challenging to obtain an accurate measurement of PD-L1, a protein on the cell surface of immune and tumour cells which may be up or down regulated by a variety of internal and external factors including prior treatment with other therapies. In addition, the ERG notes that it is not routinely measured in melanoma patients in the UK. However, the ERG considers the results of CheckMate 238 to suggest a trend toward a greater RFS benefit with adjuvant nivolumab compared to ipilimumab in those patients with PD-L1 ≥ 5% although the ERG acknowledges that treatment with nivolumab was favoured in both the PD-L1 ≥ 5% and PD-L1 < 5% subgroups ([redacted]). The ERG notes that [redacted] PD-L1 subgroup analyses (i.e. [redacted] ≥ 5% and [redacted] baseline PD-L1 expression) using the minimum 18-month follow-up data set, nivolumab was associated with a [redacted] compared to ipilimumab although the recurrence rates [redacted] PD-L1 expression level ([redacted]).

Figure 6. Forest plot of RFS by PD-L1 expression level, CheckMate 238, 18-month follow-up (reproduced from CS Document B, Figure 7)

Abbreviations: CI, confidence interval; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: BMS Data on File, 2017[23]

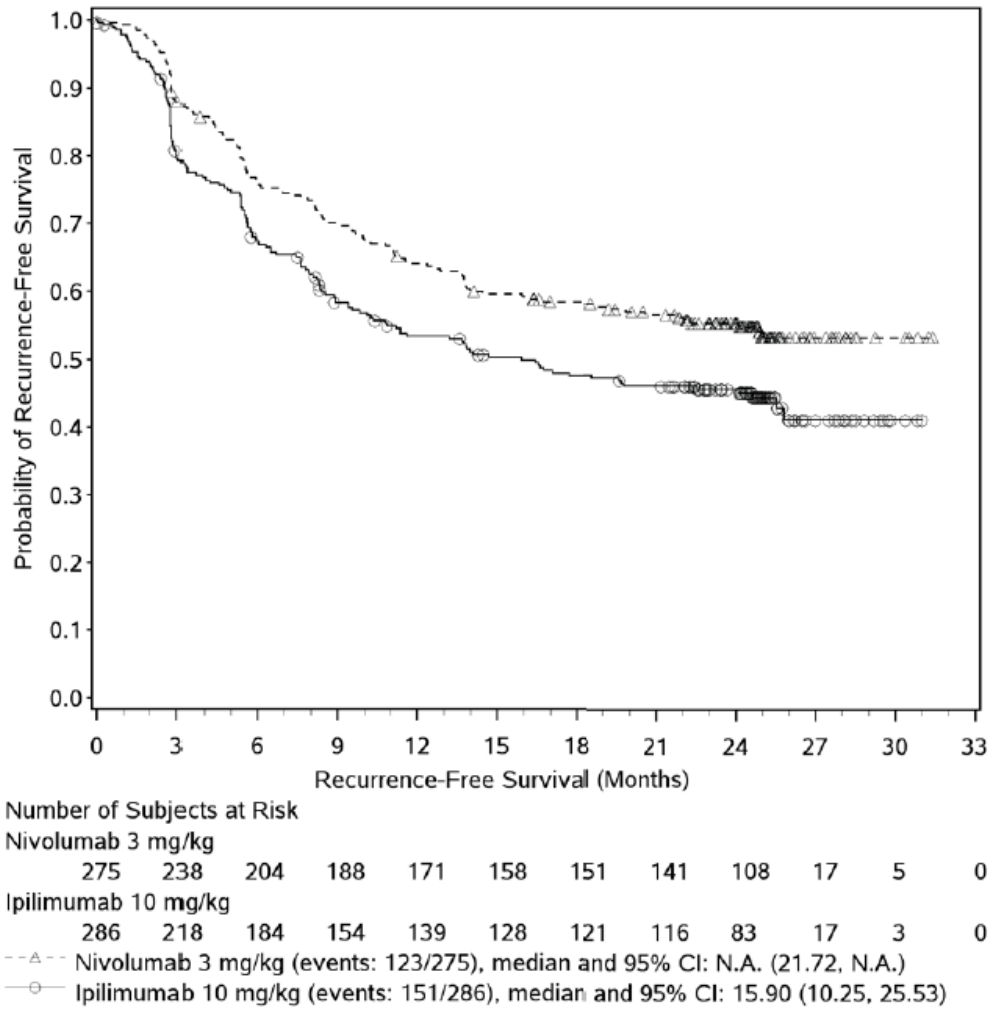
The company presented additional data on RFS for the ≥ 5% PD-L1 and < 5% PD-L1 subgroups using the minimum 24-months' follow-up data set (Data-cut: 19 December 2017). The median RFS for the patients with ≥ 5% PD-L1 expression was 30.8 months (95% CI: 30.8 to NA) in the nivolumab arm and 27.2 months (95% CI: 22.4 to NA) in the ipilimumab arm, resulting in a HR of 0.54 (95% CI: 0.36 to 0.81) (Figure 7).[20] In comparison, median RFS was not reached in the nivolumab arm of the < 5% PD-L1 subgroup (95% CI: 21.7 to NA) and was 15.9 months (95% CI: 10.3 to 25.5) in the ipilimumab arm, resulting in a HR of 0.73 (95% CI: 0.57 to 0.92) (Figure 8). The ERG notes that there is heavy censoring at the tails of the KM curves and therefore considers it difficult to draw any conclusions on these data. The ERG does, however, consider the trend in higher RFS rates in patients with ≥ 5% PD-L1 expression compared to those with < 5% PD-L1 seen in the 18-month data to also be present in these 24-month results and that it affects both the nivolumab and ipilimumab treatment groups, although in both subgroups RFS rates are higher with nivolumab compared to with ipilimumab.

Figure 7. KM curve for RFS, ≥ 5% PD-L1 expression, CheckMate 238, 24-month follow-up (reproduced from CS Document B, Figure 8)



Abbreviations: CI, confidence interval; KM, Kaplan–Meier; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: BMS Data on File, 2018[20]

Figure 8. KM curve for RFS, < 5% PD-L1 expression, CheckMate 238, 24-month follow-up (reproduced from CS Document B, Figure 9)



Abbreviations: CI, confidence interval; KM, Kaplan–Meier; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: BMS Data on File, 2018[20]

4.3.5.2 Staging and RFS

As discussed in Section 3.1, patients in CheckMate 238 were classified by disease stage based on the AJCC 7th edition which followed clinical practice at the time of initiation of the RCT, whereas the AJCC 8th edition is now the standard for staging melanoma. The 8th edition of AJCC places more prognostic important on Breslow thickness than lymph node involvement. The largest shift is an upstaging of patients with thicker Breslow from IIIA to IIIB or IIIC under the new staging system. Some patients with low Breslow and 2-3 microscopic deposits will however shift stage from IIIB to IIIA under the new staging system. This change in AJCC staging definitions means that a subset of the [redacted] CheckMate 238 patients who were defined as Stage IIIB using the AJCC 7th edition would now be considered Stage IIIA as per AJCC 8th edition (N=[redacted]) and a further subset would now be classified as Stage IIIC/IIID (N = not reported in the CS).

The ERG notes that using the AJCC 7th edition Staging and the 18-month follow-up dataset, there was a consistent trend with fewer recurrence events with nivolumab compared to ipilimumab across Stage IIIB, IIIC, and IV M1a and M1b subgroups, although the only subgroup that reached statistical significance was the Stage IIIC subgroup (HR 0.65; 95% CI: 0.49 to 0.87; Figure 9).

The ERG also notes that the company reported the RFS results for the [redacted] reclassified Stage IIIA patients (per AJCC 8th edition) in CheckMate 238 and that they demonstrated [redacted] between nivolumab and ipilimumab (minimum follow-up of [redacted], HR nivolumab versus ipilimumab: [redacted] However, the ERG also acknowledges that the subgroup was small and not powered to detect statistically significant differences in treatment effects.

4.3.5.3 Geographic region

The ERG notes that patients in CheckMate 238 were not stratified by geographic region and the patient numbers across some of the subgroups are small and therefore it is not feasible to draw conclusions based on geographic region. However, the ERG agrees with the company that the [redacted] (Table 8). [redacted]

[redacted]

	Nivolumab Survival Rate (95% CI)	Ipilimumab Survival Rate (95% CI)
Population ITT	[redacted]	[redacted]
6-Month	[redacted]	[redacted]
12-Month	[redacted]	[redacted]
18-Month	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]
6-Month	[redacted]	[redacted]
12-Month	[redacted]	[redacted]
18-Month	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Western Europe	[redacted]	[redacted]
6-Month	[redacted]	[redacted]
12-Month	[redacted]	[redacted]
18-Month	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Eastern Europe	[redacted]	[redacted]

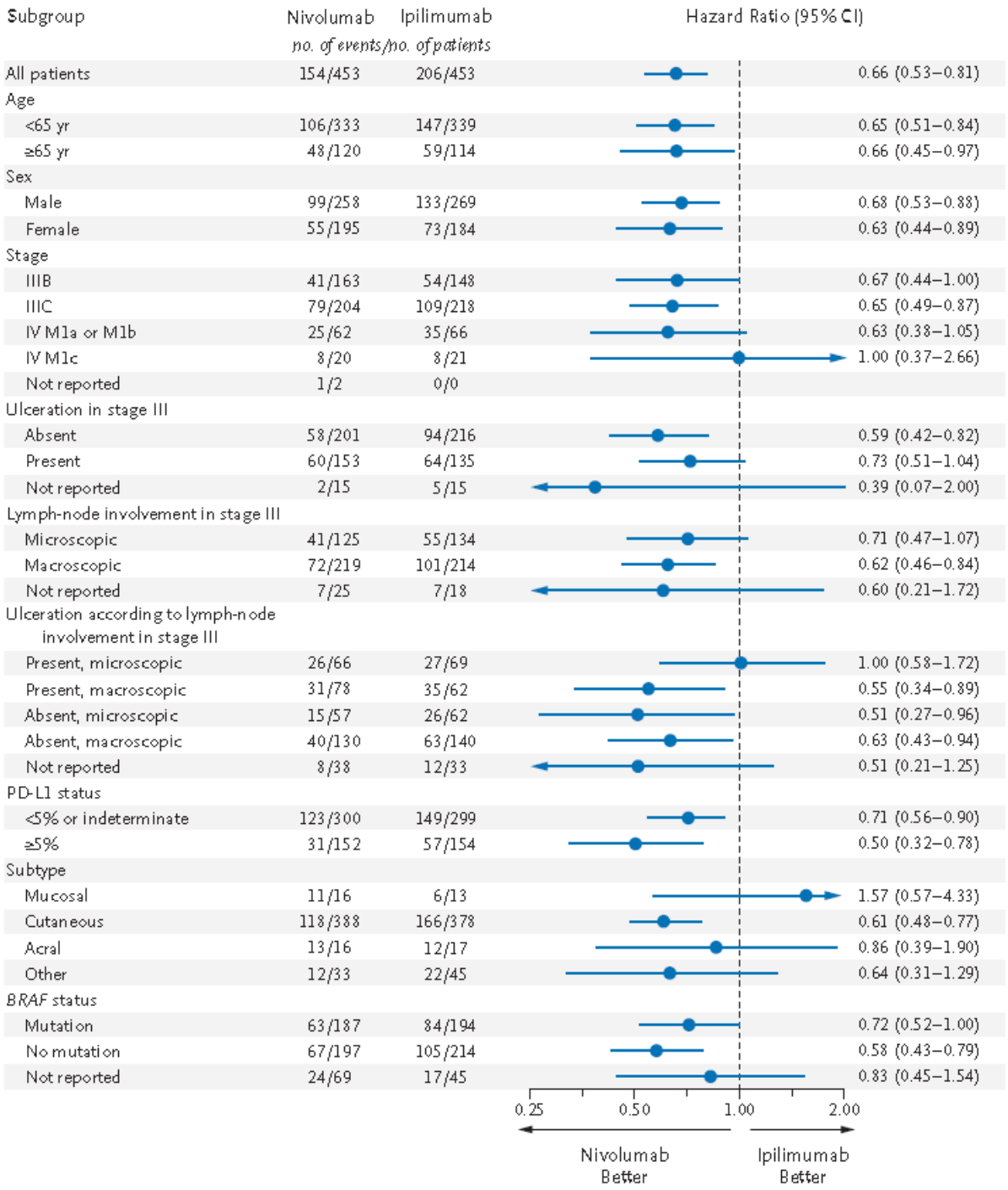
6-Month	[redacted]	[redacted]
12-Month	[redacted]	[redacted]
18-Month	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]
6-Month	[redacted]	[redacted]
12-Month	[redacted]	[redacted]
18-Month	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Australia	[redacted]	[redacted]
6-Month	[redacted]	[redacted]
12-Month	[redacted]	[redacted]
18-Month	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITT, intension-to-treat; N, number of patients.

4.3.5.4 Other subgroup analyses - RFS

The company provided a forest plot with the RFS results for the additional pre-specified subgroup analyses conducted after a minimum of 18-months' follow-up (15 May 2017 data-cut; Figure 9). The ERG notes that the results of these analyses are generally consistent with the overall trial analysis of RFS, with the exception of the subgroups of patients with mucosal melanoma, Stage IV M1c disease, and those with ulceration present plus microscopic lymph node involvement. The ERG also notes that several of the other subgroups failed to demonstrate a statistically significant benefit of nivolumab over ipilimumab but acknowledges that there were small patient and event rates in many of the subgroups and they were not adequately powered to detect statistically significant differences in treatment effects.

Figure 9. Forest plot of RFS subgroup analyses, ITT population, CheckMate 238, 18-month follow-up (reproduced from CS Document B, Figure 12)



Abbreviations: CI, confidence interval; ITT, intention-to-treat; PD-L1, programmed death receptor ligand-1; RFS, recurrence-free survival.
Source: Weber *et al.*, 2017[1]

4.3.6 Adverse effects

The safety data presented in the CS related to the clinical cut-off of 15 May 2017 and, in response to a clarification question, the company reported that updated safety analyses were not available for the

December 2017 data-cut. However, the ERG notes that some AE data from the December 2017 data-cut were provided in the company's clarification response for the AE in the economic model (immune-related [any grade], diarrhoea [Grade ≥2] and any other Grade ≥3 AE). Due to the limited amount of AE data from the December 2017 data-cut, the ERG discusses both sets of results.

AEs were reported in nearly all of the patients in both the nivolumab and ipilimumab treatment groups of CheckMate 238, although they were of lesser severity with nivolumab compared to ipilimumab (Grade 3–4 AEs reported by 25.4% of nivolumab patients compared to 55.2% of ipilimumab patients; Table 9).[1] In addition, the AEs were more frequently deemed to be treatment-related with ipilimumab (95.8%) compared to nivolumab (85.2%) and to lead to treatment discontinuation (ipilimumab 41.7% compared to nivolumab 7.7%). The ERG's clinical experts reported that the AE results from CheckMate 238 are as expected and that they are consistent with the results seen for these drugs in the metastatic melanoma treatment setting.

Table 9. Summary of adverse events, all treated patients, CheckMate 238, 18-month follow-up (reproduced from CS Document B Table 18, page 84)

	Nivolumab (n=452)	Ipilimumab (n=453)
Any AE, n (%)	438 (96.9)	446 (98.5)
Grade 3–4	115 (25.4)	250 (55.2)
Any SAE, n (%)	79 (17.5)	183 (40.4)
Grade 3–4	[redacted]	[redacted]
Drug-related AE, n (%)	385 (85.2)	434 (95.8)
Grade 3–4	65 (14.4)	208 (45.9)
Drug-related SAE, n (%)	[redacted]	[redacted]
Grade 3–4	[redacted]	[redacted]
Discontinuations due to AEs, n (%)	44 (9.7)	193 (42.6)
Grade 3–4	21 (4.6)	140 (30.9)
Discontinuations due to drug-related AEs, n (%)	35 (7.7)	189 (41.7)
Grade 3–4	16 (3.5)	136 (30.0)
Treatment-related deaths, n (%)	0 (0)	2 (0.4)
Abbreviations: AE, adverse event; SAE, serious adverse event. Source: Weber *et al.*, 2017[1]; CheckMate 238 CSR[22]		

The company reported that the median time until the onset of treatment-related select AEs was generally shorter among patients receiving ipilimumab, although the time until the resolution of AEs was similar in the two groups, with the exception of skin disorders, which took longer to resolve in the nivolumab group.[1] The company provided a summary of treatment-related select AEs in Appendix F of the CS and the ERG notes that generally AEs occurred more frequently in the ipilimumab treatment group compared to the nivolumab group. Diarrhoea was reported in 24.3% of nivolumab-treated patients and 45.9% of ipilimumab-treated patients, with 1.5% and 9.5% classed as Grade 3–4, respectively. Thyroid

disorders were reported more frequently in the nivolumab arm (20.4%) compared to the ipilimumab arm (12.6%), with both hypothyroidism and hyperthyroidism more common with nivolumab.[1]

Immune-mediated AEs (IMAEs) were defined as "specific events occurring within 100 days of the last dose, which includes pneumonitis, diarrhoea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine abnormalities (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis)". The ERG notes that across both the nivolumab and ipilimumab treatment groups, the majority of IMAEs were [redacted] (Table 10).[22] The most frequently reported any-grade IMAEs were [redacted]. The most frequently reported Grade 3–4 IMAEs were [redacted]

Table 10. IMAEs, safety population, CheckMate 238, 18-month follow-up (reproduced from CS Document B Table 19, pages 85–86)

	Nivolumab (n=452)		Ipilimumab (n=453)	
	Total	**Grade 3–4**	**Total**	**Grade 3–4**
Endocrine				
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Adrenocortical insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]
Hypopituitarism	[redacted]	[redacted]	[redacted]	[redacted]
Lymphocytic hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Basedow's disease	[redacted]	[redacted]	[redacted]	[redacted]
Primary hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]
Type 1 diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]
Fulminant type 1 diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea/Colitis				
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune colitis	[redacted]	[redacted]	[redacted]	[redacted]
Enteritis	[redacted]	[redacted]	[redacted]	[redacted]
Enterocolitis	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis				
ALT increase	[redacted]	[redacted]	[redacted]	[redacted]
AST increase	[redacted]	[redacted]	[redacted]	[redacted]

Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increase	[redacted]	[redacted]	[redacted]	[redacted]
Drug-induced liver injury	[redacted]	[redacted]	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis				
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]	[redacted]	[redacted]
Nephritis and renal dysfunction				
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Tubulointerstitial nephritis	[redacted]	[redacted]	[redacted]	[redacted]
Rash				
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity/Infusion				
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; IMAE, immune-mediate adverse event.
Source: CheckMate 238 CSR[22]

The 24-month CheckMate 238 AE data for immune-relate (any grade) AEs, diarrhoea (Grade ≥2) and any other Grade ≥3 AE demonstrated [redacted] (Table 11).

[redacted]

	Immune-related (Any grade)	Diarrhoea (grade ≥2)	Other AEs (grade ≥3)
Nivolumab	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]	[redacted]	[redacted]

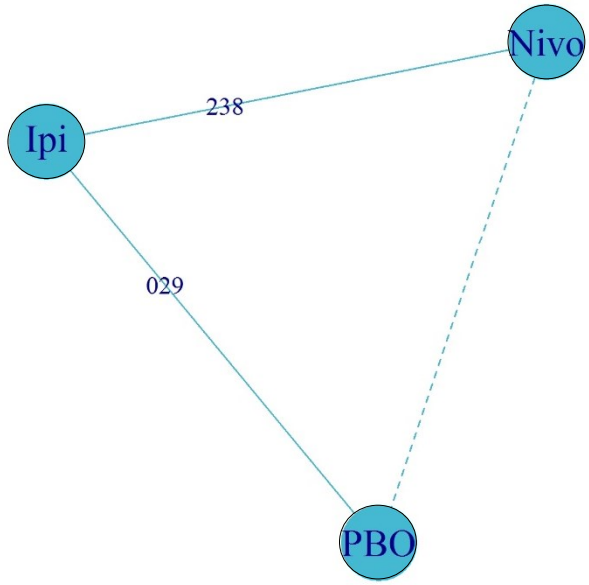
Abbreviations: AEs, adverse events; RR, relative risk.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As discussed in Section 4.1, there were no studies identified through the SLR that investigated adjuvant therapy with nivolumab in comparison to routine surveillance (i.e. placebo) in patients with completely resected Stage III and IV melanoma. However, two studies were identified to facilitate an ITC between nivolumab and placebo using ipilimumab as the common comparator (CheckMate 238 and CA184-029; Figure 10) and the company had access to PLD for both studies.

Figure 10. Available network of evidence (reproduced from CS Appendix D, Figure 2)



Abbreviations: Ipi, ipilimumab 10mg/kg; Nivo, nivolumab 3 mg/kg; PBO, placebo.
Notes: The dashed line indicates there is no direct evidence available, whereas the solid line indicates there is direct evidence available.

4.4.1.1 CA184-029

CA184-029 was a multinational, randomised, double-blind, Phase III study of adjuvant ipilimumab in patients with Stage III cutaneous melanoma who had undergone complete regional lymph node surgical removal.[2] Patients in CA184-029 were required to be at least 18 years of age and have histologically confirmed melanoma that was metastatic only to lymph nodes. The inclusion criteria of CA184-029, therefore, restricted the inclusion of patients to those with Stage IIIA, IIIB or IIIC melanoma and used the staging criteria from the AJCC 6th edition. The ERG notes from its clinical experts that there were no differences between the 6th and 7th editions (7th edition was used in the CheckMate 238 study) that would significantly affect the classification of Stage III patients in CA184-029. However, the ERG also notes that CA184-029 study restricted inclusion to patients with cutaneous melanoma, whereas in CheckMate 238 approximately 15% of patients had non-cutaneous cancer. The company reported that melanoma subtype was not found to be prognostic or a treatment effect modifier in CheckMate 238. The ERG does not consider this to be sufficient justification to assume it has no effect on treatment outcomes as the subgroup was not adequately powered for this purpose.

Patients in CA184-029 were randomly assigned to receive either ipilimumab 10mg/kg or placebo every 3 weeks for four doses, and then every 3 months up to a maximum of 3 years. Treatment was discontinued on disease recurrence, unacceptable toxicity, major protocol violation or treatment refusal. The ERG notes that the treatment dosing regimen of ipilimumab in CA189-029 was consistent with that of CheckMate 238 with the exception of the treatment duration; in CheckMate 238 treatment was for a maximum of one year, whereas in CA184-029 it was for up to 3 years. The patients in the ipilimumab

arms of both CA184-029 and CheckMate 238 received a median of four doses of ipilimumab although the range was wider for CA184-029 (range: 1–16) compared to CheckMate 238 (range: 1-7). The company reported in the CS that approximately [redacted] of patients continued ipilimumab treatment beyond 1 year in CA184-029 and the ERG notes that 26.9% of those in the ipilimumab group of CheckMate 238 achieved the full one year of treatment, although due to the study protocol they could not continue treatment beyond one year. The ERG considers that [redacted] of patients continuing treatment beyond one year in CA184-029 is a substantial proportion of patients and therefore requested at the clarification stage that the company appropriately account for this in their analyses. These analyses will be discussed alongside the results (Section 4.4.4).

Randomisation in CA184-029 was stratified by disease stage (Stage IIIA versus IIIB versus IIIC with 1–3 positive nodes versus IIIC with ≥4 positive nodes) and region of enrolment (North America, European countries and Australia). The ERG notes that PD-L1 status (a stratification factor in CheckMate 238) wasn't measured at baseline in CA184-029.

The primary endpoint in CA184-029 was RFS similar to CheckMate 238, although the definition of RFS differed between the two studies. In CA184-029, RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis) or death from any cause, whichever occurred first, with assessments conducted by an independent review committee. Patients in CA184-029 were censored for recurrence at the time of their last disease assessment irrespective of whether or not they were in receipt of subsequent therapy. By contrast, RFS in CheckMate 238 was assessed only by an investigator and patients were censored for recurrence at the time of their last disease assessment prior to receipt of subsequent therapy. Sensitivity analyses were conducted in CA184-029 to assess the impact of these factors on RFS, although there was no analysis conducted that matched both the subsequent treatment censoring and investigator assessment features of CheckMate 238. The RFS data used in the ITC from CA184-029 did, however, match the censoring aspect of CheckMate 238, which the ERG agrees with the company is the key criterion to match and the ERG considers the use of the independent review data to be a conservative estimate of ipilimumab versus placebo.

The ERG notes that the RFS definition in CheckMate 238 also included new primary melanoma events and second non-melanoma primary cancers, both of which were not reasons for censoring in CA184-029 and were not adjusted for in the company's ITC analyses. However, the ERG notes that there were only [redacted] and [redacted] patients, respectively, censored for these reasons in CheckMate 238 in the 24-month data-cut and, therefore, agrees with the company that the overall impact on the inclusion of these patients in the study results is likely to be small.

The secondary endpoints in CA184-029, similar to CheckMate 238, included DMFS, OS, safety and HRQL. Study CA1840-029 has completed and the results are more mature than those reported from CheckMate 238; median follow-up was 5.3 years in CA184-029 and in CheckMate 238 follow-up was a minimum of 24 months in the latest data-cut, although the median follow-up wasn't reported.

Patient randomisation (in CA184-029) occurred between 10 July 2008 and 1 August 2011, with 475 patients randomised to the ipilimumab group and 476 to the placebo group.[2] Baseline characteristics of patients in CA184-029 are summarised in Table 12. The ERG's clinical experts reported that the baseline characteristics for CA184-029 appear broadly consistent with those of CheckMate 238, although CA184-029 included a slightly lower risk population due to the inclusion of Stage IIIa and exclusion of resected Stage IV. The ERG also notes that median age of patients in CA184-029 is slightly younger compared to CheckMate 238. In addition, approximately 20% of the patients in CA184-029 had Stage IIIA disease and Stage IIIA patients were excluded from CheckMate 238. The ERG notes that the company applied co-variate adjustments in the ITC analyses to adjust for some of these baseline differences and these are discussed further in Section 4.4.3.1.1.

Table 12. Baseline characteristics, CA184-029 (reproduced from CS Document B Table 8, page 41)

Characteristic	Ipilimumab (n=475)	Placebo (n=476)
Male, n (%)	296 (62)	293 (62)
Age, median (range):	51 (20–84)	52 (18–78)
Disease stage[a], n (%):		
Stage IIIA	98 (21)	98 (21)
Stage IIIB	182 (38)	182 (38)
Stage IIIC (1–3 LN+)	122 (26)	121 (25)
Stage IIIC (≥4 LN+)	73 (15)	75 (16)
AJCC 2002[b], n (%):		
Stage IIIA	98 (21)	88 (18)
Stage IIIB	213 (45)	207 (43)
Stage IIIC (1-3 LN+)	69 (15)	83 (17)
Stage IIIC (≥4 LN+)	95 (20)	98 (21)
Lymph node involvement, n (%):		
Microscopic	210 (44)	193 (41)
Macroscopic	265 (56)	283 (59)
Number of positive lymph nodes, n (%):		
1	217 (46)	220 (46)
2–3	163 (34)	158 (33)
≥4	95 (20)	98 (21)
Ulceration, n (%)		
No	257 (54)	244 (51)
Yes	197 (41)	203 (43)
Unknown	21 (4)	29 (6)

Abbreviations: AJCC, American Joint Committee on Cancer; EORTC, European Organisation for Research and Treatment of Cancer; LN, lymph node.
Notes: [a], As provided at randomisation; [b], As indicated on case report forms.
Source: Eggermont *et al.*, 2015.[2]

The company provided details of subsequent therapies used in CA184-029 and CheckMate 238 split by line of therapy (first line [1L] and second line or beyond [2L+]) in the company response to clarification questions (Table 13 and Table 14). The data provided in Table 14 are based on the 18-month data-cut for CheckMate 238, whereas the data discussed in Table 6 are from the 24-month data-cut which the company reported were not available for the same level of analysis as the 18-month data-cut. In study CA184-029 patients in both the ipilimumab and placebo groups were most likely to receive either 'other' not further classified treatments 1L after disease recurrence or dacarbazine. By contrast, patients in CheckMate 238 were most likely to receive pembrolizumab, nivolumab, ipilimumab or dabrafenib+trametinib as 1L treatment following disease recurrence. The ERG notes that part of the reason for these differences in subsequent therapy is likely to be related to advances in clinical practice since the time CA184-029 was carried out. The ERG also notes that due to the outcome censoring selected for the ITC analyses, these differences in subsequent therapies will have the largest impact in the analysis of OS. However, the ERG is unsure of the exact impact of these differences in subsequent therapies on the ITC results although the ERG considers that more effective subsequent treatments will minimise any difference in OS, whereas less effective subsequent treatments will have less impact on subsequent OS.

Table 13. Subsequent treatments split by line – CA184-029 (reproduced from company clarification response Table 15, page 44)

Treatment	Ipilimumab 10 mg/kg				Placebo			
	1L		2L+		1L		2L+	
	Patients	Records	Patients	Records	Patients	Records	Patients	Records
Cisplatin	[redacted]							
Dabrafenib	[redacted]							
Dabrafenib + trametinib	[redacted]							
Dacarbazine (DETICENE)	[redacted]							
Interferon	[redacted]							
Interleukin	[redacted]							
Ipilimumab	[redacted]							
Ipilimumab plus nivolumab	[redacted]							
Nivolumab	[redacted]							
Other	[redacted]							
Other palliative chemotherapy	[redacted]							
Paclitaxel (Taxol)	[redacted]							
Pembrolizumab	[redacted]							
TEMOZOLOMIDE (Temodal)	[redacted]							
Talimogene laherparepvec	[redacted]							

Unassigned	[redacted]							
Vemurafenib	[redacted]							
Vemurafenib plus cobimetinib	[redacted]							
Total	[redacted]							

Abbreviations: 1L, first-line; 2L+, second-line plus.
Notes: *Includes high-dose, low-dose, PEGylated and unspecified interferon. **Includes encorafenib, fotemustine, carboplatin, cobimetinib, cysplatine, lomustine and rituximab

Table 14. Subsequent treatments split by line – CheckMate 238 - 18-month cut off (reproduced from company clarification response Table 16, pages 44-45)

Treatment	Ipilimumab 10 mg/kg				Nivolumab 3 mg/kg			
	1L		2L+		1L		2L+	
	Patients	Records	Patients	Records	Patients	Records	Patients	Records
Cisplatin	[redacted]							
Cobimetinib+vemurafenib	[redacted]							
Dabrafenib	[redacted]							
Dabrafenib+trametinib	[redacted]							
Dacarbazine	[redacted]							
Interleukin 2	[redacted]							
Ipilimumab	[redacted]							
Ipilimumab+nivolumab	[redacted]							
Interferon	[redacted]							
Nivolumab	[redacted]							
Other palliative Chemotherapy	[redacted]							
Other/unassigned	[redacted]							
Paclitaxel	[redacted]							
Pembrolizumab	[redacted]							
Talimogene laherparepvec	[redacted]							
Temozolomide	[redacted]							
Vemurafenib	[redacted]							
Total	[redacted]							

Abbreviations: 1L, first-line; 2L+, second-line plus.
Notes: *Includes alpha 2B and beta.

4.4.1.2 CA184-029 results

Table 15 provides a summary of the trial-level results of interest from CA184-029, which report after a median follow-up of 5.3 years. Ipilimumab demonstrates a consistent benefit in RFS, OF and DMFS compared with placebo. However, the ERG notes that median OS was not reached in either treatment group; the 5-year OS rate was 65% in the ipilimumab group compared with 54% in the placebo group (HR 0.72; 95% CI: 0.58 to 0.88; p=0.001).[21]

Table 15. Summary of efficacy results, ITT population, CA184-029 (reproduced from CS Document B Table 9, page 42)

	Ipilimumab (n=475)	Placebo (n=476)
RFS		

Events, n (%)	264 (55.6)	323 (67.9)
Median months (95% CI)	27.6 (19.3 to 37.2)	17.1 (13.6 to 21.6)
5-year RFS rate (95% CI)	40.8 (36.0 to 45.6)	30.3 (26.0 to 34.6)
HR (95% CI)	0.76 (0.64 to 0.89)	
p-value	<0.001	
OS		
Events, n (%)	162 (34.1)	214 (45.0)
Median months (95% CI)	Not reached	Not reached
5-year OS rate (95% CI)	65.4 (60.8 to 69.6)	54.4 (49.7 to 58.9)
HR (95% CI)	0.72 (0.58 to 0.88)	
p-value	0.001	
DMFS		
Events, n (%)	227 (47.8)	279 (58.6)
Median months (95% CI)	48.3 (35.5 to 71.6)	27.5 (21.9 to 34.8)
5-year DMFS rate (95% CI)	48.3 (43.4 to 53.0)	38.9 (34.3 to 43.5)
HR (95% CI)	0.76 (0.64 to 0.92)	
p-value	0.001	

Abbreviations: CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; RFS, recurrence-free survival.
Source: Eggermont *et al.* 2016.[21]

4.4.1.2.1 Restricted mean RFS results

The company reported the results of a restricted mean analysis of RFS for CheckMate 238 and for CA184-029 (Table 16). The ERG notes that the mean RFS for ipilimumab is [redacted]

Table 16. Mean RFS for CheckMate 238 (24-month data) and CA184-029 (reproduced from company clarification response Table 12, page 39)

Follow-up	CheckMate 238 RFS mean (95% CI) – months		CA184-029 RFS mean (95% CI) - months	
	Nivolumab	Ipilimumab	Ipilimumab	Placebo
0–12 months	[redacted]	[redacted]	[redacted]	[redacted]
0–18 months	[redacted]	[redacted]	[redacted]	[redacted]
0–24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; RFS, recurrence-free survival.

4.4.1.2.2 Safety data for CA 184-029

Table 11 presents the safety data outcomes from CA184-029 used to inform the economic model, alongside the equivalent data from CheckMate 238. The safety data indicate ipilimumab in both CA184-

029 and CheckMate 238 studies was associated with larger proportion of any-grade immune-related AEs, grade ≥2 diarrhoea AEs and other grade ≥3 AEs compared to the nivolumab arm of CheckMate 238.

Table 17. Trial level safety data relative risks with CheckMate 238 24-month data (reproduced from company clarification response Table 14, page 41)

	Immune-related (Any grade)	Diarrhoea (grade ≥2)	Other AEs (grade ≥3)
CheckMate 238 (24-month data)			
Nivolumab	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]	[redacted]	[redacted]
CA184-029			
Ipilimumab	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]	[redacted]	[redacted]
Abbreviations: AEs, adverse events; RR, relative risk			

4.4.2 Indirect treatment comparison methods

The company reported in the CS that OS data in CheckMate 238 were not available and that RFS was the only survival endpoint required for the economic model where an ITC could be formed. However, the company also reported that it was possible to use OS and post-local/regional recurrence survival data from CA184-029 to support the economic model. The company used parametric survival models in order to enable a comparison of nivolumab with routine surveillance in the economic model and to extrapolate the trial-level data. The company reported that they followed NICE Decision Support Unit (DSU) technical support document (TSD) 14.[24]

The company used two approaches for the ITC for RFS:

- PLD meta-regression using parametric survival models; and
- Bucher adjusted indirect comparison.

The PLD meta-regression was reported by the company to be the most robust estimate of the ITC between nivolumab and placebo[25] with the Bucher indirect comparison carried out to validate the PLD analysis and to provide HRs deemed to be easier to interpret. The ERG notes that the PLD data were used in the company economic base case and a scenario analysis was conducted using the HR for the RFS with routine surveillance (and parametric curves fit directly to CheckMate 238 for the RFS of nivolumab).

4.4.3 PLD meta-regression using parametric survival models – RFS methods

The company's parametric survival modelling was performed in R using the 'survival' and 'flexsurv' packages. The company reported that survival models for the following parametric distributions were estimated, as per NICE DSU TSD 14[24]:

- Exponential;
- Weibull;
- Log-normal;
- Log-logistic;
- Gompertz; and
- Generalised gamma.

The company reported in the CS how they had investigated the use of non-stratified models using PH and accelerated failure time (AFT) assumptions. However, they decided to use stratified models as they had access to the patient level data (PLD) for both studies (CheckMate 238 and CA184-029) and cited NICE DSU TSD 14[24] in support of this decision.

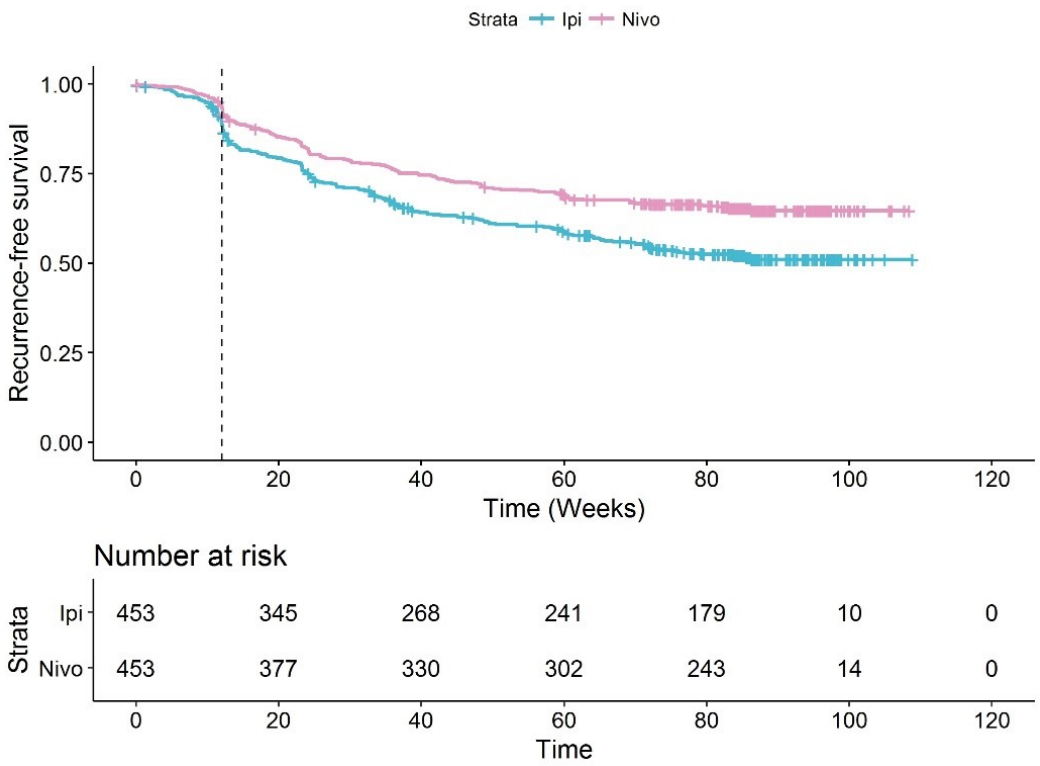
The company also used the guidance in TSD 14[24] to aid the assessment of the model fit and selection of the base case survival curves. The following were used in this model fit assessment:

- Goodness of fit measures, the Akaike information criterion (AIC) and the Bayesian information criterion (BIC);
- Visual inspection of the fitted survival curves in relation to the trial level KM data;
- Clinical validation by clinical experts;
- Long-term melanoma data to particularly help inform the tails of the curves.

The company highlighted an issue in the use of the parametric survival curves for RFS in relation to observing a kink in the KM curves for both CheckMate 238 (Figure 11) and CA184-029 (Figure 12) around 12 weeks. The ERG notes that the first assessment date is not until 12 weeks in either of the two trials and then there is a large change in hazard at 12 weeks. The company highlighted that parametric

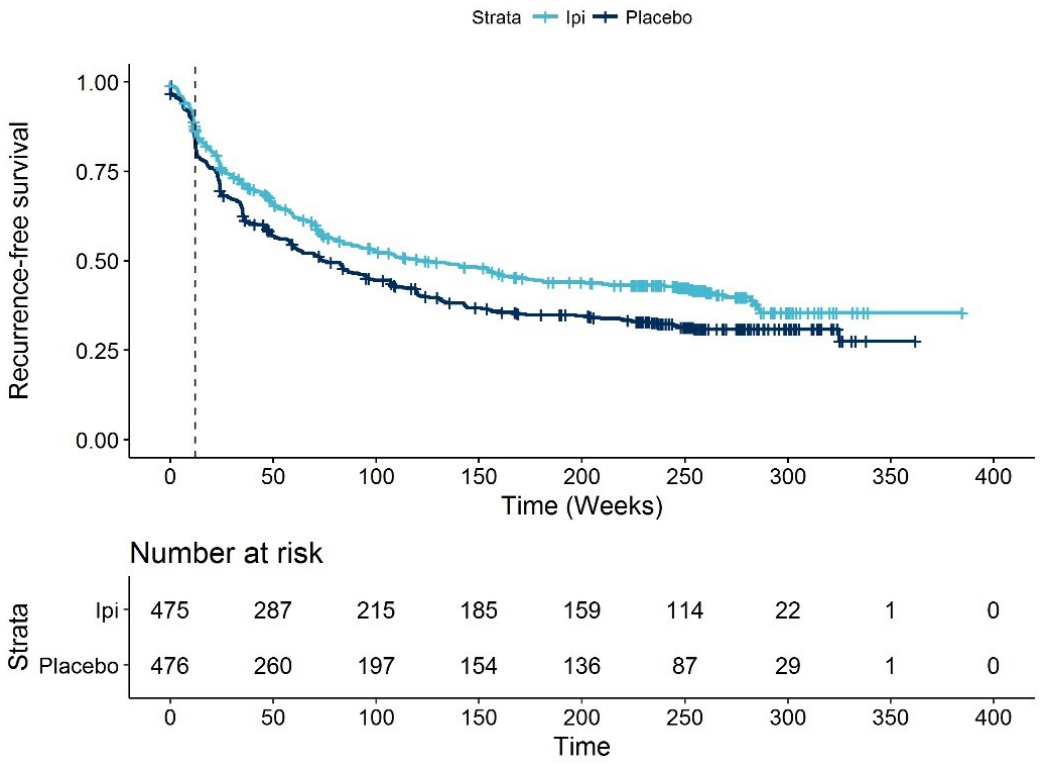
survival models fit to the full KM data would therefore provide a poor fit to the observed data, and so the company decided to identify a relevant timepoint to rebase the RFS data.

Figure 11. Recurrence-free survival 238 Kaplan–Meier split by treatment (reproduced from CS Document B, Figure 24)



Abbreviations: Ipi, ipilimumab, Nivo, nivolumab.
Notes: Dashed line indicates time of first efficacy assessment (12 weeks).

Figure 12. Recurrence-free survival 029 Kaplan–Meier split by treatment (reproduced from CS Document B, Figure 25)



Abbreviations: Ipi, ipilimumab; PBO, placebo.
Notes: Dashed line indicates time of first efficacy assessment (12 weeks).

The company explored the use of different cut-offs in-line with the possible variations in timing of first RFS assessment in the two studies (12 weeks ±1 week for CheckMate 238 and 12 weeks ±2 weeks in CA184-029). The company concluded that the best option for the RFS analysis was to use the KM data from baseline to 12 weeks and then rebase the parametric curves from 12 weeks (i.e. date of first assessment for RFS). The company reported that it was unlikely that the choice of rebase point would have a major impact on the outcomes of this analysis.

4.4.3.1.1 Covariate adjustment

The company considered covariate adjustment to address any differences in patient characteristics between the CheckMate 238 and CA184-029 studies, for both characteristics that influenced the relative treatment effect (effect modifiers) or absolute survival (prognostic factors). The list of covariates chosen was validated by the company's clinical experts.[26] The company reported that there were no obvious treatment effect modifiers in either CheckMate 238 or CA184-029, although they also acknowledged that there were some differences in the treatment effectiveness across some subgroups. For example, in CheckMate 238, the RFS treatment effect was consistent in all pre-defined subgroups with the exception of patients with Stage IV M1c melanoma, ulceration present plus microscopic lymph node involvement, and mucosal melanoma. Similarly, in the CA184-029 study, treatment effect was consistent in each of

the pre-defined subgroups with the exception of patients with unknown ulceration status. However, there were small patient numbers in these subgroups and therefore high levels of uncertainty in the relative treatment effect estimates (confidence intervals overlap) and so it is unclear whether the relative treatment effect within these subgroups is different. The ERG notes that in both trials, the subgroup analyses were not adequately powered to detect differences in the subgroup populations, and therefore undetected treatment effect modifiers may exist.

In terms of covariate adjustment for prognostic factors, [redacted] were significant prognostic variables for RFS CheckMate 238 and [redacted] were reported as key prognostic variables in CA184-029. The company reported that a patient's disease stage is highly correlated with lymph node involvement and ulceration status (disease stage is partially defined by these two factors; Stage IIIA by definition must have microscopic lymph node involvement and no ulceration), and so it is not advisable to perform regression analysis with covariates for disease stage together with ulceration status or lymph node involvement. The company selected disease stage as a covariate for inclusion in their economic base case model as, "disease stage is a better predictor than ulceration status or lymph node involvement for RFS in CheckMate 238", and because the long-term data used to validate the model extrapolations are also presented by disease stage. A sensitivity analysis within the Bucher ITC was conducted to explore the effect of also including using lymph node involvement within the covariate adjustment and demonstrated little change to the results.

[redacted]", The company cited clinical opinion and challenges associated with measuring and assessing PD-L1 as the rationale for this decision. The ERG notes that PD-L1 status was not captured in CA184-029[27,28] but also notes that patients in CheckMate 238 were stratified at randomisation based on PD-L1 status. In addition, BRAF status was not included as a covariate because of the high level of missing data in CA184-029 (88.2% in the ipilimumab arm and 86.6% in the placebo arm).

The company included covariates for patient age and trial in addition to the covariates identified as prognostic for RFS across the two trials. The rationale for including patient age [redacted], and the rationale for including the trial covariate was that it, "it will account for all unobserved differences between trials, thus maintaining randomisation". The ERG is unclear as to exactly what differences are addressed by the trial level covariate.

In summary, the following covariates were included within the company's analyses:

- Gender (Male or female);
- Age (<65 or ≥65);
- Stage (Stage IIIA or Stage IIIB or Stage IIIC or Stage IV); and
- Trial (CA184-029 or CheckMate 238; trial was included as a covariate in the RFS ITC PLD meta-regression analysis only.

4.4.3.1.2 Corrected group prognosis

The company used the corrected group prognosis (CGP) method to calculate the parametric survival curves used in the economic model. The method used was to group patients based on the four types of covariate adjustments which resulted in the creation of 32 groups. The company then calculated a survival curve for each of the 32 unique groups using the proportion of patients in each group to weight the individual survival curves, and using these to create a weighted average curve for the entire population.

The company reported that a within trial analysis was conducted using the CGP method and matching the proportion of patients within each group based on that observed in the trial. The company were therefore able to directly compare the weighted curve produced by the CGP method with the trial-level KM data to help assess goodness of fit. In addition, the company highlighted that because disease stage coefficients are estimated irrespective of treatment, the CGP method enabled them to predict survival curves for the total population of interest (Stages III–IV) despite the only partial overlapping populations between the two trials, as it was assumed that the Stage IIIA and Stage IV coefficient values could be applied to the nivolumab and placebo arms, respectively, without modification of the treatment effects. To form the ITC, the proportion of patients within each CGP group was then held constant between the treatment groups (irrespective of trial) to give a simulated treatment comparison. Long-term survival estimates were produced for each treatment while controlling for differences within patient characteristics and trials through the use of the covariates and CGP method.

4.4.3.2 PLD meta-regression using parametric survival models – RFS results

The ITC presented in the CS used the 18-month follow-up data (data cut-off 15 May 2017) for CheckMate 238 and the 13 May 2016 cut-off for CA184-029, although an updated analysis using the 24-month follow-up data (December 2017 data cut-off) for CheckMate 238 was presented in the company response to clarification questions. As discussed in Section 4.4.3, the parametric survival models were rebased at 12 weeks for the parametric survival model ITC. The company presented model fit statistics and the details of the coefficients used to estimate the curves in the CS.

The company reported that they selected the log-logistic curve for the economic model and that it was the best statistical fitting curve (using both the 18-month and 24-month CheckMate 238 data) as well as being a good fit on visual inspection and clinically plausible according to the company's clinical experts. The resulting curves from the log-logistic meta-regression model suggest that for the matched population, nivolumab is associated with the longest RFS compared to both ipilimumab and placebo (Figure 13; for details of curve fitting see Section 5.4.5).

Figure 13. Recurrence-free survival –long-term survival extrapolation from meta-regression model rebased at Week 12 split by treatment using matched population (Reproduced from company clarification response, Figure 7)

Abbreviations: Ipi, ipilimumab 10 mg; ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab; PBO, placebo.

4.4.3.3 Bucher indirect treatment comparison methods- RFS

The company used a Bucher ITC to estimate the RFS of nivolumab compared to placebo using ipilimumab as a common comparator. The resulting HRs were derived from Cox models which assume a proportional hazard between treatments with in a study; the company considered this to be a reasonable assumption for both the CheckMate 238 and CA184-029 studies and reported that the PH assumption in each trial was checked using a log-cumulative hazard plot. The Bucher method also assumes that the HRs are normally distributed on the log scale. The indirect estimate of the HR between placebo and nivolumab was estimated using the following equation:

$$\log\left(HR_{Nivo\ PBO}^{indirect}\right) = \log\left(HR_{Nivo\ Ipi}^{direct}\right) - \log\left(HR_{PBO\ Ipi}^{direct}\right)$$

With variance (var):

$$\mathrm{Var}\left\{\log\left(HR_{Nivo\ PBO}^{indirect}\right)\right\} = \mathrm{Var}\left\{\log\left(HR_{Nivo\ Ipi}^{direct}\right)\right\} + \mathrm{Var}\left\{\log\left(HR_{PBO\ Ipi}^{direct}\right)\right\}$$

The company conducted an analysis using the full ITT populations of CheckMate 238 and CA182-029 with no covariate adjustments and a further analysis with covariate adjustments for the prognostic factors and covariates adjusted for in the PLD meta-regression analyses already discussed in Section 4.4.3.1.1 (with the exception of the trial covariate). The following covariates were therefore included in the covariate adjusted analysis:

- Gender (male or female);
- Age (<65 or ≥65); and
- Stage (Stage IIIA or Stage IIIB or Stage IIIC or Stage IV).

In addition to the Bucher ITC analyses on the full ITT populations, the company conducted sensitivity analyses using only the Stage IIIA and Stage IIIB patient subgroup from each study to assess whether the treatment effect was consistent when only the directly overlapping disease stage patients were considered, i.e. excluding the Stage IIIA patients from CA184-029 and Stage IV patients from CheckMate 238. The ERG notes that randomisation in both trials was stratified by disease stage, although the company also reported that there were some small differences in the patient characteristics of these subgroups between the arms in the trials such as the proportion of patients with each disease stage (CheckMate 238 and CA184-029) and the proportion of patients with tumour ulceration (CheckMate 238). The company, therefore, conducted a further covariate adjusted analysis on Stage IIIB and IIIC subgroup to control for the differences in patient characteristics. This resulted in four analyses conducted using the Bucher ITC method reported in the CS:

- ITT population with no covariate adjustment;
- ITT population with covariate adjustment;
- Stage IIIB and IIIC population with no covariate adjustment; and
- Stage IIIB and IIIC population with covariate adjustment.

4.4.3.4 Bucher indirect treatment comparison – RFS results

The results of the four RFS analyses using the Bucher ITC method and the 24-month follow-up data-cut for CheckMate 238 are presented in Table 18. The results are [redacted] demonstrating [redacted] for nivolumab versus ipilimumab or placebo [redacted] (Table 18). This suggests that following adjuvant treatment with nivolumab (compared to ipilimumab or placebo), [redacted] The results also indicate that the treatment effect is [redacted] The results do indicate that [redacted]

Table 18. Results of the recurrence free survival indirect treatment comparison using the Bucher method (reproduced from company clarification response Table 3, page 11)

Covariate Adjusted	Population	CheckMate 238 HR (95% CI) Nivo vs Ipi	CA184-029 HR (95% CI) PBO vs Ipi*	Bucher HR (95% CI) Nivo vs PBO
No	ITT	[redacted]	[redacted]	[redacted]
Yes	ITT	[redacted]	[redacted]	[redacted]
No	Stage IIIB/C	[redacted]	[redacted]	[redacted]
Yes	Stage IIIB/C	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; Ipi; ipilimumab; ITT, intention-to-treat; Nivo, nivolumab; PBO, placebo; TRT, treatment.
Note: * HRs presented are comparing placebo against ipilimumab, hence HR>1 means that ipilimumab performs better than placebo.

4.4.4 ITC subgroup analysis with ipilimumab censoring in CA184-029 for RFS

The ERG requested additional analyses during the clarification question stage to investigate the potential impact of including patients from study CA184-029 who had received treatment beyond one year in the RFS ITC analyses of nivolumab versus placebo. The company provided a KM plot of the RFS in CA184-029 for both the ITT population and the subgroup of patients who received up to 1 year's treatment split by treatment (ipilimumab or placebo) in their clarification response (Figure 14). The KM plots suggest that the patients who receive a maximum of a year's treatment with ipilimumab (or placebo) have a higher rate of recurrence compared to the full ITT population, which includes patients who received more than a year's treatment with ipilimumab (or placebo). However, the ERG acknowledges that this analysis is biased as it is likely to be selective towards patients with the worst prognosis as those who discontinue treatment in the first year are more likely to be at increased risk of relapse. However, the ERG also notes that the baseline characteristics for the ipilimumab arm of this

subgroup are similar or slightly less favourable to the baseline characteristics of the all treated ipilimumab population in terms of age, disease stage and lymph node involvement (Table 12).

Figure 14. CA184-029 recurrence-free survival KM for the ITT population and subgroup of patients who received up to one year treatment split by treatment (Reproduced from company clarification response, Figure 10)

Abbreviations: Ipi, ipilimumab 10 mg; ITT, intention-to-treat KM, Kaplan–Meier; PBO, placebo; TRT, treatment; yr, year.

Table 19. Characteristics summary on subgroup of people who received up to 1 year of ipilimumab, all treated vs all ipilimumab-treated patients from CA184-029 (reproduced from company clarification response Table 8, page 30)

	Ipilimumab (n=475)	[redacted]
Male, n (%)	296 (62)	[redacted]
Age, median (range):	51 (20–84)	[redacted]
Disease stage[a], n (%):		
Stage IIIA	98 (21)	[redacted]
Stage IIIB	182 (38)	[redacted]
Stage IIIC (1–3 LN+)	122 (26)	[redacted]
Stage IIIC (≥4 LN+)	73 (15)	[redacted]
AJCC 2002[b], n (%):		
Stage IIIA	98 (21)	[redacted]
Stage IIIB	213 (45)	[redacted]
Stage IIIC (1-3 LN+)	69 (15)	[redacted]
Stage IIIC (≥4 LN+)	95 (20)	[redacted]
Lymph node involvement, n (%):		
Microscopic	210 (44)	[redacted]
Macroscopic	265 (56)	[redacted]
Number of positive lymph nodes, n (%):		
1	217 (46)	[redacted]
2–3	163 (34)	[redacted]

≥4	95 (20)	[redacted]
Ulceration, n (%)		
No	257 (54)	[redacted]
Yes	197 (41)	[redacted]
Unknown	21 (4)	[redacted]

Abbreviations: AJCC, American Joint Committee on Cancer; EORTC, European Organisation for Research and Treatment of Cancer; LN, lymph node.
Notes: [a], As provided at randomisation; [b], As indicated on case report forms.
Source: Eggermont *et al.*, 2015.[2]

The company also provided an analysis in which patients in CA184-029 who were still on ipilimumab treatment at one year were censored. The ERG agrees with the company that an analysis censoring patients still receiving ipilimumab after 1 year is more robust than simply looking at the subgroup that only received treatment for a maximum of 1 year (as it retains the benefits of randomisation). A KM plot for this analysis alongside the ITT population results is presented in Figure 15 and suggests that the censored at 1-year population have a slightly shorter RFS compared to the ITT population beyond approximately 18 months. The ERG agrees with the company that this analysis is likely to bias against ipilimumab as the censored patients are likely to be those will the best prognosis at 1 year.

Figure 15. CA184-029 recurrence-free survival KM for the ITT population and for the ITT population where patients are censored at one year if they remained on treatment (Reproduced from company clarification response, Figure 11)

[redacted]

Abbreviations: Ipi, ipilimumab 10 mg; ITT, intention-to-treat KM, Kaplan–Meier; PBO, placebo; TRT, treatment; yr, year.

4.4.4.1 ITC results using one-year censoring of ipilimumab treatment in CA184-029

The company conducted a PLD meta-regression analysis using parametric survival models incorporating the censored at one-year ipilimumab patient data from CA184-029 as well as a Bucher adjusted indirect comparison using these data in their clarification response. Similar to the primary PLD

meta-regression analysis conducted by the company (Section 4.4.3), a log-logistic meta-regression model was deemed to be the best fit and a CGP matched population was used (i.e. the covariate proportions in the CGP were consistent across all treatment groups). The resulting long-term RFS plots for nivolumab and placebo are presented in Figure 16 and suggest the difference in RFS with ipilimumab compared to placebo is reduced compared to the original PLD meta-regression analysis (where ipilimumab treatment in CA184-029 wasn't censored at 1 year).

Figure 16. Recurrence-free survival – long-term survival extrapolation from meta-regression model (patients in the ipilimumab arm in CA184-029 censored at 1 year if still on treatment) rebased at Week 12 split by treatment using matched population (reproduced from company clarification response, Figure 18)

Abbreviations: Ipi, ipilimumab 10 mg; ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab; PBO, placebo.

The results of the Bucher ITC analyses using the 24-month follow-up for CheckMate 238 and data from CA184-029 in which ipilimumab patients are censored at 1 year for the same four analyses conducted in the CS are presented in Table 20. These results for the comparison of nivolumab versus placebo are consistent with the ITC results included in the CS (primary analysis), with nivolumab being associated with a statistically significant longer RFS compared to placebo. The HRs estimated by the Bucher ITC for nivolumab versus placebo were numerically [redacted] higher when the ipilimumab censored at 1-year data were used rather than the full ipilimumab dataset, [redacted].

Table 20. Results of the recurrence-free survival indirect treatment comparison using the Bucher method (ipilimumab patients censored at 1 year if still receiving treatment) (adapted from company clarification response Table 7, page 27)

Covariate Adjusted	Population	CheckMate 238 HR (95% CI) Nivo vs Ipi	CA184-029 HR (95% CI) PBO vs Ipi*	Bucher HR (95% CI) Nivo vs PBO	Bucher HR (95% CI) Nivo vs PBO Primary analysis in CS
No	ITT	[redacted]	[redacted]	[redacted]	[redacted]
Yes	ITT	[redacted]	[redacted]	[redacted]	[redacted]
No	Stage IIIB/C	[redacted]	[redacted]	[redacted]	[redacted]
Yes	Stage IIIB/C	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; Ipi; ipilimumab; ITT, intention-to-treat; Nivo, nivolumab; PBO, placebo; TRT, treatment.
* HRs presented are comparing placebo against ipilimumab, hence HR>1 means that ipilimumab performs better than placebo.

In summary, the ERG agrees with the company that there is an inherent bias against ipilimumab in the ITC using the 1-year censored ipilimumab data, however, the ERG considers this will produce a conservative estimate of the benefit of nivolumab compared to placebo as opposed to the over-optimistic results provided by the ITT ipilimumab population. This is discussed further in Section 5.4.5.

4.4.5 PD-L1 status ≥ 5%

The ERG attempted to investigate the impact of PD-L1 status on the results of the ITC as PD-L1 status was used as a stratification factor in CheckMate 238 and the RFS results suggested a potential difference in RFS benefit with nivolumab according to PD-L1 status (Section 4.3.5.1). However, the company reported that patients recruited to CA184-029 were not assessed for PD-L1 status and therefore an ITC analysis by PD-L1 status was not possible. The company also highlighted that PD-L1 status was not anticipated to be related to the EMA marketing authorisation for adjuvant nivolumab therapy and also that no subgroups were requested in the final scope issued by NICE. The ERG is unable to comment

on the possible impact of PD-L1 status on the cost-effectiveness of nivolumab but nevertheless considers it a possible subgroup of interest.

4.4.6 Staging

The ERG requested a re-analysis of the clinical data from CheckMate 238 and CA184-029, re-staging patients into the new AJCC 8th edition disease stages for melanoma as a clarification question in an attempt to assess the impact of the change in the AJCC staging criteria. However, the company clarification response reported that it was not possible to conduct such an analysis as the clinical data collected for CA209-238 was insufficient to restage all patients under the AJCC 8th edition.

4.4.7 Overall survival

In the CS, the OS data for nivolumab versus routine surveillance for use in the economic model was estimated using a surrogacy analysis (discussed in more detail in Section 4.4.7.2) with a scenario analysis assuming the OS benefit of nivolumab over routine surveillance is equivalent to the benefit of ipilimumab compared to placebo in CA184-029. The ERG requested ITC analyses using the PLD and using the Bucher ITC method given that OS data for nivolumab were made available in the 24-month CheckMate 238 data-cut. The company [redacted]

4.4.7.1 Bucher ITC [redacted]

[redacted]

Method	Population	[redacted]	CA184-029 HR (95% CI)	[redacted]

		[redacted]	PBO vs Ipi *	[redacted]
Bucher ITC	ITT	[redacted]	1.39 (1.14 to 1.72)	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; Nivo, nivolumab; PBO, placebo; TRT, treatment.
* HRs presented are comparing placebo against ipilimumab, hence HR>1 means that ipilimumab performs better than placebo.

4.4.7.2 OS surrogacy analysis

The company estimated the OS for nivolumab for use in the partitioned survival economic model using a surrogacy relationship. This involved a predictive equation for the OS treatment effect based on the RFS treatment effect derived from [redacted] and then applied this HR to the routine surveillance OS parametric curve generated from the placebo arm of CA184-029. The company cited a recent publication that concluded that RFS appears to be a valid surrogate endpoint for OS in Stage II–III melanoma adjuvant therapy as their rationale for conducting the surrogacy analysis.[29] The ERG notes that the study referred to by the company used 13 interferon trials to derive a regression equation to estimate a HR for OS (HR_{OS}) from a HR for RFS (HR_{RFS}).

[redacted] The ERG notes that the new study is funded by the company (Bristol-Myers Squibb). The first part is considered an update of the recent surrogacy publication and uses summary [redacted]. The company reported that the framework of this new study is based on the approach described by Burzykowski *et al.* for two time-to-event endpoints.[31, 32] [redacted]. The analysis for this surrogacy publication uses [redacted]

The ERG notes that the OS surrogacy analysis used to generate the OS HR from the CheckMate 238 RFS, for use in the company economic model included the [redacted] Table 22 provides a summary of the [redacted] studies that were included in the surrogacy relationship equation for generating the OS HR for CheckMate 238. The company also provided a separate report to the CS alongside their

clarification response that provided additional detail on the surrogacy equation methodology.30 The company reported that the inclusion of the [redacted] in the surrogacy equation for estimating the OS HR for CheckMate 238 was because there were deemed to be the most relevant [redacted] with OS and RFS data.

[redacted] The ERG is unsure as to how reliable this approach is and this unaware of any other publications in support of this method. The ERG notes from the additional publication supplied by the company that the analysis is [redacted] the ERG is concerned that it is not a robust analysis.

Table 22. Studies included in the base case correlation relationship (reproduced from CS Document B Table 26, pages 120–121)

Study	Intervention (dose)	Comparator (dose)	Included in Suciu et al.[29]	Number of patients	HR RFS	HR OS	Included in analysis
ECOG1684[34]	High dose IFN alpha-2b (20MU/m^2 IV for 5 days/week for 4 weeks, then 10MU/m^2 SC 3 days/week for 48 weeks)	Observation	Y	287	0.76	0.84	Y
ECOG1690[35]	High dose IFN alpha-2b (20MU/m^2 IV for 5 days/week for 4 weeks, then 10MU/m^2 SC 3 days/week for 48 weeks) and low dose IFN (3MU a day for 3 days a week for 2 years)	Observation	Y	642	0.88	0.95	Y
NCCTG83-7052[36]	High dose IFN alfa-2a (20MU/m^2 IM 3 days/week for 12 weeks)	Observation	Y	264	0.89	0.92	Y
EORTC18952[37]	Intermediate dose IFN alfa-2b (10MU SC 5 days/week for 4 weeks, then 10MU SC 3 days/week for 1 year or 5MU SC 3 days/week for 2 years)	Observation	Y	1388	0.88	0.9	Y
WHO16[38]	Low dose IFN alfa-2a (3MU SC 3 days/week for 3 years)	Observation	Y	444	0.95	0.96	Y
UKCCCRAIM-High[39]	Low dose IFN alfa-2a (3MU 3 days/week for 2 years)	Observation	Y	674	0.94	0.93	Y
DeCOG[40]	Low dose IFN alfa-2a (3MU SC 3 days/week for 2 years)	Observation	Y	293	0.72	0.63	Y
Scottish MG[41]	Low dose IFN alfa-2b (3MU SC 3 days/week for 6 months)	Observation	Y	94	0.78	0.81	Y
EORTC18871[42]	Low dose IFN alfa-2b (1MU SC every other day for 1 year)	Observation	Y	281	0.94	0.88	Y
DKG80-1[42]	Low dose IFN alfa-2b (1MU SC every other day for 1 year)	Observation	Y	203	1.09	1.09	Y
EORTC18991[43]	PEGylated IFN-alfa-2b (6µg/kg SC per week for 8 weeks, then 3µg/kg SC per week for 5 years)	Observation	Y	1256	0.87	0.96	Y
ECOG1694[44]	High and low dose IFN alfa-2b (20MU/m^2 IV for 5 days/week for 4 weeks, then 10MU/m^2 SC 3 days/week for 48 weeks)	GMK vaccine (1mL SC on Days 1, 8, 15 and 22, then every 12 weeks until l96 weeks)	Y	882	0.84	0.86	Y
ECOG2696[45]	High and low dose IFN alfa-2b (20MU/m^2 IV for 5 days/week for 4 weeks, then 10MU/m^2 SC 3 days/week for 48 weeks) and GMK vaccine	GMK vaccine alone (30µg of GM2 and 100µg SC on Weeks 1, 2, 3, 4, 12, 24, and 36)	Y	107	0.72	1.11	N
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GMK, GM2-KLH/QS-21; HR, hazard ratio; OS, overall survival; Q3W, every three weeks; RFS, recurrence free survival; SC, subcutaneously.

The ERG also has concerns that the majority of studies used to inform the OS estimate in CheckMate 238 are based on interferon (12 studies), which unlike nivolumab and ipilimumab, is not an immunotherapy and is also not routinely used in the adjuvant melanoma setting in the UK. The ERG is, therefore, concerned about the transferability of the RFS–OS relationship identified in interferon studies to immunotherapy and other adjuvant melanoma therapies.

The surrogacy relationship equation used for generating the HR_{OS} for nivolumab versus ipilimumab in CheckMate 238 was as follows:

[redacted]

The HR_{RFS} from CheckMate 238 of nivolumab vs ipilimumab (HR 0.65)[1] was used in the equation to calculate the HR_{OS} of nivolumab vs ipilimumab [redacted] This hazard ratio of [redacted] for nivolumab versus ipilimumab from CheckMate 238 was then compared to the HR_{OS} of ipilimumab vs placebo (HR 0.72) from the CA184-029 trial to produce the HR_{OS} of nivolumab vs placebo [redacted] The HR for nivolumab versus placebo is then applied to the routine surveillance curve estimated from the CA184-029 placebo OS data. In addition, the equation derived from the previous Suciu *et al*. surrogacy analysis is explored as a scenario in the economic model:

$$HR_{OS} = \exp(0.0106 + 0.9874 \times \ln(HR_{RFS}))$$

Using this equation HR_{OS} for nivolumab compared to routine surveillance is 0.48. The ERG notes that this is [redacted] However, as already discussed, the ERG is concerned about the reliability of using interferon studies to calculate OS and the novel methodology [redacted] The ERG, therefore, considers the HR generated via the Bucher ITC to be the most reliable estimation at present for nivolumab versus routine surveillance based on the CheckMate 238 data. The ERG also considers it important to highlight that it is unclear whether PH holds for the OS of nivolumab versus routine surveillance and that if it does not hold then the results for OS calculated using the surrogacy equation will be flawed.

4.5 Summary and conclusions of the clinical effectiveness section

- The company proposes the use of adjuvant nivolumab in the treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection and that nivolumab will replace the current use of routine surveillance, i.e. no active therapy.

- In June 2018, the CHMP issued a positive opinion on the use of adjuvant nivolumab, and a change in the marketing authorisation was recommended for the use of nivolumab in this new indication for

the treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

- Clinical effectiveness data in the CS for adjuvant nivolumab are derived from the large international, double-blind, CheckMate 238, RCT designed to evaluate the efficacy and safety of nivolumab versus ipilimumab. In addition, clinical effectiveness data on ipilimumab versus placebo from study CA184-029 were included to inform the economic model inputs and to enable an ITC to be conducted between nivolumab and routine surveillance (using placebo as a surrogate for routine surveillance) to address the comparison requested in the NICE final scope.

- Patients enrolled in CheckMate 238 were required to have had complete surgical resection of Stage IIIB, IIIC or IV melanoma, according to the 2009 classification of the AJCC 7th edition, whereas the patients enrolled in CA184-029 had Stage IIIA, IIIB or IIIC melanoma defined according to the AJCC 6th edition. There was therefore a discrepancy between the two studies regarding the inclusion and exclusion of Stage IIIA and IV patients.

- The ERG considers the intervention and outcomes from CheckMate 238 to be consistent with those specified in the final scope issued by NICE. However, as a result of the requirement for the ITC, the ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment although the ERG notes that the company reported the data for these outcomes in CheckMate 238 and CA184-029 were unsuitable for combining in an ITC.

- The company conducted a global level SLR and refined the results to address the decision problem specified in the NICE final scope. The ERG considers the company's searches were adequate to identify the key RCT evidence, although the ERG notes that foreign language publications were omitted. In terms of methodological practice for study inclusion and data extraction, the ERG considers the company to have used robust and standard methods. The ERG and the ERGs clinical experts also agrees with the company decision that the most relevant studies for addressing the decision problem in the NICE final scope are CheckMate 238 and CA184-029.

- CheckMate 238 was assessed to be of high methodological quality by both the company and the ERG. The results of CheckMate 238 in the CS were reported using two different data-cuts, one with a minimum of 18-months follow-up and the other following a minimum of 24-months follow-up. The ERG focuses its report and critique on the later data-cut and notes that follow-up in CheckMate 238 is still ongoing with [redacted]

- Following a minimum of 24 months follow-up, nivolumab demonstrated a statistically significant improvement in RFS (HR 0.66; 95% CI: 0.54 to 0.81) and DMFS (HR 0.76; 95% CI: 0.59 to 0.98)

compared to ipilimumab. The company supplied results from [redacted]

- The company did not report any numerical data for HRQL in the clinical effectiveness review section of the CS although the information provided suggests that there were no significant differences in HRQL with nivolumab compared to ipilimumab.

- There were no subgroup analyses specified in the NICE final scope, although the company presented a series of subgroup analysis results in the CS. Of particular note, the ERG considers the results of CheckMate 238 to suggest a trend toward a greater RFS benefit with adjuvant nivolumab compared to ipilimumab in those patients with PD-L1 ≥ 5% although the ERG acknowledges that treatment with nivolumab was favoured in both the PD-L1 ≥ 5% and PD-L1 < 5% subgroups. In terms of the subgroup data by geographic location in CheckMate 238, the ERG considers the results suggest that the [redacted].

- AEs were reported in nearly all of the patients in both the nivolumab and ipilimumab treatment groups of CheckMate 238, although they were of lesser severity with nivolumab compared to ipilimumab (Grade 3–4 AEs reported by 25.4% of nivolumab patients compared to 55.2% of ipilimumab patients). In addition, the AEs were more frequently deemed to be treatment-related with ipilimumab (95.8%) compared to nivolumab (85.2%) and to lead to treatment discontinuation (ipilimumab 41.7% compared to nivolumab 7.7%). The ERG's clinical experts reported that the AE results from CheckMate 238 are as expected and that they are consistent with the results seen for these drugs in the metastatic melanoma treatment setting.

- CA184-029, the study used in the ITC, was a multinational, randomised, double-blind, phase III study of adjuvant ipilimumab in patients with Stage III cutaneous melanoma who had undergone complete regional lymph node surgical removal. The ERG notes that in addition to differences in baseline age and disease stage there were also comparability issues in terms of the RFS definitions used in CheckMate 238 and CA184-029. The ERG considers the main difference unaccounted for in the ITC analyses was that RFS was assessed by the investigator in CheckMate, whereas in CA184-029 it was assessed independently and therefore is likely to result in a conservative estimate of the efficacy of ipilimumab versus placebo.

- The ERG also noted that there was a difference in the maximum duration of ipilimumab treatment between CheckMate 238 and CA184-029; in CheckMate 238 a maximum of one-year of treatment was allowed whereas in CA184-029 ipilimumab treatment could continue for up to three-years (and

approximately [redacted] of patients continued ipilimumab treatment beyond one year). The company conducted additional analyses in their clarification response using data where ipilimumab patients who were treated beyond one-year were censored at one year, which the ERG considers to be a more conservative estimate of the benefit of nivolumab compared to placebo, as opposed to the over-optimistic results provided by using the ITT ipilimumab population of CA184-029.

- The ERG also noted that the subsequent therapies differed between CheckMate 238 and CA8184-029 and the ERG's clinical experts reported that the types of subsequent therapies given in CheckMate 238 were likely to be generally more consistent with the types used in UK clinical practice. The ERG notes that part of the reason for the differences in subsequent therapy is likely to be related to advances in clinical practice since CA184-029. The ERG also notes that due to the outcome censoring selected for the ITC analyses, these differences in subsequent therapies will have the largest impact in the analysis of OS.

- The company conducted an ITC analysis for RFS using PLD meta-regression and parametric survival models. For the PLD ITC the company included covariates for gender, age, stage and trial, with the rationale for including a trial covariate being, "it will account for all unobserved differences between trials, thus maintaining randomisation". The ERG is unclear as to exactly what these differences addressed by the trial level covariate are. The resulting parametric curves from the log-logistic meta-regression model (that was deemed to be the best-fitting model) suggest that for the matched population (CheckMate 238 and CA184-029), nivolumab is associated with the longest RFS compared to both ipilimumab and placebo.

- The company also conducted a Bucher adjusted indirect comparison for RFS using the full ITT populations of CheckMate 238 and CA182-029. This was conducted with and without covariate adjustments for age, gender and stage. [redacted]

- The HRs estimated by the Bucher RFS ITC for nivolumab versus placebo were numerically slightly higher when the ipilimumab censored at one-year data were used rather than the full ITT ipilimumab dataset, however, they all remained statistically significant in favour of treatment with nivolumab.

- The ERG requested the company conduct a re-analysis of the clinical data from CheckMate 238 and CA184-029, re-staging patients into the new AJCC 8th edition disease stages for melanoma, and an analysis by baseline PD-L1 status although the company reported that they were unable to conduct these analyses due to insufficient PLD. The ERG nevertheless considers them both to be potential subgroups of interest.

[redacted]The OS data for nivolumab versus routine surveillance for use in the economic model was estimated using a surrogacy analysis.[redacted].

[redacted]In terms of the surrogacy analysis, the ERG has numerous concerns regarding the methodology and exploratory nature of the analysis. The ERG notes that the original surrogacy analysis cited by the company used PLD data from interferon studies to generate the surrogacy equation whereas the method used in the CS was based on [redacted]The ERG also has concerns that the majority of studies used in the surrogacy analysis to inform the OS estimate in CheckMate 238 are based on interferon [redacted]which unlike nivolumab and ipilimumab, is not an immunotherapy and is also not routinely used in the adjuvant melanoma setting in the UK. The ERG is, therefore, concerned about the transferability of the RFS–OS relationship identified in interferon studies to immunotherapy and other adjuvant melanoma therapies. The ERG, therefore, considers the HR generated via [redacted]

4.5.1 Clinical issues

- No head-to-head clinical trial data and so an indirect treatment comparison (ITC) has been conducted between nivolumab and routine surveillance (using placebo as a surrogate for routine surveillance). The two trials used in the ITC (CheckMate 238 and CA184-029) are heterogenous due to differences in inclusion criteria, duration of ipilimumab treatment and the use of subsequent therapies.

- The ERG is concerned by the small proportion of UK patients in CheckMate 238 and the absence of Stage IV patients from CA184-029, which potentially limits the validity of the ITC results for the comparison of nivolumab with routine surveillance.

- The ERG has concerns around the potential impact and applicability to the UK population of the subsequent non-randomised therapies used in both CheckMate 238 and CA184-029; this particularly affects the estimates for the outcome of overall survival.

- The ERG considers the validity and generalisability of the results of the ITC to be questionable based on differences in the ipilimumab treatment duration between the CheckMate 238 and CA184-029 studies (up to one-year in CheckMate 238 and up to three years in CA184-029).

- The ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment.

- Data for nivolumab, and in particular for the outcome of OS, [redacted] ongoing nature of the CheckMate 238 study.

- Use of non-standard methods for the surrogacy analysis which was reported to be a first-step 'statistical exercise' to estimate OS for nivolumab versus routine surveillance. In addition, the surrogacy relationship was based on predominantly interferon studies, which is potentially unreliable when applied to data for an immunotherapy.

Subsequent therapies in the trials do not reflect clinical practice in the UK. Following routine surveillance, a larger proportion of patients are likely to receive more effective subsequent immunotherapies than in the CA184-029 trial, meaning that the overall survival is potentially underestimated.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft® Excel based economic model. Table 23 summarises the location of the key economic information within the company's submission (CS).

Table 23. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	B.3.1
Model structure	B.3.2
Population	B.3.2
Intervention technology and comparators	B.3.2
Clinical parameters and variables	B.3.3
Measurement and valuation of health effects and adverse events	B.3.4
Resource identification, valuation and measurement	B.3.5
Summary of inputs and assumptions	B.3.6
Results	B.3.7
Sensitivity analysis	B.3.8
Subgroup analysis	B.3.9
Validation	B.3.10
Interpretation and conclusions	B.3.11
Abbreviations used in table: CS, company submission.	

5.2 Summary of the company's key results

The company's preferred base case results based on the updated 24-month data cut from the CheckMate 238 trial are given in Table 24. The company only provided probabilistic sensitivity analysis (PSA) results for the 18-month data cut; the results of this are given in Table 25. For comparison, the ICER for the deterministic base case using the 18-month data cut was £8,769 per QALY.

Table 24. Company's base case results (extracted from company's economic model)

Results per patient	Nivolumab	Routine surveillance	Incremental
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	13.96	[redacted]
ICER			**£8,882**
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life year			

Table 25. PSA results base on 18-month data cut (adapted from CS, page 170, Table 58)

Results per patient	Nivolumab	Routine surveillance	Incremental
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	7.30	[redacted]
ICER			**£9,002** 95% CI: £4,981–£13,022
Abbreviations used in the table: CI, confidence interval; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life year			

5.3 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review (SLR) to identify economic evaluations and utility studies relating to adjuvant therapies for patients with melanoma. The process used by the company followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and consisted of three key stages: a comprehensive search of electronic databases and key relevant websites; a systematic selection of relevant studies based on pre-specified inclusion and exclusion criteria; and, an extraction of relevant data from eligible studies matching those criteria.

The key sources of evidence used in the search included:

- Embase®;
- The Cochrane Library, including:
    - Health Technology Assessment Database (HTAD);
    - National Health Service Economic Database (NHSEED);
- MEDLINE®;
- EconLit®.

The company also searched proceedings from a wide range of conferences from the last 3 years as well as HTA websites including NICE.

The economic evaluation search, conducted on 29 August 2017, was restricted to studies published since 2012, as changes in clinical practice for adjuvant melanoma meant that older studies were less applicable. Despite the reduced applicability of older studies, the utility studies search was not restricted by date. This was because of the expected paucity of published evidence for utility data. Full details of the inclusion and exclusion criteria are provided in Table 26.

Table 26. Inclusion and exclusion criteria for the economic and utility studies (CS, page 97, Table 20)

Category	Inclusion criteria		Exclusion criteria	
	Economic studies	**Utility studies**	**Economic studies**	**Utility studies**
Population	Adolescents and adults (≥12 years) patients with Stage III and IV resected (adjuvant) melanoma		Healthy volunteers Paediatric population (<12 years) Disease other than melanoma Stage I and II melanoma patients	
Interventions	Nivolumab, either alone or in combination with any other therapy Ipilimumab, either alone or in combination with any other therapy Interferon, either alone or in combination with any other therapy	No specific inclusion criteria	Non-drug treatments (e.g. surgery, radiotherapy) Studies assessing interventions not in included list of intervention	None
Comparators	No restriction; all therapies were included.	No specific inclusion criteria	No exclusion based on comparator	None
Outcomes	Incremental costs, LYs gained and QALYs, and any other measure of effectiveness (in term of which ICER is reported like RFS/PFS/OS/DMFS) reported together with costs Model inputs Sensitivity analysis	Studies reporting utility data (EQ-5D®, SF-6D, HUI, etc.)	Cost-only outcomes	Studies not reporting utility values will be excluded
Study design	Full-economic evaluations (cost-consequence, cost-effectiveness, cost–utility, cost–benefit, cost-minimisation, budget impact, all economic evaluation studies based on models)/HTA evaluations Economic evaluations alongside a trial	Utility studies Observational studies	Reviews, letters, and comment articles Simple cost analysis	Reviews, letters, and comment articles
Time limit	Studies published in the last 5 years were included	No restriction	Studies published before 2012	None
Language	English and French language		Other than English and French	
Country of study	No restriction		Not excluded on basis of country	

Abbreviations in table: HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LY, life year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year.

Initial screening of identified studies by title and abstract was performed by two reviewers independently to apply basic selection criteria for population, intervention and study design. Any uncertainty was checked by a senior reviewer. A second level of screening of full articles was then performed, again by two reviewers independently, with a senior reviewer checking where there is uncertainty. Data extraction was performed by one reviewer using a pre-specified extraction table. A second reviewer independently checked for errors against the original study reports.

The search did not identify any economic evaluations that matched the inclusion/exclusion criteria so no data were extracted by the company. The utility search identified 3 studies (from 4 publications) matching the inclusion/exclusion. The results of these are discuss in Section 5.4.7.

Full details of the search terms and excluded study tables are given in Appendix G of the company submission (CS)

Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases. However, the ERG considers that the company conducted a thorough search of the available literature and is likely to have identified all evidence relevant to the decision problem that is the focus of this STA.

5.4 Overview and critique of company's economic evaluation

The company conducted an economic evaluation of adjuvant nivolumab compared with routine surveillance for people with melanoma who have undergone complete resection. The company developed a *de novo* economic model to perform the evaluation, which is described in further detail in the following subsections.

5.4.1 NICE reference case checklist

Table 27 summarises the ERG's assessment 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 scope outlined in Section 3.

Table 27. NICE reference case checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
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 time horizon was set at 60 years, which was deemed sufficient to capture the lifetime of patients.
Synthesis of evidence on outcomes	Systematic review	Yes. A systematic review was conducted to identify data sources for outcome measures including disease recurrence, mortality and quality of life.
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	EQ-5D-3L
Benefit valuation	Time-trade off or standard gamble	Yes. Time-trade of valuation of the EQ-5D-3L.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes. EQ-5D-3L UK tariff.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
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	Yes
Abbreviations: EQ-5D, EuroQol-five dimensions questionnaire; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.		

5.4.2 Population

The population used in the economic analysis is intrinsically determined by the populations of the CheckMate 238 and CA184-029 trials.[1, 21] The CheckMate 238 trial compared nivolumab with ipilimumab and CA184-029 compared ipilimumab with placebo. These studies were in the adjuvant setting. And included adults with melanoma who had undergone a complete tumour resection. Patients who were 15 years or older were eligible for the CheckMate 238 trial but no patients under the age of 18 were enrolled due the limited number of patients in this age group.

There were differences in the distribution of disease stage across the two trials populations, with CheckMate 238 including more severe patients with Stage IV disease but no patients with less sever Stage IIIA disease. In contrast, the CA184-029 trial included patients with Stage IIIA disease but not Stage IV. The distribution of patients by disease stage is summarised in Table 28.

Table 28. Stage distribution in CA184-029 and CheckMate 238 (CS, page 102, Table 21)

Stage	CA184-029	CheckMate 238	Total	Adjusted for the overall population
Stage IIIA	186 (19.6%)	0 (0%)	186 (10.0%)	364* (16.5%)
Stage IIIB	420 (44.2%)	311 (34.5%)	731 (39.4%)	731 (33.1%)
Stage IIIC	345 (36.3%)	422 (46.8%)	767 (41.4%)	767 (41.4%)
Stage IV NED	0 (0%)	169 (18.7%)	169 (9.1%)	345** (15.6%)
Notes: *364 is 19.6% of total Stage IIIA, IIIB and IIIC (364/(364+731+767)) in line with CA184-029 distribution. **345 is 18.7% of total Stage IIIB, IIIC and IV (345/(731+767+345)) in line with CheckMate 238 distribution.				

The trials were conducted globally and the company's base case analysis uses the intention-to-treat (ITT) population to inform treatment effectiveness. However, for the estimation of nivolumab treatment costs, for which doses are determined by patient weight, data were taken only from the Western European population, which was considered to be more reflective of the UK than the global population.

5.4.2.1 ERG critique

The ERG considers the company's analysis to be largely in line with that proposed in the NICE final scope. Differences between trial populations, such as the distribution of disease stage, were adjusted for to provide a more reliable treatment effect, and the ERG considers the ITT population to be appropriate and to be reflective of the expected population in the UK.

The ERG considers the use of the Western European population to be appropriate for the estimation of treatment costs, as differences in patient characteristics globally are not likely to be reflective of the UK population.

5.4.3 Interventions and comparators

Nivolumab was assumed to be given intravenously at a dose of 3mg/kg every two weeks. This is in line with the study protocol for CheckMate 238 as well as the summary of product characteristics (SmPC).[1]

In CheckMate 238, treatment was given up to a maximum of 12 months or until disease recurrence, unacceptable toxicity, or patient withdrawal.[1] To estimate the costs of nivolumab treatment, PLD for time on treatment were used to provide an accurate reflection of the expected costs incurred. This is described in more detail in Section 5.4.3.

The comparator is routine surveillance, which consists of monitoring and follow up costs. These are described in more detail in Section 5.4.8.

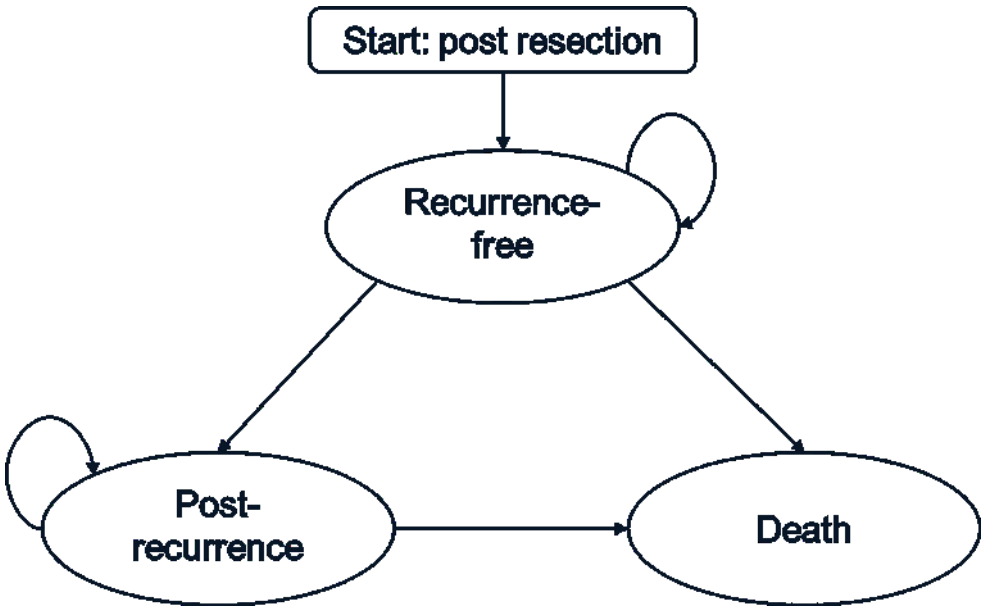
5.4.3.1 ERG critique

The ERG considers the intervention and comparator to be in line with the NICE final scope and is reflective of UK clinical practice. The company's use of PLD to estimate treatment costs accurately, based on the time on treatment as well as the patients' weight, is likely to be reflective of the costs that would be incurred by patients receiving nivolumab in clinical practice in the UK.

5.4.4 Modelling approach and model structure

The company's *de novo* economic model includes options for two alternative model structures: a partitioned survival structure, used in the company's base case analysis; and, a Markov structure, which is used to provide two alternative modelling options using alternative data sources and assumptions. Both structures are formed on the basis of three health states defined as recurrence-free (RF), post-recurrence (PR) and death, as depicted in Figure 17. The model has a time horizon of 60 years and a cycle length of 28 days. The alternative structures are discussed in turn in Sections 5.4.4.1 and 5.4.4.2.

Figure 17. Model structure for partitioned survival and Markov models (CS, page 104, Figure 33)



5.4.4.1 Partitioned survival (Base case)

The partitioned survival model (PSM), which was used in the company's base case analysis, uses overall survival (OS) and recurrence-free survival (RFS) data to directly inform the proportion of patients remaining in each of three health states at any given time. The OS data informs the proportion who are in the death state, the RFS data informs the proportion who are in the RF state, and the difference

between the two is the proportion in the PR state. Appropriate costs and utility values are applied in each health state, which are described in Section 5.4.8 and Section 5.4.7, respectively.

This approach is a simple application of the key outcome data relating to disease-free survival and mortality that is often collected in cancer drug trials. For this reason, it is a common approach taken to model the cost effectiveness of cancer drugs for NICE technology appraisals, and generally considered appropriate.

For this appraisal, RFS was informed by an indirect treatment comparison (ITC) between the CA184-029 trial, which compared ipilimumab with placebo, and the CheckMate 238 trial, which compared nivolumab with ipilimumab. The ipilimumab groups of the two trials provides the link to indirectly form the desired comparison of nivolumab and placebo.[1, 21] This is discussed further in Section 4.4.

The proportion of patients in the death state at any given cycle was informed by a surrogate relationship between RFS and OS that had previously been estimated using interferon trials in the adjuvant setting. The implementation of this and the estimation of long term treatment effects is discussed further in Section 5.4.5.

5.4.4.2 Markov model (alternative scenario analyses)

The company's economic model also includes an alternative Markov structure, which was used to test structural uncertainty and to provide a range of scenario analyses that enabled the modelling of alternate assumptions for long term treatment effectiveness. The Markov structure has the same health states and the same time horizon as the PSM but the key differences lie in application of the effectiveness data.

In contrast to the PSM, the Markov model relies on transition probabilities between each of the states, which are applied at each cycle to determine the proportion of patients in a particular health state at a particular time. This structure allows for alternative data sources to inform post-progression survival, which, in a PSM, would be inherently determined for the time horizon of the model by survival models used to inform the analysis.

5.4.4.3 ERG critique

The ERG considers the company's PSM and Markov structures used in the base case analysis and scenarios to be suitable structures for the decision problem. The model is generally well constructed and the ERG did not identify any errors in the functioning of the model.

The model contains relevant health states to capture the key changes in the natural history of the disease; namely, recurrence-free, disease recurrence and death. The time horizon is long at 60 years but the ERG considers this to be appropriate given that patients as young as 18 are included in the population. The

ERG also considers the cycle length of 28 days to be appropriate and likely to capture the key changes in events and resource use with sufficient granularity.

The key differences between the two model structures are that the Markov structure requires the RFS data to be "split" into transition probabilities to the PR state, and to the death state. To do this the company weighted the RFS parametric curves by the proportion of patients who had a recurrence and those who had died while in the RF state during trial follow-up. This assumes that the proportion is constant throughout the model time horizon. In contrast, the PSM structure uses the RFS and OS data directly, therefore, retaining the "true" proportion of patients in each state at any given time.

The Markov structure does, however, allow for flexibility in applying alternative sources to estimate transition probabilities from the PR state to death. The company did this using data from a meta-static setting to inform survival following particular subsequent treatments. The approach to this, along with the reasons and potential benefits for doing so, are discussed further in Section 5.4.5.

5.4.5 Treatment effectiveness

5.4.5.1 Partitioned survival model (Base case)

The PSM relies on parametric survival functions to estimate and extrapolate RFS and OS outcomes for the trial period and beyond. The key sources of evidence for this were the CheckMate 238 trial comparing nivolumab with ipilimumab, and the CA184-029 trial that compared ipilimumab with placebo.[1, 21]

Recurrence-Free Survival

For RFS, the CheckMate 238 and CA184-029 trials were used to form an ITC to estimate the relative effectiveness for nivolumab compared with placebo (assumed to be equivalent to routine surveillance), with the ipilimumab groups forming a common comparator. The company's primary method for the ITC was to use meta-regression to fit independent parametric survival functions to the data, which were adjusted for imbalances in key covariates, and importantly, for the trial difference between the ipilimumab groups. The company applied this method using the exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma functions. The best fitting models were identified by assessing the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics as well as the clinical plausibility of the resulting extrapolations.

Before fitting the parametric survival models, the company rebased the RFS data at 12 weeks, at which point there was substantial change in hazard. This improved the chances of providing a good model fit, as the parametric survival models used are not likely to be flexible enough to model such a change. For the first 12 weeks of the model, KM data from the CheckMate 238 trial were used directly for the

nivolumab group. For the routine surveillance group, a HR was derived by fitting a Cox proportional hazards (PHs) model to the ipilimumab groups of the CheckMate 238 and CA184-029 trials, with censoring applied at 12 weeks. The resulting HR was [redacted] and this was applied to the KM data from the placebo group of the CA184-029 trial and applied in the model for the first 12 weeks for the routine surveillance group.

For the post 12-week period, the best fitting curves chosen by the company were the log-logistic curves, for which the baseline curve was adjusted to the population of interest using the corrected group prognosis (CGP) method. This method was applied by weighting adjusted curves fitted for groups of patients with various combinations of specific covariates including, age, sex and disease stage, rather than the typical individual level approach. The unadjusted RFS curves fitted to the CheckMate 238 and CA184-029 trial data are given in Figure 18 and Figure 19, respectively, and the resulting adjusted curves used in the company's base case analysis are shown in Figure 20

Figure 18. CheckMate 238 RFS curves derived from log-logistic meta-regression ITC using 24-month datacut (Figure 3 from company's response to clarification questions)

Figure 19. CA184-029 RFS curves derived from log-logistic meta-regression ITC using 24-month datacut (Figure 6 from company's response to clarification questions)

Figure 20. RFS curves adjusted to relevant population for economic model (Figure 7 of the company's response to clarification questions)

The company applied different estimates of RFS after 10 years in the model. This was done by applying a HR for RFS relative to OS, which the company derived by fitting a Cox PH model to digitised KM data from the Argawala *et al.* 2017 trial, which assessed interferon in the adjuvant setting.[46] The resulting HR was [redacted], which was applied to the long-term OS data (beyond 10 years) described in the remainder of this section. The same method was applied to estimate a similar HR using data from the CA184-029 trial.[21] This resulted in a HR of [redacted], which was used in a scenario analysis, presented in Section 5.5.

Overall Survival

OS data from the CheckMate 238 trial were not available to the company at the time of conducting their analysis and, therefore, the company used RFS as a surrogate. To estimate OS from the RFS data in the CheckMate 238 trial, the company used a published study that predicted an OS HR from an RFS HR.[29] The equation was derived from a regression analysis using PLD, which used predominantly interferon trials in the adjuvant setting. The company used the HRs from this study, along with HRs from the CA184-029 trial and the recently published COMBI-AD trial, which compared dabrafenib in combination with trametinib against placebo, as adjuvant treatment for melanoma, and performed a

regression analysis to predict an OS HR from an RFS HR.[30] An outlier was removed from the group of trials used in the published study.

The company estimated a HR for RFS for nivolumab compared to ipilimumab and inputted this into the predictive equation to produce an estimated OS HR for nivolumab compared to ipilimumab. This was then multiplied by the OS HR for ipilimumab compared to placebo from the CA184-029 trial to produce an OS HR for nivolumab versus placebo. The resulting HR was [redacted].

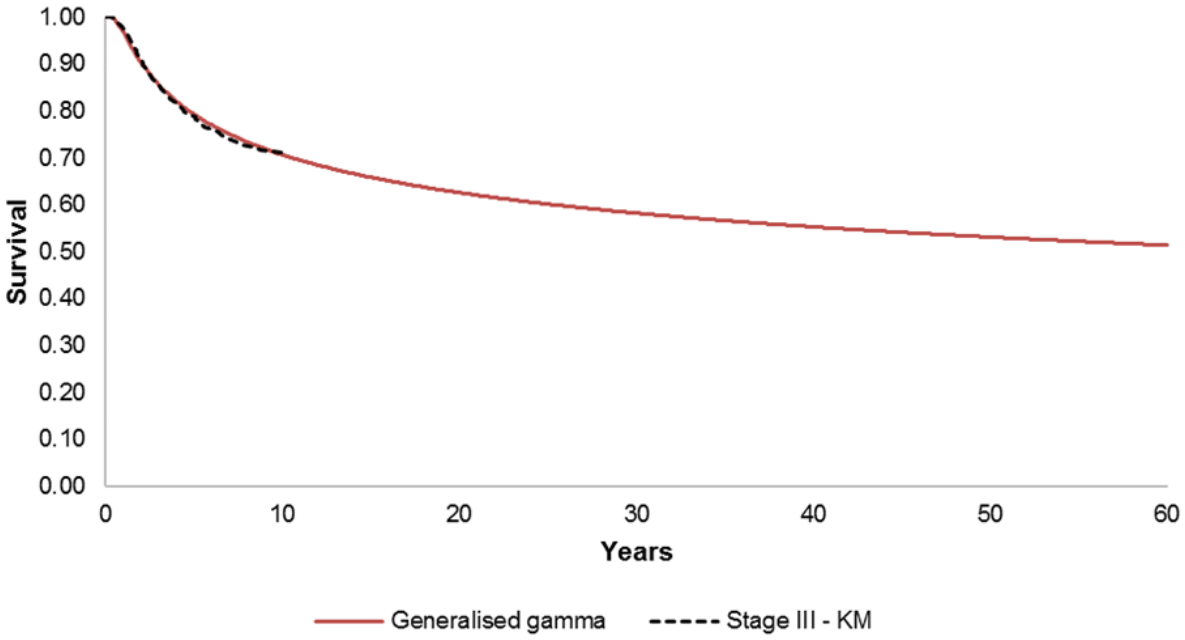
OS data was available from the CA184-029 trial, which the company used to fit a parametric survival curve for the placebo group. The best fitting curve for these data was determined by the company to be the generalised gamma distribution. The company used this as the baseline curve, adjusting using the CGP approach, as described previously, to align the curves to the population of interest. This adjustment included the assumption that the trial effect derived from the RFS ITC would be the same for OS. The resulting curve (along with the unadjusted curve) is shown in Figure 21. To estimate the long-term survival for the nivolumab group, the OS HR ([redacted]) derived from the predictive surrogacy equation was applied to this placebo survival curve.

Figure 21. OS curve fitted to placebo group of CA184-029 trial (CS, page 124, Figure 38)

These survival curves were used to determine the proportion of patients who have survived up to 10 years. From 10 years onwards, the company uses 8th edition AJCC registry data. The company digitised the Stage III KM plot and used the Guyot *et al.* 2012 algorithm to generate pseudo PLD, to which the

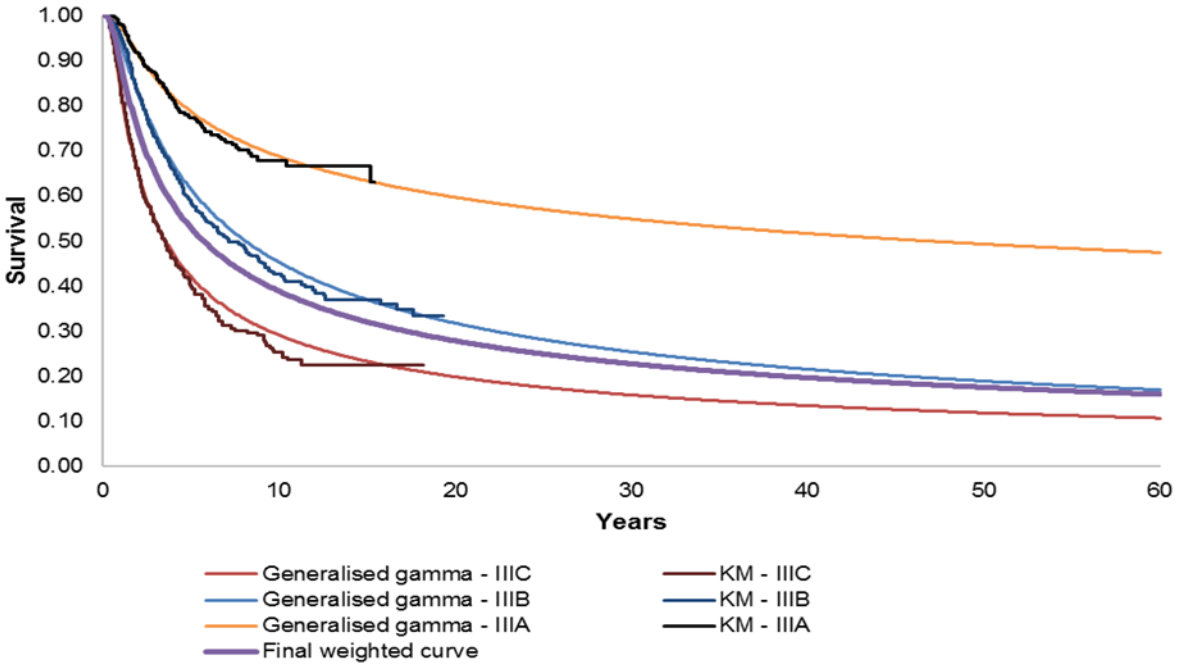
company fitted parametric survival curves.[47] The chosen best fitting curve was the generalised gamma function, as assessed using AIC and BIC statistics.

Figure 22. Generalised gamma curve fitted to Stage III AJCC 8th registry data (CS,page 126, Figure 39)



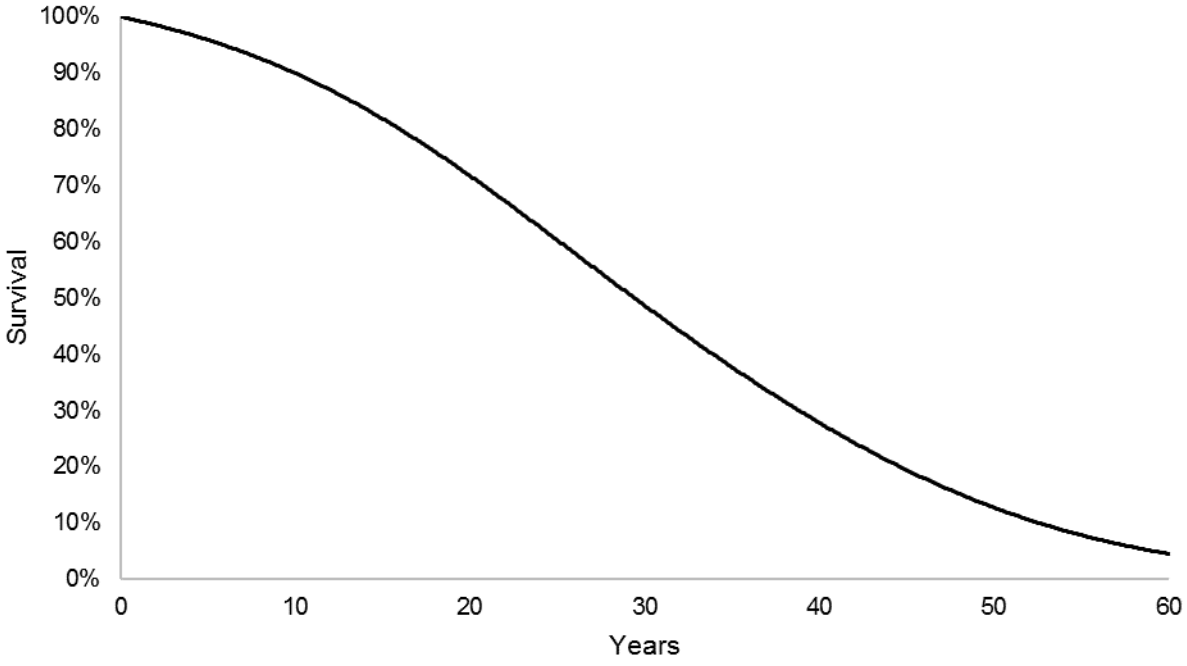
As an alternative scenario, the company digitised the Stage IIIA, IIIB, and IIIC KM data from the 7th edition AJCC data and fitted parametric curves.[17] The generalised gamma curve was also the best fitting curve for each stage subtype after assessing AIC and BIC statistics. The adjusted distribution of disease stage, as outlined in Table 28, was used to weight these curves. The fitted curves along with the final weighted curve are shown in Figure 23.

Figure 23. AJCC 7th edition registry data – Stage III with generalised gamma curves and final weighted curve (CS, page 127, Figure 40)



General population mortality data from the Office of National Statistics (ONS) were also used as a minimum mortality rate if predictions from the survival modelling became lower than this rate at any point across the time horizon of the model.[48] The general population mortality data are presented in Figure 24.

Figure 24. General population mortality (CS, page 128, Figure 41)



The resulting health-state partitions from the company's base case are depicted in Figure 25 and Figure 26, for nivolumab and routine surveillance, respectively. These figures show the proportions of patients in each of the health-states across the time horizon of the model.

[redacted]

[redacted]

[redacted]

5.4.5.2 Markov model (Option 1)

The Markov model uses the same RFS modelling from the ITC as per the PSM. However, to estimate the probability of remaining in the PF state and the probability of transitioning to death from the PF state, the composite RFS measure needed to be "split" to separate out the rates of recurrence and the rates of death. This was approximated by weighting the RFS curves by the proportion of patients from the CheckMate 238 trial who had disease recurrence and who died, from those patients who had experienced an event. This split was used up to 10 years after which the proportion of patients used to determine the weights was taken from the Agarwala *et al*. 2017 trial; a longer-term trial comparing interferon with routine surveillance in the adjuvant setting.[46]

Post-recurrence survival (PRS) uses the same OS data as in the PSM. To estimate PRS transition probabilities from the OS data, Cox PH models were fitted to the data in the CA184-029 trial to estimate treatment specific HRs for PRS compared with OS. The resulting HRs, which were applied to the OS modelling used in the PSM, were [redacted] and [redacted] for ipilimumab and placebo, respectively, which were used to estimate PRS for nivolumab and routine surveillance, respectively.

The resulting health-state partitions for the company's Markov scenario (Option 1), demonstrating the proportions of patients in each health-state across the time horizon of the model, are depicted in Figure 27 and Figure 28, for nivolumab and routine surveillance, respectively.

[redacted]

[redacted]

5.4.5.3 Markov model (Option 2)

The company also provided a second Markov option in the model, which used the same approach as the first option in terms of RFS, but had differences to the approach for estimating PRS.

The OS estimates for this modelling approach were derived from numerous data sources. For patients with a local/regional recurrence, the survival curves that were fitted to data from the CA184-029 trial were used. For patients with distant recurrence, a range of data sources, including Kaplan–Meier (KM) data from drug trials for advanced and/or metastatic melanoma, and registry data, were used to fit survival curves, which were then weighted to produce estimates expected to be reflective of the relevant population.

These curves were weighted by the subsequent treatments as per the treatments assessed in each of the data sources, and were assumed to apply up to 10 years. Beyond 10 years, registry data were used to estimate the proportion of patients alive at each cycle, and again, general population mortality data were used to impose a minimum mortality rate.

For patients in either the CheckMate 238 or CA184-029 trial who received nivolumab, ipilimumab or a combination of the two as a subsequent therapy, PRS was determined by the OS in the relevant group of the CheckMate 067 trial.[49]

PRS following pembrolizumab was determined by applying a HR to the ipilimumab data from the CheckMate 067 trial. The HR was determined using HRs reported in the KEYNOTE 006 trial,[50] comparing pembrolizumab 10mg/kg with ipilimumab (HR = 0.69), and KEYNOTE 002,[51] comparing pembrolizumab 10mg/kg with pembrolizumab 2mg/kg (HR = 0.87). The Bucher method was applied to estimate the HR for pembrolizumab 2mg/kg compared with ipilimumab (HR = 0.79), which was applied to the ipilimumab parametric curve.

Vemurafenib OS was estimated by fitting parametric survival curves to KM data from the BRIM-3 trial, which compared against dacarbazine for patients with untreated metastatic melanoma.[52] Dabrafenib subsequent treatment was assumed to have equal efficacy to vemurafenib. To estimate the OS for dabrafenib and trametinib combination, a HR was applied to the assumed dabrafenib parametric curve (equivalent to vemurafenib). This HR was taken from the COMBI-d study.[53]

For treatment with talimogene laherparepvec (T-VEC), it was assumed that efficacy was equal to ipilimumab based on the same assumption being used in TA410. A scenario was also conducted, which used digitised survival curves from Andtbacka *et al.* 2015, a randomised controlled trial (RCT) comparing T-VEC with granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with unresected Stage IIIB to Stage IV melanoma.[54]

For the final subsequent treatment that was included in the model, dacarbazine, the HR from the BRIM-3 trial (HR=0.76) was applied to the vemurafenib parametric survival curve. A scenario analysis was also conducted, in which it was assumed, based on a meta-analysis by Wada *et al.*2018,[55] that dacarbazine efficacy was equivalent to glycoprotein 100 (GP100), and therefore, applied a HR for ipilimumab compared to GP100 from Hodi *et al.* 2010 (HR=0.64).[56]

The resulting parametric survival curves fitted for each subsequent treatment are shown in Figure 29.

[redacted]

The health-state partitions, showing the proportion of patients in each health-state across the time horizon of the model, are presented in Figure 30 and Figure 31 for nivolumab and routine surveillance, respectively.

[redacted]

[redacted]

An alternative approach to estimating survival for these subsequent therapies was provided by a network-meta analysis (NMA) conducted by Precision Health. This NMA used dacarbazine as the reference treatment and estimated relative treatment effects for: nivolumab in combination with ipilimumab; nivolumab monotherapy; ipilimumab monotherapy; vemurafenib; dabrafenib; dabrafenib in combination with trametinib; and, pembrolizumab monotherapy.

Treatment effects were estimated as effectively time-varying hazard ratios by fitting parametric survival curves (including Weibull, Gompertz and a range of fractional polynomials) within an NMA framework. These curves are fitted independently to the trial data but the use of a single suitable parametric form allows a transitive and additive relationship between the estimated parameters that determines the treatment effect. The limitation of this approach is that a single functional form is required to be specified across the network, which may not provide the best fit for each individual treatment. The best fit is instead determined as a global best fit across the network by minimising the deviance information criterion (DIC) statistic.

The company used the second order fractional polynomials with parameters P1=0 and P2=1; this was determined to be the best fitting model as stated in the publication, as it had the least DIC value. The company fitted an exponential model to the dacarbazine data from the CA209-066 trial and used this as the reference curve. The company calculated the time-varying HRs as determined by the fractional polynomials and applied these to the dacarbazine curve. The resulting curves were then weighted by the proportion of patients receiving each of the subsequent treatments to provide an overall estimate of PRS.

5.4.5.4 ERG critique

The company provided a fairly thorough set of analyses in order to estimate the treatment effects for adjuvant nivolumab in comparison to routine surveillance. However, key issues that make the outcomes potentially unreliable remain. The results of the cost effectiveness analysis should, therefore, be considered with caution. For clarity, the treatment effectiveness critique will be separated by model type (PSM and Markov structure) in the following subsections.

5.4.5.4.1 Partitioned survival (ERG critique)

For the estimation and extrapolation of RFS for nivolumab and routine surveillance, the company's approach was generally sound, although some issues remained that could not be fully addressed. The company considered a range of survival models and adjusted for imbalances in key covariates. The company chose the best fitting curves by minimising AIC and BIC statistics, and the ERG agreed with their chosen curves using the log-logistic distribution.

However, the ERG was concerned that disease stage had not been adequately adjusted for, given that some stages (Stage IIIA and Stage IV) lacked patients in at least one of the trials. These differences, therefore, could not be fully adjusted for, given that outcomes for these subgroups of patients are informed only by patients receiving one of the treatments.

The ERG considers the use of long term estimates of RFS, applied using a HR comparing RFS with OS in the Agarwala *et al.* 2017 study, to be potentially unreliable.[46] This relative measure is based on a study of adjuvant interferon and may not be applicable to an immunotherapy like nivolumab. The ERG considers that a plausible extrapolation from the ITC modelling should inform long term RFS.

Further uncertainty in the estimation of RFS is the reliability of the ITC. One key issue with the ITC is that patients in the ipilimumab group of the CA184-029 trial received treatment for up to three years, whereas patients in the CheckMate 238 trial were restricted to just one year. This means that the effectiveness of the two trials may not be comparable, making the relative effect for nivolumab compared with placebo also potentially unreliable. The ERG disagrees with the company's view that [redacted] of patients remaining on treatment beyond one year is not likely to be an important factor. In the ERG's opinion, this proportion of patients could influence the effectiveness substantially.

In response to clarification questions, the company provided an analysis whereby the patients in the CA184-029 trial were censored if treatment discontinuation occurred after one year. The ERG notes that the effectiveness of ipilimumab was reduced slightly after censoring and still had a reasonable number of patients at risk beyond one year for the analysis to be considered reliable. This analysis indicates that the RFS treatment effect estimates from the ITC using the ITT population are potentially overestimated. The KM plots for the censored data compared to the ITT data are shown for comparison in Figure 32.

Figure 32. CA184-029 recurrence-free survival KM for the ITT population and for the ITT population where patients are censored at one year if they remained on treatment (Figure 11 of the company's response to clarification questions)

Abbreviations in figure: Ipi, ipilimumab 10 mg; ITT, intention-to-treat KM, Kaplan–Meier; PBO, placebo; TRT, treatment; yr, year.

Another potentially greater area of uncertainty within the company's PSM analysis is the estimation of overall survival for patients who receive adjuvant nivolumab and for those who receive routine surveillance. The first aspect of this uncertainty lies with the reliance on a surrogate relationship between RFS and OS, given the lack of OS data available to the company from the CheckMate 238 trial. This surrogate relationship was based on data from predominantly interferon-based studies and may not accurately reflect the expected outcomes for an immunotherapy such as nivolumab. This issue is one that the company could not fully resolve given the lack of studies for immunotherapies in the adjuvant setting. An additional issue, however, is that the derived HR from the surrogacy relationship was applied to a baseline generalised gamma survival model; a model that does not support the use of PH. This potentially leads to implausible extrapolations, as the resulting model for nivolumab would not be an equivalent generalised gamma model.

The ERG considers their preferred approach for estimating OS for nivolumab [redacted] to the CHMP. This is shown in Figure 33.

Figure 33. CheckMate 238 [redacted]

Although the company do not have the PLD required to provide an adjusted ITC for OS, [redacted]. This allows for a comparison where randomisation is retained and avoids the need to assume a surrogacy between RFS and OS, by using the CA184-029 OS data directly. However, the population of the CA184-029 is not equivalent to the CheckMate 238 trial so an adjustment would be required to allow this data to be reliably used in combination with the RFS ITC, which is adjusted relative to the CheckMate 238 trial population.[1, 21]

Even after potentially resolving the unreliable OS issue, a second key problem regarding estimates of OS remains. This issue is that the subsequent treatments received by patients in the two trials are not reflective of current UK clinical practice, according to clinical expert advice sought by the ERG. This was particularly important for the CA184-029 trial, which is an older trial conducted at a time when the available therapies were less effective in comparison to, for instance, immunotherapies that are becoming commonplace today. The consequence of this is that the OS estimates in the placebo group of the CA184-029 trial are likely to be underestimated and, therefore, the relative benefit of nivolumab over routine surveillance is likely to be overestimated. An alternative approach to assess the impact of this issue is discussed within the Markov structure critique in Section 5.4.5.4.2

5.4.5.4.2 Markov structure (ERG critique)

The first modelling option within the company's Markov structure (Option 1) provides an alternative to the surrogacy relationship to estimate OS; however, this alternative brings with it, different issues that do not necessarily mitigate the uncertainty in the results.

This Markov model structure avoids the requirement for the surrogate relationship to predict the OS benefits based on the RFS benefits, by using alternative data sources to estimate PRS transition probabilities. However, a key concern that the ERG has is with the application data used to inform PRS and the assumptions made in the application.

In particular, the ERG is uncertain that the assumption of a constant relative effect on the OS hazard, regardless of the applicability in the Agarwala *et al.* 2017 study, may not be a reliable measure of estimating PRS.[46] However, the company also provide a scenario analysis using the CA184-029 trial, which may be preferable given that it is a trial assessing an immunotherapy in the adjuvant setting rather than interferon. This modelling approach does not, however, resolve the issue of inappropriate subsequent therapies influencing OS outcomes.

The alternative modelling approach provided by the company using the Markov structure (Option 2) allows for the issues of inappropriate subsequent treatments to be explored. The data sources used are from various trials of different drugs used in the post-recurrence setting, meaning that both of these issues can be explored by applying a suitable proportion of patients to the subsequent treatments as used in UK clinical practice. The validity of applying the OS data from these alternative sources also needs to be considered, which is discussed later in this section.

The ERG sought clinical expert opinion to inform the expected proportions of subsequent therapies in order to assess the potential impact on OS and on the ICER. The experts suggested that a greater use of immunotherapies such as pembrolizumab and ipilimumab would be used in clinical practice. A key point that the experts raised is that nivolumab would be used in a metastatic setting following routine surveillance, and may in fact have the same efficacy as using nivolumab in the adjuvant setting. The ERG conducted a scenario using the Markov Option 2 model, which set all patients in the routine surveillance group who had a distant recurrence to receive subsequent nivolumab. All other subsequent treatments were kept the same. This increased the ICER from £18,685 per QALY to £161,658 per QALY.

The ERG emphasises the fact that this analysis uses a range of potentially disparate sources of evidence to inform PRS, so it is unlikely that the estimates of PRS and the applicability to the population on which the ITC was formed is robust and reliable. However, even if the analysis was considered reliable, the range of ICERs resulting from plausible scenarios demonstrates the potentially serious uncertainty

that currently exists within the results. The ERG considers it difficult to fully account for this uncertainty without an OS ITC using the CheckMate 238 trial data, with appropriate adjustments for subsequent treatments.

The scenarios assuming all patients with a distant recurrence in the routine surveillance group receive subsequent nivolumab using data from the metastatic NMA with fractional polynomial models, resulted in ICERs of £589,557 per QALY. These results merely act to reiterate the uncertainty, as the applicability of these data is not certain, nor has it fully been justified by the company. Further to this, the company applied the underlying time-varying HRs to an exponential model for dacarbazine. This is methodologically flawed as it breaks the transitivity between survival models in the NMA and, hence, breaks the applicability of the relative treatment effect. The company should have instead fitted a fractional polynomial with parameters P1=0 and P2=1 to the dacarbazine data in order to retain the transitivity of the treatment effect across the network.

5.4.5.4.3 Summary of critique

Overall, the ERG considers there to be a large degree of uncertainty remaining in the analysis, although it appears difficult to mitigate this uncertainty without the availability of PLD from the CheckMate 238 trial to form an adjusted ITC for OS. Based on the data available, the ERG considers it preferable to assume OS for nivolumab is equivalent to ipilimumab, and to use the Markov Option 2 structure to apply subsequent therapy costs and survival outcomes reflective of treatments expected to be received in the UK. The ERG acknowledges that this is still a very uncertainty analysis and only partially mitigates the uncertainty in the company's analysis. However, the ERG considers the company's analyses to be no less certain than the ERG's scenario that resulted in an ICER greater than £300k per QALY, hence, emphasising the potential impact of the uncertainty.

5.4.6 Adverse events

Adverse events (AEs) were included in the economic analysis to account for resources required to management those that occur in patients who receive nivolumab. The company included immune-related AEs of any grade, diarrhoea of grade 2 or above, and any other AE of grade 3 or above.

The company noted that previous metastatic melanoma NICE submissions of immunotherapies had applied a similar approach, using endocrine disorders instead of immune-related AEs. The company considered immune-related AEs to be more appropriate given that the comparator is routine surveillance, making the broader inclusion of AEs a potentially more important factor.

For nivolumab, data were taken directly from the all-cause data in the CheckMate 238 trial. For the proportions of immune-related AEs and diarrhoea in the routine surveillance group, the risk of AEs

from the placebo group of CA184-029 was adjusted for the difference in risks across the ipilimumab groups of the two trials. This adjustment is demonstrated in the following equation:

$$Routine\ surveillance\ AEs\ \% = 029\ placebo\ \% \times \frac{238\ ipi\ \%}{029\ ipi\ \%}$$

The impact of AEs on utilities was based only on the average AE risk in the CheckMate 238 trial, as treatment specific utility values were not used in the model.

5.4.6.1 ERG critique

The ERG considers the inclusion criteria for AE events to be reasonable and to be comprehensive enough to capture the key differences in the impacts of AEs expected to be observed between the treatment and comparator.

However, the ERG considers the use of adjusted AE risks for the routine surveillance group to be methodologically incorrect. The differences in AE risks between the ipilimumab groups of the two trials is likely to be influenced by the differences in treatment duration, as ipilimumab was given for a maximum of one year in CheckMate 238 and a maximum of three years in CA184-029. Differences related to treatment duration will be independent of the risk of AEs for the comparator treatments and, therefore, the indirect relative risk of nivolumab compared to placebo would be unaffected by this. It could be affected by imbalances in patient characteristics across the trial groups but the company did not adjust for this, and the impact would likely be minimal.

Overall, the ERG considers the company's approach to be incorrect. However, the resulting AE risks for routine surveillance are not implausible and are not too dissimilar to the unadjusted data from the CA184-029 trial. The impact of this on the ICER is likely to be minimal.

5.4.7 Health-related quality of life

Health-related quality-of-life (HRQoL) was measured in the CheckMate 238 trial using the EQ-5D-3L generic health questionnaire. The CA184-029 trial did not obtain EQ-5D data but did use the EORTC QLQ-C30 cancer specific HRQoL measure, as did the CheckMate 238 trial. As the NICE-preferred measure is the EQ-5D, the company used only the EQ-5D data from the CheckMate 238 trial in the base case analysis. However, the company also used to the EORTC QLQ-C30 data to map to the EQ-5D index scores and provided a scenario analysis using these estimated utility values.

5.4.7.1 CheckMate 238 data

Data were collected at weeks 1, 5, 7, 11, 17, 25, 37, and 49 in the CheckMate 238 trial. The number of EQ-5D observations recorded in the CheckMate 238 trial is summarised in Table 29.

Table 29. Number of patients and EQ-5D observations by treatment (CS, page 139, Table 31)

TRT	Patients (ITT population)	Patients (analysis)	Observations	Mean number of observations
All	[redacted]	[redacted]	[redacted]	[redacted]
Ipi	[redacted]	[redacted]	[redacted]	[redacted]
Nivo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: Ipi, ipilimumab; ITT, intention-to-treat; Nivo, nivolumab; TRT, treatment.

The company's first analysis of this data was to assess the mean and median values by health state and treatment group. A summary of this is shown in Table 30. The company noted that the utility observed in the group of patients whose health state was unknown, was greater than the values for the pre-recurrence health state. Given that there were only a relatively small number of observations for the unknown group, the company removed these from subsequent exploratory analyses.

The company also noted a difference in the pre-recurrence and post-recurrence values across treatment groups, and therefore, considered including an interaction term in a regression model to be appropriate. Interestingly, the nivolumab group had a greater mean utility for the pre-recurrence period but a lower utility for the post-recurrence period. The company stated that the change may be a result of the differences in subsequent treatments received in the different primary treatment groups.

Table 30. Utility summaries by health state and treatment (CS, page 140, Table 32)

Health state	TRT	Patients	Observations	Mean (SD)	Median (IQR)	Range
Pre-recurrence	All	868	5624	[redacted]	[redacted]	[redacted]
Post-recurrence	All	290	909	[redacted]	[redacted]	[redacted]
Unknown[a]	All	196	251	[redacted]	[redacted]	[redacted]
All	Ipi	434	3093	[redacted]	[redacted]	[redacted]
All	Nivo	449	3691	[redacted]	[redacted]	[redacted]
Pre-recurrence	Ipi	423	2443	[redacted]	[redacted]	[redacted]
Post-recurrence	Ipi	162	527	[redacted]	[redacted]	[redacted]
Pre-recurrence	Nivo	445	3181	[redacted]	[redacted]	[redacted]
Post-recurrence	Nivo	128	382	[redacted]	[redacted]	[redacted]

Abbreviations in table: Ipi, ipilimumab; IQR, inter-quartile range; Nivo, nivolumab; SD, standard deviation; TRT, treatment.
Notes: [a], Observations after recurrence-free survival censoring.

The company also assessed utilities for people in the pre-recurrence health state by time to event (recurrence or death) and found that there was a positive correlation; i.e. a longer time to event was associated with a greater utility. These are summarised in Table 31. However, there were 529 people

who had yet to experience an event in the trial, which the company considered to be too great for time-to-event to be a reliable predictor of utility.

Table 31. Pre-recurrence utility summaries by time to event (CS, page 141, Table 33)

Time to event	Number of patients	Number of observations	Mean (SD)	Median (IQR)	Range
≤76	257	442	[redacted]	[redacted]	[redacted]
77–193	202	435	[redacted]	[redacted]	[redacted]
>193	126	439	[redacted]	[redacted]	[redacted]
Censored	529	4308	[redacted]	[redacted]	[redacted]
Abbreviations in table: IQR, inter-quartile range; SD, standard deviation.					

The company assessed patients' baseline characteristics before performing a regression analysis. These are given in Table 32.

Table 32. Utility summaries by patient characteristics (CS, page 142, Table 34)

Characteristic	Level	Patients (%)	Observations	Mean (SD)	Median (IQR)	Range
Age (years)	< 65	657 (0.74)	4910	[redacted]	[redacted]	[redacted]
	≥ 65	226 (0.26)	1623	[redacted]	[redacted]	[redacted]
Sex	F	370 (0.42)	2767	[redacted]	[redacted]	[redacted]
	M	513 (0.58)	3766	[redacted]	[redacted]	[redacted]
Disease Stage	IIIB	302 (0.34)	2323	[redacted]	[redacted]	[redacted]
	IIIC	415 (0.47)	3018	[redacted]	[redacted]	[redacted]
	IV	162 (0.18)	1156	[redacted]	[redacted]	[redacted]
	Other/ NR	4 (0.00)	36	[redacted]	[redacted]	[redacted]
B-RAF	Mutant	373 (0.42)	2773	[redacted]	[redacted]	[redacted]
	Wildtype	114 (0.13)	2924	[redacted]	[redacted]	[redacted]
	NR	396 (0.45)	836	[redacted]	[redacted]	[redacted]
PD-L1	< 5% / unknown	583 (0.66)	4270	[redacted]	[redacted]	[redacted]
	≥ 5%	300 (0.34)	2263	[redacted]	[redacted]	[redacted]
Abbreviations in table: F, female; IQR, inter-quartile range; M, male; NR, not reported; SD, standard deviation.						

The company then used patient level data PLD in a regression analysis to adjust for baseline covariates as well as health states and time to event variables. The following variables were those considered in the regression:

- Health state (pre-recurrence, post-recurrence or unknown);
- Treatment (nivolumab or ipilimumab);
- Time to event (recurrence or death; continuous characteristic);
- Baseline utility;
- Age (< 65 or ≥ 65 years old);
- Gender (male or female);
- Stage (IIIa [mapped analysis only], IIIb, IIIc or IV);
- B-RAF status (mutant, wildtype or not reported);
- PD-L1 status (< 5% / unknown or ≥ 5%).

A forward selection procedure was applied to determine the inclusion of these covariates in the regression model, which added variables one-by-one and remained in the model if the AIC was reduced. All models included a random effect for patients to adjust for the correlation between multiple observations, and a fixed effect for baseline utility.

The resulting regression model included all the above covariates as well as an interaction between post-recurrence and treatment with ipilimumab. The reference for the indicators of treatment group and health state were nivolumab and pre-recurrence; hence, the interaction term being specified as post-recurrence and ipilimumab. The results of the regression are given in Table 33, with the resulting utilities by health state and treatment group given in Table 34.

Table 33. Regression model coefficients (CS, page 145, Table 35)

Coefficient	Value	Standard error	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility	[redacted]	[redacted]	[redacted]	[redacted]
Treatment: Ipi (ref: Nivo)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence: post (ref: pre-recurrence)	[redacted]	[redacted]	[redacted]	[redacted]
Disease Stage: IIIc (ref: IIIb)	[redacted]	[redacted]	[redacted]	[redacted]
Disease Stage: IV (ref: IIIb)	[redacted]	[redacted]	[redacted]	[redacted]
Interaction: post*Ipi	[redacted]	[redacted]	[redacted]	[redacted]
Key: CI, confidence interval; Ipi, ipilimumab; Nivo, nivolumab.				

Table 34. Estimated utilities from the final regression model (CS, page 145, Table 36)

Health state	Nivolumab*	Ipilimumab
Pre-recurrence	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]
Notes: Nivolumab utilities are applied to both nivolumab and routine surveillance in the base case		

5.4.7.2 Mapping from EORTC QLQ-C30 to EQ-5D

As the utility data in the CheckMate 238 trial only provide utility estimates from patients who received either nivolumab or ipilimumab, the company also mapped EORTC QLQ-C30 scores, which were collected in both the CheckMate 238 and the CA184-029 trial, onto the EQ-5D index. This allows an indirect comparison of HRQoL measures between nivolumab and placebo, which was used to provide a scenario analysis in the economic model.

A suitable mapping algorithm was searched for using the University of Oxford Health Economic Research Centre mapping database.[57] There were 12 mapping studies identified that mapped from EORTC QLQ-C30 to EQ-5D but none of these were based on data from patients with melanoma. The company assessed suitability of the available studies based on the similarity of the observed utilities in CheckMate 238; model fit statistics in the mapping study, including mean absolute error (MAE) and root mean squared error (RMSE); similar statistics in a published external validation; and, the use of the UK tariff.

After applying these criteria, the company narrowed down the selection to two studies: Crott and Briggs 2010,[58] which used data with a high utility score similar to CheckMate 238 and good fit statistics in an external validation study; and the second algorithm was by Longworth *et al.* 2013*,* which used the full range of EQ-5D scores and also demonstrated good fit statistics in an external validation.[59]

The company applied both mapping algorithms onto the CheckMate 238 data for validation as this trial contains both the measures, so predicted and observed EQ-5D values can be compared. The company plotted these values on a scatterplot with a line of perfect fit for comparison, and calculated MAE and RMSE. These demonstrated that the Longworth *et al.* 2013 provided the best fit. The scatterplots and fit statistics can be found in Appendix O of the CS. The baseline mapped utilities are given in Table 35

Table 35. Mapped utilities by trial and treatment (CS, Appendix O, page 140, Table 52)

Trial	TRT	Patients (%)	Observations (%)	Mean (SD)	Median (IQR)	Range
Trial 029	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial 238	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial 029	Ipi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial 029	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial 238	Ipi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial 238	Nivo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: Ipi, ipilimumab; IQR, inter-quartile range; Nivo, nivolumab; PBO, placebo; SD, standard deviation; TRT, treatment.

After applying a forward selection procedure to adjust for baseline utility, sex and repeated measures, the resulting mapped utilities by treatment and disease recurrence were determined and the result are given in Table 36.

Table 36. Mapped utilities by health state and treatment (CS, page 148, Table 38)

Health state	Nivolumab	Ipilimumab	Placebo
Pre-recurrence	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]	[redacted]

The company also identified three studies from the SLR, as stated in Section 5.3. These are summarised in Table 37.

Table 37. Summary of published utilities (CS, page 149, Table 39)

Study	Mean utilities		Mean disutility for toxicity*	
Middleton *et al.* 2016[60]		(Overall/UK/Australia)	Diarrhoea	-0.09
	Adjuvant no toxicities	0.890/0.840/0.942	Toxicity-hospital	-0.16
	Induction treatment	0.878/0.845/0.914	Hypophysitis	-0.13
	No treatment	0.855/0.837/0.875	Depression	-0.11
	Recurrence	0.620/0.581/0.662	Toxicity-outpatient	-0.11
	Recurrence long-term treatment survival	0.737/0.703/0.774	Flu	-0.08
			Rash	-0.08
			Nausea	-0.08
			Fatigue	-0.06
Crott *et al.* 2004[61]		Mean (SD), median	NR	
	IFN treatment	0.52 (0.29), 0.58		
	Recurrence	0.23 (0.23), 0.08		
	RFS	1		
	Death	0		
Hillner *et al.* 1997[62]		Mean (range)	NR	
	Induction IFN	0.7 (0.0–1.0)		
	Maintenance IFN	0.8 (0.0–1.0)		
	Recurrent disease	0.5 (0.0–1.0)		
	Disease-free, no treatment			
Abbreviations in table: IFN, interferon; NR, not reported; RFS; recurrence-free survival; SD, standard deviation. **Note:** *No toxicity disutilities differed by country.				

5.4.7.3 Adverse event utility decrements

The disutilities for diarrhoea and toxicity (hospital and outpatient) from Middleton *et al.* 2016 were applied in the economic analysis using the AE frequencies and average durations in the CheckMate 238 trial.[60] They are applied as a one-off impact at the start of the model, with immune-related AEs and other AEs weighted by inpatient visits to apply the appropriate toxicity decrement.

The company acknowledge that there may be some double counting with adverse events experienced in CheckMate 238, but they consider the impact likely to be low given that the utilities are assumed to

be equal across treatment groups. A scenario analysis was also conducted to assess the impact of potential double counting and this is provided in Section 5.5.

5.4.7.4 ERG critique

The ERG considers the company's approach to utility estimation within the economic analysis to be generally sound. The company appropriately applied EQ-5D-3L values from the trial informing the treatment effectiveness where data were available, i.e. CheckMate 238 trial for nivolumab. Where evidence was not available, i.e. for routine surveillance, the company's approach to estimating utilities by applying a mapping algorithm was suitable and they provided a clear justification for the selection of the mapping study used. The company also considered the use of published utilities from other studies to assess the potential uncertainty in this data. The ERG considers the company's approach to be thorough and appropriate.

However, for the impact of AEs, the ERG considers inclusion of AE decrements using an external source to be unnecessary. The company apply the same utilities and same utility decrements to each treatment group so there is no benefit in capturing the differences between treatments. Further to this, the impact of AEs would already be captured within the trial data itself, so the purpose of applying these utility decrements is unclear. The ERG considers a more plausible approach would be to attempt to remove the impact of AEs from the health-state utility values (HSUVs) by adding the decrements to the utility values for the routine surveillance group. However, the ERG considers this to be unlikely to affect the results of the cost-effectiveness analysis.

5.4.8 Resources and costs

The company conducted a SLR to identify evidence relating to resource use and costs to be unnecessary, given that they had access to PLD for both the CheckMate 238 and CA184-029 trials that inform the treatment effectiveness within the economic analysis. The company also considered that the treatment pathways in the metastatic setting have changed considerably in recent years making it unlikely that relevant and up-to-date evidence would be publicly available.

5.4.8.1 Drug costs

The unit cost of nivolumab per vial based on the list price and the current agreed patient access scheme (PAS) are given in Table 38. There are two vial sizes available; 4ml and 10ml, both with a concentration of 10mg/ml, providing a dose per vial of 40mg and 100mg, respectively.

Table 38. Nivolumab unit costs (CS, page 153, Table 42)

Nivolumab vial options		
Concentration	10mg/ml	10mg/ml
Vial volume	4ml	10ml
Dose per vial	40mg	100mg
Price per vial (no PAS)	£439.00	£1097.00
Price per vial (with PAS) – base case	[redacted]	[redacted]
Source for prices without PAS	MIMS September 2017[63]	

Abbreviations in table: MIMS, Monthly Index of Medical Specialities; PAS, patient access scheme.

To estimate the expected overall cost of nivolumab, the company used data from the CheckMate 238 trial for the proportion of patients who received each of the planned doses. This was used to calculate the average cost per patient per administration cycle. The administration cost was taken from NHS reference costs and assumed to be a day case setting, which was associated with a cost of £259.76 (ref: SB12Z).

The required dose for a patient is dependent on their body mass. Therefore, to estimate the average number of vials required to fulfil each of the received doses, the method-of-moments technique was implemented, using data from the Western European populations in the CheckMate 238 and CA184-029 trials. This method uses the distribution of patient's weight from the trials, approximated using a lognormal distribution, and applies the relevant vial unit costs to form the distribution of costs. The mean of this distribution is then used to as the cost per patient per treatment cycle. A scenario was also conducted using only the UK population data.

5.4.8.2 Health state resource use and costs

The company conducted a survey of six UK clinicians to elicit resource use for each of the health states in the economic model. [redacted]

Clinicians were asked for resource use frequencies for patients who are recurrence-free; those who have local/regional unresectable recurrences; those who have local/regional resectable recurrences; and, those who have distant recurrences. Changes over time were also factored into the resource use estimates by specifying it separately for years 1, 2, 3–5, and beyond year 5. The results of the survey outlining the model inputs for resource use are given in Appendix P of the CS.

These resource use frequencies were then applied to unit costs, which were taken from NHS Reference Costs 2016-17 or the Personal Social Services Research Unit (PSSRU) 2017 publication .[64, 65] These unit costs are given in Table 39. The resulting health state costs for each time frame are given in

Table 40.

Table 39. Medical resource use unit costs (CS, page 155, Table 43)

Resource	Cost (£)	Reference
Outpatient visits		
Oncologist/ Surgeon	107.00	PSSRU 2017 - Hospital Based Doctors. Consultant Surgical cost per working hour
GP/PCP	28.00	PSSRU 2017 - General Practitioners cost per 9.22-minute consultation without qualifications
Dermatologist	106.00	PSSRU 2017 - Hospital Based Doctors. Consultant Medical cost per working hour
Nurse visits	37.00	PSSRU 2017 - Band 5 Hospital based Nurse cost per working hour
Imaging		
Chest x-ray	85.69	NHS reference costs 16/17 - RD20A - Computerised Tomography Scan of One Area, without Contrast, 19 years and over
PET-CT (chest and abdomen)	334.28	NHS reference costs 16/17 - RN02A - Positron Emission Tomography with Computed Tomography (PET-CT) of Two or Three Areas, 19 years and over
CT (chest and abdomen)	112.33	NHS reference costs 16/17 - RD24Z - Computerised Tomography Scan of Two Areas, with Contrast
MRI (head)	139.30	NHS reference costs 16/17 - RD01A - Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over
CT (head)	97.39	NHS reference costs 16/17 - RD21A - Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over
Other*	118.35	Average between NHS reference costs RD01A and RD21A
Laboratory tests		
CBC	1.69	NHS reference costs 16/17 - DAPS03 - Integrated Blood Services
Comprehensive metabolic panel	1.13	NHS reference costs 16/17 - DAPS04 - Clinical Biochemistry
LDH	1.13	
Albumin	1.13	
Calcium	1.13	
C-reactive protein	1.13	
Liver function test	1.13	

Abbreviations in table**:** CBC, complete blood count; CT, computed tomography; GP, general practitioner; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCP, primary care physician; PET, positron emission tomography; PSSRU, Personal Social Services Research Unit.
Notes: *One clinician reported that the 'other' was a CT scan of the neck; the other clinicians did not specify. It is assumed that 'other' is a single scan of one area either by MRI or CT.

Table 40. Monitoring costs for patients split by timeframe and health state applied within the model (CS, page 156, Table 44)

Health state	Year 1 cost (£)	Year 2 cost (£)	Year 3–5 cost (£)	Year 5+ cost (£)
Recurrence-free	[redacted]	[redacted]	[redacted]	[redacted]
Local/regional recurrence (unresectable)	[redacted]	[redacted]	[redacted]	[redacted]
Local/regional recurrence (resectable)	[redacted]	[redacted]	[redacted]	[redacted]
Distant recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Weighted average for post-recurrence monitoring costs*	[redacted]	[redacted]	[redacted]	[redacted]

Notes: *Weighted average for post-recurrence monitoring costs based on post-recurrence patient proportions as reported in the CheckMate 238 patient-level data.

5.4.8.3 Resource use for adverse reactions

As discussed in Section 5.4.6, the company included costs associated with any grade of immune-related disorders, diarrhoea grade ≥2, and other AEs grade ≥3, which occurred in at least 5% of patients. For nivolumab, this data was taken from the CheckMate 238 trial, which also collected data for the number of hospitalisations required for treatment of AEs. For routine surveillance, AEs were based on the relative difference between the ipilimumab and placebo groups of the CA184-029 trial and the ipilimumab and nivolumab groups of the CheckMate 238 trial, with the exception of "other" AEs, which were assumed to be the same as nivolumab in the base case analysis because of an implausible difference making AEs higher for the placebo group.

The model captures the different resources expected to be incurred by inpatient and outpatients. Costs for inpatients were calculated using the weighted non-elective excess bed day unit costs for endocrine disorders, and for other AEs, the total HRG excess bed day cost was used; both from NHS reference costs 2016-17. These costs are summarised in Table 41.

Table 41. Adverse event inpatient costs (CS, page 157, Table 45)

Treatment	Hospital cost (£)	Type of stay	Reference
Hospital bed day (immune-related)	£297.41	Non-elective excess bed days	Weighted average between KA08A, DZ29H and FD01C- NHS reference costs 2016/17[64]
Hospital bed day (other AEs)	£305.85	Total HRGs - Non-elective inpatients	Excess bed days - NHS reference costs 2016/17[64]

Abbreviations in table: AE, adverse events; HRG, healthcare resource group; NHS, National Health Service.
Note: Endocrine disorders used as costs for immune-related disorders.

The proportion of patients treated for AEs in an inpatient or outpatient setting was not recorded in either the CA184-029 or CheckMate 238 trials. To inform this, the company used a study by Oxford Outcomes,[66] which was designed to estimate resource use associated with advanced melanoma in the UK, Italy, Sweden, Spain and Portugal. The UK resource estimates were used to inform the model and these were inflated to 2016-17 prices using the PSSRU inflation indices.[65]

Table 42. Adverse event outpatient costs (CS, page 158, Table 46)

Outpatients and unit costs	Value	Reference
% Treated as outpatient (immune-related disorders)	24.2%	Oxford Outcomes. Table 91
Unit outpatient cost (immune-related disorders)	£428.08	Oxford Outcomes. Table 17
% Treated as outpatient (diarrhoea)	19.2%	Oxford Outcomes. Table 91
Unit outpatient cost (diarrhoea)	£649.85	Oxford Outcomes. [66 27] Table 17
% Treated as outpatient (other Grade 3+ AEs)	21.7%	Oxford Outcomes. Table 91
Unit outpatient cost (other Grade 3+ AEs)	£403.68	Oxford Outcomes. Table 16/17

Abbreviations in table: AE, adverse events.

The company calculated the average AE costs per patient (taking account for those who do not have AEs) and applied this as a one-off cost at the beginning of the model for simplicity. The summary of the costs per patient are given in Table 43.

Table 43. Summary of AE costs per patient (CS, page 158, Table 47)

	Nivolumab	Routine surveillance
Hospitalisation costs – immune-related disorders (any grade)	[redacted]	[redacted]
Hospitalisation costs – diarrhoea (Grade ≥2)	[redacted]	[redacted]
Hospitalisation costs – other AEs (Grade ≥3)	[redacted]	[redacted]
Hospitalisation costs – subtotal	[redacted]	[redacted]
Outpatient costs – immune-related disorders (any grade)	[redacted]	[redacted]
Outpatient costs – diarrhoea (Grade ≥2)	[redacted]	[redacted]
Outpatient costs – other AEs (Grade ≥3)	[redacted]	[redacted]
Outpatient costs – subtotal	[redacted]	[redacted]
Total cost (per trial patient)	[redacted]	[redacted]
Abbreviations in table: AE, adverse event.		

5.4.8.4 Subsequent therapies

5.4.8.4.1 Systemic therapies

The company's model included the costs of subsequent systemic therapies received in the CA184-029 and CheckMate 238 trials to account for differences in those received following adjuvant nivolumab and routine therapy. The company sought clinical expert opinion, which suggested that the CheckMate 238 trial was likely to be more reflective of current clinical practice given changes in the metastatic melanoma pathway over the last 5 years. As a result, the company used CheckMate 238 to inform the base case analysis, by assuming that the nivolumab and ipilimumab groups of the trial reflect the proportions of subsequent treatments for nivolumab and routine surveillance, respectively. The proportions of subsequent therapies by treatment group and by location of recurrence (local/regional or distant) from the CheckMate 238 trial is given in Table 44.

Table 44. Subsequent treatmeant sreceived in CheckMate 238 by treatment group and recurrance location (CS, page 160, Table 48)

	Local/regional recurrence		Distant recurrence	
	Nivolumab	Routine surveillance*	Nivolumab	Routine surveillance
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]

	Local/regional recurrence		Distant recurrence	
	Nivolumab	Routine surveillance*	Nivolumab	Routine surveillance
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Note: *Subsequent treatment data from ipi arm following recurrence.				

Unit costs were taken from either MIMS or eMIT and applied to the proportions of taken from the CheckMate 238 trial to estimate an overall subsequent treatment cost per person by treatment and location of recurrence.[63, 67] PASs for nivolumab and ipilimumab were applied but the company did not have access to PASs for the other subsequent treatments. The total costs of subsequent systemic therapies per person is summarised in Table 45.

Table 45. Subsequent systemic treatment cost per person (extracted from economic model)

Recurrence location	Nivolumab	Routine surveillance
Local/regional	[redacted]	[redacted]
Distant	[redacted]	[redacted]

5.4.8.4.2 Subsequent surgery and radiotherapy

Subsequent surgery and radiotherapy costs were also included in the economic analysis base on the proportions of patients receiving these in the CheckMate 238 trial, again with the ipilimumab group assumed to be reflective of patients who have routine surveillance. The unit costs were taken from NHS reference costs. These data are summarised in Table 46, with the subsequent surgery/radiotherapy cost per person given Table 47.

Table 46. Subsequent surgery and radiotherapy in CheckMate 238 (CS, page 163, Table 50)

Subsequent treatment	Local/regional recurrence		Distant recurrence		Unit cost	Reference
	CheckMate 238		CheckMate 238			
	Ipi	Nivo	Ipi	Nivo		
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	£100.72	NHS reference costs 16/17 – 160 Plastic surgery – total outpatients
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£297.09	NHS reference costs 16/17 – SC29Z – other radiotherapy – day case

Subsequent treatment	Local/regional recurrence		Distant recurrence		Unit cost	Reference
	CheckMate 238		CheckMate 238			
	Ipi	Nivo	Ipi	Nivo		
Abbreviations in table: Ipi, ipilimumab; Nivo, nivolumab; NHS, National Health Service.						

Table 47. Subsequent surgery or radiotherapy cost per person (extracted from economic model)

Recurrence location	Nivolumab	Routine surveillance
Local/regional	[redacted]	[redacted]
Distant	[redacted]	[redacted]

These costs were combined and applied to each model cycle by weighting by the proportion of newly post-disease patients, estimated by the difference in RFS at each cycle multiplied by the proportion of RFS events of which were recurrence events. The total costs are shown in Table 48.

Table 48. Total subsequent treatment cost per person (extracted from economic model)

Recurrence location	Nivolumab	Routine surveillance
Local/regional	[redacted]	[redacted]
Distant	[redacted]	[redacted]

5.4.8.4.3 End-of-life costs

The company also applied a one-off cost representing the costs incurred for end-of-life (EoL) treatment. This cost was based on a total cost derived from Round *et al.* 2015, which estimated the costs of caring for cancer during the final stages of before death.[68] This study estimated the costs of health, social and informal care for patients with either breast, colorectal, lung or prostate cancer in England and Wales. The company used the average costs and applied an inflation factor from the PSSRU indices to uplift to 2016-17 prices.[65] The total cost for each treatment and the average costs are given in Table 49.

Table 49. End-of-life costs (CS, page 164, Table 52)

Category	Breast	Colorectal	Lung	Prostate	Average
Health care	4,346	4,854	3,157	6,687	4,254
Social care	2,843	1,489	1,358	2,728	1,829
Informal care – indirect costs*	4,868	2,850	2,420	4,814	3,265
Note: All costs are in GBP. *Indirect costs are those costs arising from the illness but where a payment is not made, such as lost wages due to time off work. This has been valued using the human capital approach.					

5.4.8.5 ERG critique

The ERG was initially concerned that the company had not conducted a SLR to search for appropriate sources of resource use data; however, the ERG considers the model inputs for resource use and costs to be generally suitable with only a few exceptions.

5.4.8.5.1 Subsequent therapies (ERG critique)

The most important of these issues concerns the application of subsequent therapy costs. However, the appropriateness of this application of subsequent therapies needs to be considered in parallel with the appropriateness of the treatment effectiveness measures and the impact of subsequent therapies on post-progression survival. This aspect of the critique will, therefore, need to be considered in relation to the issues discussed in Section 5.4.5.4.

The first issue with subsequent therapies that the ERG considers to be potentially unreliable are the data used to inform the proportion of patients receiving each therapy. The ERG agrees with the company that the CheckMate 238 trial is a closer reflection of UK current practice given the more recent undertaking of the trial in comparison to CA184-029. However, the use of ipilimumab data to inform routine surveillance subsequent treatments is potentially unreliable.

Clinical expert opinion sought by the ERG suggests that these data are not reflective of UK clinical practice and there would be a greater use of more effective subsequent systemic therapies such as nivolumab following routine surveillance. The company's scenario using the placebo group of the CA184-029 is even less reflective given the age of the trial, as it includes the use of therapies such as interferon and interleukin, which would not be used in UK clinical practice today.

Another issue with using subsequent therapies that are not current UK practice, and have not been appraised by NICE, is that the associated cost may not reflect the value gained by that therapy as judged against a cost-effectiveness threshold. For instance, if the routine surveillance group received ineffective subsequent therapies with a large cost, this would bias the economic analysis in favour of nivolumab, if only cost-effective subsequent therapies were applied to the nivolumab group. Scenarios relating to this issue are considered in Section 6 in conjunction with alternate approaches to estimating treatment effectiveness, which is likely to be the more influential variable on the ICER.

5.4.8.5.2 Imaging costs (ERG critique)

After seeking clinical expert opinion, the ERG considers the assumptions regarding imaging resource use to be potentially excessive. For example, for the imaging costs for patients who are recurrence-free in the first year, the company assumes that [redacted] of patients will have a computed tomography (CT) scan of the chest and abdomen, and [redacted] of patients will have positron emission tomography (PET) scan of the chest and abdomen; both every six months. This implies that the majority of patients will receive two scans. While clinical experts acknowledge that the PET scan may be used to confirm the findings of the CT scan, this is not considered to be commonly undertaken in UK clinical practice. This issue applies to resource use for disease recurrence as well as imaging for the head, which implies many patients receive both CT and magnetic resonance imaging (MRI). The impact of this potentially

excessive resource use was assessed by removing the cost of PET scans, which reduced the company's base case ICER by £30, while removing the costs of MRI scans, reduced the ICER by £60.

5.4.8.5.3 End-of-life costs (ERG critique)

A final minor issue with resource use is application of EoL costs. These costs include health care costs as well as social care costs. Although the NHS does reimburse some social care costs, this does not necessarily apply to all patients considered in the economic analysis. However, given the costs applied are equivalent in each treatment group, this is likely to have a negligible impact on the ICER.

5.5 Results included in company's submission

In response to clarification questions, the company submitted a model with an updated 24-month data cut for the CheckMate 238 trial. The results presented throughout this section are based on these updated data, unless stated otherwise.

5.5.1 Base case results

The company's base case analysis is based on the PSM structure, which uses data from the ITC between the CheckMate 238 and CA184-029 trials for RFS, and the application of a surrogacy relationship to estimate OS from the RFS data. The results of the base case are given in Table 50, with a summary of LYs and QALYs given in Table 51 and Table 52, respectively.

Table 50. Company's base case results (extracted from company's economic model)

Results per patient	Nivolumab	Routine surveillance	Incremental
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	13.96	[redacted]
ICER			**£8,882**
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life year			

Table 51. Summay of life-years by health state (extracted from company's economic model)

Health State	Nivolumab	Routine surveillance	Incremental LY	Absolute increment	% Absolute increment
Recurrence-free	[redacted]	8.75	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	5.21	[redacted]	[redacted]	[redacted]
Total	[redacted]	**13.96**	[redacted]	[redacted]	**100.00%**
Abbreviations used in the table: LY, life year.					

Table 52. Summay of QALYs by health state (extracted from company's economic model)

Health State	Nivolumab	Routine surveillance	Incremental QALY	Absolute increment	% Absolute increment
Recurrence-free	[redacted]	4.50	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	2.68	[redacted]	[redacted]	[redacted]
Disutility	[redacted]	-0.01	[redacted]	[redacted]	[redacted]
Total	[redacted]	**7.18**	[redacted]	[redacted]	**100.00%**
Abbreviations used in the table: QALY, quality-adjusted life year.					

5.5.2 Alternative Markov model (Option 1)

The company provided an alternative model structure that was largely in line with the base case analysis using the PSM structure but required an assumption to split the RFS data into transition probabilities for recurrence and death from the RF health state. The estimation of PRS was also a difference between the two, as treatment-specific HRs comparing PRS to OS were derived from the CA184-029 trial and applied to the modelled OS used in the PSM. The results of this alternative approach are given in Table 53, with a summary of LYs and QALYs given in Table 54 and Table 55, respectively.

Table 53. Company's preferred assumptions (extracted from company's economic model)

Results per patient	Nivolumab	Routine surveillance	Incremental
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	11.26	[redacted]
ICER			**£8,567**
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life year			

Table 54. Summay of life-years by health state (extracted from company's economic model)

Health State	Nivolumab	Routine surveillance	Incremental LY	Absolute increment	% Absolute increment
Recurrence-free	[redacted]	6.44	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	4.82	[redacted]	[redacted]	[redacted]
Total	[redacted]	**11.26**	[redacted]	[redacted]	**100.00%**
Abbreviations used in the table: LY, life year.					

Table 55. Summay of QALYs by health state (extracted from company's economic model)

Health State	Nivolumab	Routine surveillance	Incremental QALY	Absolute increment	% Absolute increment
Recurrence-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health State	Nivolumab	Routine surveillance	Incremental QALY	Absolute increment	% Absolute increment
Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	**100.00%**
Abbreviations used in the table: QALY, quality-adjusted life year.					

5.5.3 Alternative Markov model (Option 2)

The company provide a second Markov alternative, which used alternative sources of OS data from a metastatic setting to inform PRS. The data from these alternative sources were used to fit survival curves, which were weighted by the proportion of patients receiving subsequent treatments in the CheckMate 238 trials; routine surveillance subsequent treatments being informed by the ipilimumab group. The results of this alternative approach are given in Table 56, with a summary of LYs and QALYs given in Table 57 and Table 58, respectively.

Table 56. Company's preferred assumptions (extracted from company's economic model)

Results per patient	Nivolumab	Routine surveillance	Incremental
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	14.08	[redacted]
ICER			**£18,685**
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life year			

Table 57. Summay of life-years by health state (extracted from company's economic model)

Health State	Nivolumab	Routine surveillance	Incremental LY	Absolute increment	% Absolute increment
Recurrence-free	[redacted]	6.44	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	7.64	[redacted]	[redacted]	[redacted]
Total	[redacted]	**14.08**	[redacted]	[redacted]	**100.00%**
Abbreviations used in the table: LY, life year.					

Table 58. Summay of QALYs by health state (extracted from company's economic model)

Health State	Nivolumab	Routine surveillance	Incremental QALY	Absolute increment	% Absolute increment
Recurrence-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

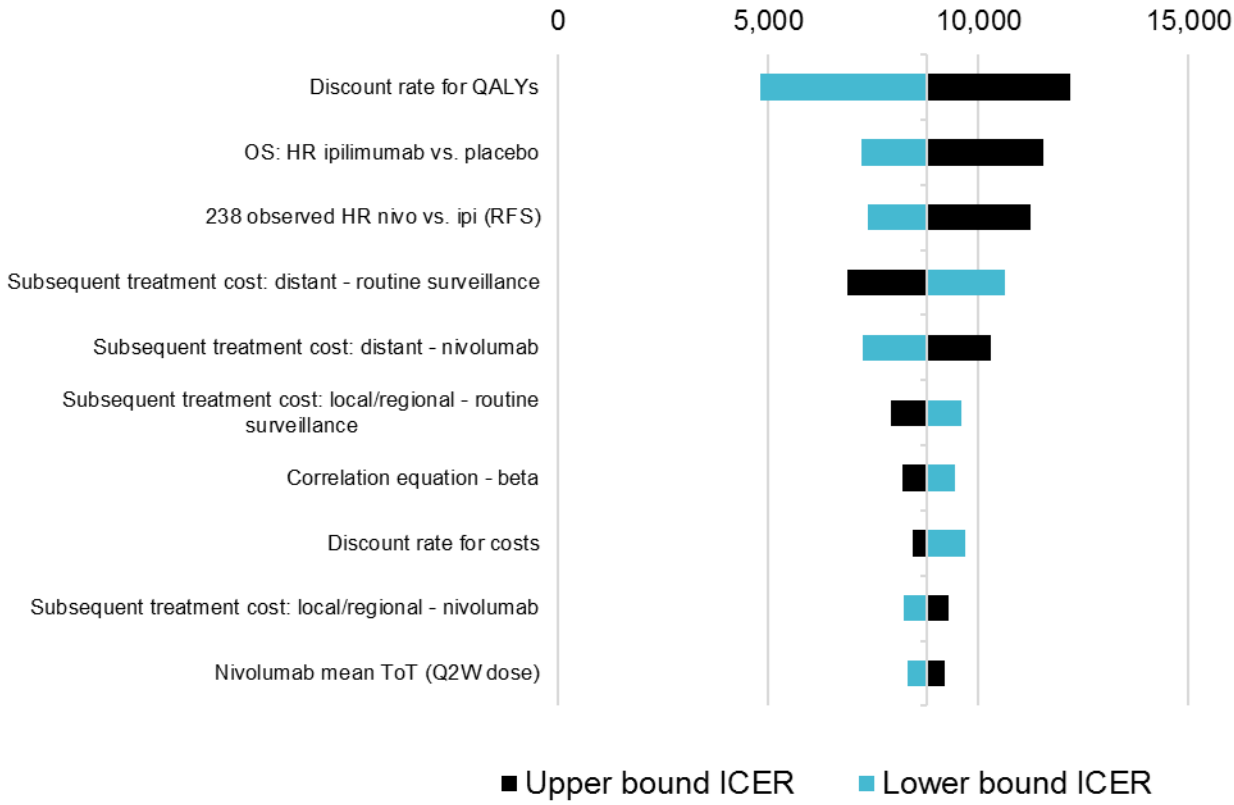
Health State	Nivolumab	Routine surveillance	Incremental QALY	Absolute increment	% Absolute increment
Total	[redacted]	[redacted]	[redacted]	[redacted]	**100.00%**
Abbreviations used in the table: QALY, quality-adjusted life year.					

5.5.4 Sensitivity analysis

5.5.4.1 One-way sensitivity analyses

The company undertook a range of one-way sensitivity analyses (OWSAs) in which each relevant parameter (i.e. an uncertain parameter) was varied over a plausible range to assess the impact on the ICER. The top ten most influential variables are displayed on the tornado plot in Figure 34.

Figure 34. Tornado diagram of the 10 most influential parameters on the ICER (CS, page 173, Figure 46)



Abbreviations in the table: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; RFS, recurrence-free survival; ToT, time on treatment.

The company also conducted a threshold analysis by varying HRs that were applied to the nivolumab groups for OS, RFS and both. They found that an increase of 58% in the HR for OS was required to increase the ICER above the £30k per QALY threshold. The results using a range of HRs based on the confidence intervals of the HR estimated for RFS from the CheckMate 238 trial are given in Table 59

Table 59. Threshold analysis results – ICER with PAS price (adapted CS, page 175, Table 59)

Scenario	Hazard ratio applied									
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. HR applied to OS	7,094	7,541	7,917	8,324	8,769	9,256	9,791	10,383	11,039	12,205
2. HR applied to RFS	7,132	7,653	8,037	8,408	8,769	9,120	9,460	9,793	10,116	10,596
3. HR applied to OS and RFS	5,855	6,626	7,277	7,988	8,769	9,632	10,594	11,669	12,884	15,094

Abbreviations in table**:** HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; RFS, recurrence-free survival.

5.5.4.2 Scenario analyses

The company also conducted a range of scenario analyses to assess structural uncertainty in the model. This included, for instance, changing the distributions for RFS and OS, changing the time horizon and using an alternative data source for the surrogacy relationship. The results of these analyses are given in Table 60.

Table 60. Results of scenario analysis (CS, page 175, Table 60)

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	8,769
Population	Patient characteristics: (029 and 238) Stage proportions: 029 & 238 adjusted RFS for nivolumab and routine surveillance: ITC (029 and 238)	CheckMate 238 CheckMate 238 Nivo: 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	8,309
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	8,469
Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	9,070
		50 years	[redacted]	[redacted]	[redacted]	8,832
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	8,740
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	8,357
Subsequent treatment data source	Trial '238 data	Trial '029 data	[redacted]	[redacted]	[redacted]	7,067
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	12,464
		Gompertz*	[redacted]	[redacted]	[redacted]	4,613
		Log-normal	[redacted]	[redacted]	[redacted]	8,334
		GGamma	[redacted]	[redacted]	[redacted]	8,490
		Weibull	[redacted]	[redacted]	[redacted]	9,272
Long-term survival adjustment	Gershenwald, applied after 10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	8,010
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	10,886

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	8,055
		Balch, 5 years	[redacted]	[redacted]	[redacted]	14,789
		Balch, 10 years	[redacted]	[redacted]	[redacted]	10,239
		Balch, 20 years	[redacted]	[redacted]	[redacted]	8,454
		OS/RFS HR from '029 trial	[redacted]	[redacted]	[redacted]	8,928
		Balch, OS/RFS HR from '029 trial	[redacted]	[redacted]	[redacted]	10,491
Source for correlation equation RFS/OS	Coart et al. 2018	Suciu et al.	[redacted]	[redacted]	[redacted]	8,189
OS for routine surveillance	Generalised Gamma	Exponential*	[redacted]	[redacted]	[redacted]	8,278
		Gompertz	[redacted]	[redacted]	[redacted]	8,722
		Log-normal	[redacted]	[redacted]	[redacted]	8,539
		Log-logistic	[redacted]	[redacted]	[redacted]	8,536
		Weibull*	[redacted]	[redacted]	[redacted]	8,770
Long-term-data curve selection	Gershenwald, GGamma	Balch, Exponential**	[redacted]	[redacted]	[redacted]	14,077
		Balch, GGamma	[redacted]	[redacted]	[redacted]	10,239
		Balch, Log-normal	[redacted]	[redacted]	[redacted]	11,576
		Balch, Log-logistic	[redacted]	[redacted]	[redacted]	11,561
		Balch, Weibull**	[redacted]	[redacted]	[redacted]	12,312
		Exponential**	[redacted]	[redacted]	[redacted]	10,597
		Gompertz	[redacted]	[redacted]	[redacted]	8,497
		Log-normal	[redacted]	[redacted]	[redacted]	9,518
		Log-logistic	[redacted]	[redacted]	[redacted]	9,712
		Weibull**	[redacted]	[redacted]	[redacted]	10,075
End-of life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	8,623
Utilities source	Observed EQ-5D Apply same utility to across treatments Separate stage covariate	Include AE disutilities: No	[redacted]	[redacted]	[redacted]	8,761
		Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	8,826

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
	Include AE disutilities: Yes	Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	8,834
		Middleton et al.	[redacted]	[redacted]	[redacted]	8,312
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	8,769
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	8,834
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	8,768
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	8,834
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	8,846
Post-recurrence survival	Treatment specific PRS (using PSM)	Assume same PRS (using Markov option 2)	[redacted]	[redacted]	[redacted]	12,112

Abbreviations in table: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; LY, life year; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival.
Note: The curve fits that are indicated (*) are those which do not meet the validation criteria (**) are those that fit the data poorly.

5.5.4.3 Probabilistic Sensitivity Analysis

The company performed a probabilistic sensitivity analysis (PSA) on the original 18-month data cut, with 1,000 iterations. The summary results for the PSA are given in Table 61, while the individual results are displayed on the cost-effectiveness plane shown in Figure 35, and the cost-effectiveness acceptability curve in [redacted].

Table 61. PSA results base on 18-month data cut (adapted from CS, page 170, Table 58)

Results per patient	Nivolumab	Routine surveillance	Incremental
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£9,002** 95% CI: £4,981 to £13,022
Abbreviations used in the table: CI, confidence interval; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life year			

Figure 35. [redacted]

Figure 36. Cost-effectiveness acceptability curve (CS, page 172, Figure 45)

Abbreviations in the table: WTP, willingness to pay.

5.5.5 Model validation

The company validated various aspects of the economic model with clinical and health economic experts. They also conducted internal validation, as well as using external sources of data to validate projections of outcomes.

The company performed internal validation by comparing the model outcomes against the CheckMate 238 and CA184–029 trial outcomes. These are summarised for RFS in Table 62, and for OS in CA184-029 in Table 63.

Table 62. Trial RFS versus model RFS (CS, page 181, Table 61)

	Data median (years)	Year 1	Year 2	Year 3	Year 4
CA184-029					
Trial '029 RFS – Placebo (KM)	1.43	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – Routine surveillance*	1.53	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 238					
Trial '238 RFS – Nivolumab (KM)	NA	[redacted]	[redacted]	NA	NA
Model RFS – Nivolumab**	NA	[redacted]	[redacted]	NA	NA

Abbreviations in the table**:** KM, Kaplan–Meier; RFS, recurrence-free survival.
Note**:** Trial data medians were sourced from trial CSR.
* Patient characteristics were based on CA184-029.
** Patient characteristics were based on CheckMate 238.

Table 63. Trial CA184-029 versus model OS (CS, page 182, Table 62)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Trial '029 OS – Placebo (KM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model OS – Routine surveillance*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in the table: KM, Kaplan–Meier; OS, overall survival. Notes: *Patient characteristics were based on CA184-029.							

The company performed external validation using long term OS data for routine surveillance from the AJCC 7th edition data (Balch *et al.* 2009)[17] and the AJCC 8th edition data (Gershenwald *et al.* 2017).[12] A comparison of the base case model outputs against various subgroups from these two sources is shown in Table 64.

Table 64. Long-term OS data for external validation (CS, page 184, Table 63)

	Year 1	Year 2	Year 5	Year 10	Year 15
Balch 2009 Stage IIIA	97.8%	91.6%	77.3%	67.7%	66.5%
Balch 2009 Stage IIIB	95.5%	83.0%	58.4%	42.6%	37.1%
Balch 2009 Stage IIIC	85.5%	64.5%	40.3%	25.3%	22.6%
Balch 2009 Stage III (weighted) - AJCC 7v	**89.0%**	**74.4%**	**52.9%**	**38.9%**	**32.1%**
Balch 2009 Stage IV abnormal LDH	33.3%	19.4%	9.7%	7.5%	NA
Balch 2009 Stage IV normal LDH	69.4%	44.1%	24.2%	18.8%	NA
Gershenwald 2017 Stage III - AJCC 8v	**97.8%**	**91.3%**	**79.3%**	**71.7%**	**NA**
Routine surveillance OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in the table: LDH, lactate dehydrogenase; OS, overall survival. Note: Data not collected after 10 years for Gershenwald *et al.* (2017).					

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG did not identify any errors in the company's model.

6.2 ERG scenario analysis

6.2.1 Partitioned survival model scenarios

6.2.1.1 Scenario 1: Alternative OS modelling using CA184-029

The ERG conducted a scenario analysis on the company's base case partitioned survival model, which changed the OS models to the adjusted generalised gamma curves that the company fitted to the CA184-029 but with a different trial adjustment applied. The company used the trial effect coefficient estimated from the RFS ITC; [redacted] The ERG instead added an arbitrary increase of 0.5 to the *mu* parameter of the models until the curve appeared to be in line with the KM. The resulting curves are without and with the change shown in Figure 37 and Figure 38, respectively.

[redacted]

[redacted]

[redacted]

6.2.1.2 Scenario 2: RFS using censoring at one-year of treatment continuation

This scenario was provided by the company in response to clarification questions. It uses RFS data that is censored for the ipilimumab group of the CA184-029 trial for patients who have treatment beyond one year.

6.2.1.3 Scenario 3: Combination of Scenario 1 and Scenario 2

This scenario uses the OS modelling as described in Scenario 1, but uses the company's RFS scenario, in which the RFS ITC was performed using data that was censored for patients who were on treatment beyond one-year in the ipilimumab group of CA184-029.

The results of these scenarios are given in Table 65, along with the company's preferred base case results for comparison.

Table 65. Scenario analyses for company's base case (PSM)

	Results per patient	Nivolumab (1)	Routine surveillance (2)	Incremental value (2-1)
0	**Company's preferred base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	13.96	[redacted]
	ICER			**£8,882**
1	**Alternative OS modelling using CA184-029 with scaling factor (*mu* increased by 0.5)**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	17.83	[redacted]
	ICER (compared with base case)			**£18,030**
2	**RFS using censoring at one-year of treatment continuation**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	14.68	[redacted]
	ICER (compared with base case)			**£9,066**
3	**Combination of Scenario 1 and Scenario 2**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	17.83	[redacted]
	ICER (compared with base case)			**£18,047**
	Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.			

6.2.2 Markov model scenarios

6.2.2.1 Scenario 1: RFS using censoring at one-year of treatment continuation

This scenario was provided by the company in response to clarification questions. It uses RFS data that is censored for the ipilimumab group of the CA184-029 trial for patients who have treatment beyond one year.

6.2.2.2 Scenario 2: Nivolumab as subsequent therapy after routine surveillance

This scenario uses Markov Option 2 and applies subsequent nivolumab to all patients with a distant recurrence following routine surveillance.

6.2.2.3 Scenario 3: Nivolumab after routine surveillance; ipilimumab after nivolumab

This scenario uses Markov Option 2 and applies subsequent nivolumab to all patients with a distant recurrence following routine surveillance, and, ipilimumab to all patients who have a distant recurrence after adjuvant nivolumab.

The results of these scenario analyses are given in Table 66 along with the company's results of their preferred analysis for the Markov Option 2 model.

Table 66. Scenario analyses for Markov Option 2 model

	Results per patient	Nivolumab (1)	Routine surveillance (2)	Incremental value (2-1)
0	**Company's Markov Option 2**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	14.08	[redacted]
	ICER			**£18,685**
1	**RFS using censoring ipilimumab at one-year**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	14.19	[redacted]
	ICER (compared with base case)			**£18,960**
2	**Nivolumab as subsequent therapy for distant recurrence after routine surveillance**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	16.89	[redacted]
	ICER (compared with base case)			**£161,688**
3	**Nivolumab after routine surveillance; ipilimumab after adjuvant nivolumab (distant recurrence only)**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	16.89	[redacted]
	ICER (compared with base case)			**£34,925**
	Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.			

6.3 ERG base case ICER

The ERG's preferred base case is based on the company's alternative model; the Markov Option 2. The ERG made three key changes to the company's preferred assumptions for this model, outlined in the following bullets:

- RFS based on the ITC analysis that used censoring for patients who received treatment beyond one year in the ipilimumab group of the CA184-029 trial;
- nivolumab applied as subsequent therapy for patients with a distant recurrence after routine surveillance;
- ipilimumab applied as subsequent therapy for patients with a distant recurrence after adjuvant nivolumab.

Although subsequent therapies can vary depending on the patient and the provider, the ERG considered a simplistic approach to assume that all patients within a particular treatment group have the same subsequent treatments following a distant recurrence.

The chosen therapies are both recommended in the metastatic setting by NICE and, therefore, represent a cost-effective use of resource. Clinical experts suggested that nivolumab is the most effective and should be the first choice; however, they were uncertain as to whether it should be used following adjuvant nivolumab. The clinicians considered ipilimumab to be an appropriate immunotherapy that could be used after adjuvant nivolumab as it is a different class of drug.

The results of the ERG's preferred base case ICER are given in Table 67.

Table 67. ERG base case ICER

Results per patient	Nivolumab	Routine surveillance	Incremental value
Company's alternative model (Markov Option 2)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	14.08	[redacted]
ICER			**£18,685**
RFS using censoring at one-year of treatment continuation			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	14.19	[redacted]
ICER (compared with company ICER)			**£18,960**
ICER with all changes incorporated			**£18,960**
Nivolumab as subsequent therapy for distant recurrence after routine surveillance			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	17.05	[redacted]
ICER (compared with company ICER)			**£161,658**
ICER with all changes incorporated			**£198,750**
Ipilimumab as subsequent therapy for distant recurrence after adjuvant nivolumab			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	17.05	[redacted]
ICER (compared with company ICER)			**£11,853**
ICER with all changes incorporated			**£36,135**
Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; LY, life-year; QALYs, quality-adjusted life years; RFS, recurrence-free survival.			

6.3.1 Scenarios using ERG's preferred base case

The ERG conducted a range of scenario analyses using the ERG's preferred base case as a basis. The results are presented in Table 68.

Table 68. Scenario analyses using ERG's preferred base case

	Results per patient	Nivolumab (1)	Routine surveillance (2)	Incremental value (2-1)
0	**ERG's preferred base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	17.05	[redacted]
	ICER			**£36,135**
1	**50% of patients with distant recurrence in each group receive dabrafenib+trametinib**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	14.21	[redacted]
	ICER (compared with base case)			**£17,045**
2	**All patients with distant recurrence in the nivolumab group receive dabrafenib+trametinib**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	17.05	[redacted]
	ICER (compared with base case)			**£250,633**
3	**Using metastatic fractional polynomial-based NMA to inform PRS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	15.16	[redacted]
	ICER (compared with base case)			**£37,891**
	Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PRS, post-recurrence survival; QALYs, quality-adjusted life years.			

7 END OF LIFE

The company have not put forward a case for end-of-life as the life expectancy of patients with melanoma is expected to be substantially greater than the criteria for end-of-life.

8 OVERALL CONCLUSIONS

The results of CheckMate 238 demonstrated that RFS with nivolumab is significantly improved compared to with ipilimumab although an ITC was required to generate estimates of nivolumab versus routine surveillance. The results of the ITC analyses for nivolumab compared to routine surveillance also suggest a significant benefit with nivolumab for RFS, however, the ERG considers the validity and generalisability of the results of the ITC to be questionable based on differences between CheckMate 238 and CA184-029, the two studies informing the ITC analyses. Co-variate analyses were applied to account for some differences between the studies, but the ERG is unclear as to exactly what factors the trial covariate is adjusting for in the patient level data (PLD) meta-regression analyses. In addition, the ERG is concerned about the difference in the ipilimumab treatment duration in CheckMate 238 compared to in CA184-029 (up to one year in CheckMate 238 and up to three years in CA184-029). The ERG notes that there is an inherent bias against ipilimumab in the ITC using the one-year censored ipilimumab data, however, the ERG considers this will produce a conservative estimate of the benefit of nivolumab compared to placebo as opposed to the over-optimistic results provided by the ITT ipilimumab population.

The ERG also notes the small proportion of UK patients in CheckMate 238 and the absence of Stage IV patients from CA184-029, which potentially limits the validity of the ITC results for the comparison of nivolumab with routine surveillance. However, the ERGs clinical experts reported that the baseline characteristics of patients in CheckMate 238 were in keeping with those of UK patients and that relatively few Stage 4 patients are likely to be suitable for adjuvant therapy as many won't have complete surgical resection. The ERG considers it important to also highlight its concerns around the potential impact and applicability to the UK population of the subsequent non-randomised therapies used in both CheckMate 238 and CA184-029, which particularly affects the estimates for the outcome of overall survival (OS). The ERG considers that following routine surveillance, a larger proportion of patients are likely to receive more effective subsequent immunotherapies than in the CA184-029 trial, meaning that the overall survival is potentially underestimated.

Data for nivolumab, in particular for the outcome [redacted] ongoing nature of the CheckMate 238 study. The ERG considers the results and use of non-standard methods for the surrogacy analysis which was reported to be a first-step 'statistical exercise' to estimate OS for nivolumab versus routine surveillance are unreliable. In addition, the ERG has concerns regarding the use of predominantly interferon studies in the surrogacy relationship as this is potentially unreliable when applied to data for an immunotherapy. The ERG therefore considers that OS estimates using [redacted] or a future PLD analysis are more robust for assessing the efficacy of nivolumab versus routine surveillance. The use of more mature OS data from CheckMate 238 would also be highly

beneficial and the ERG notes that [redacted]

The company's economic analysis remains uncertain as a result of the lack of patient-level data available to the company to provide an indirect treatment comparison (ITC) for overall survival (OS). This would still be potentially unreliable given the differences in treatment duration across the ipilimumab groups of the two key trials and the use of subsequent treatments that do not reflect current UK clinical practice. However, an attempt to adjust for these factors could have been made, which may have provided a more robust and reliable analysis.

The company's modelled OS appears to under predict in comparison to the trial data from CA184-029, which is already considered to potentially underestimate OS because of the less effective subsequent treatments available to patients at the time of the trial. A comparison against the AJCC 8th edition data shows a much lower resulting OS for the modelled routine surveillance group, which 71.7% of people alive at year 10 in the AJCC data, and only [redacted] of patients alive at year 10 in the model.

The ERG considers that the benefits of nivolumab compared to routine surveillance are potentially much smaller than the company suggest given that patients may receive the benefits of nivolumab after a potential distant recurrence of the disease anyway. This was confirmed as a possibility by the ERG's clinical experts.

This potential limited benefit, which is apparent in the scenario analysis that assumes patients who have a distant recurrence after routine surveillance will receive the benefits of nivolumab in a metastatic setting subsequently, causes ICERs to increase rapidly. This is a result of the incremental QALY becoming much closer to zero. However, this analysis does actually cause the resulting OS curves to cross, which may be implausible but this merely highlights the lack of robust and reliable OS modelling available to inform the economic analysis. The results should, therefore, be considered with serious caution.

8.1 Implications for research

In addition to the requirement for more mature OS data from CheckMate 238 to enable the analyses of OS in the ITC to be updated for the comparison of nivolumab versus routine surveillance, it would be useful to get observational evidence of nivolumab's use in a UK population, in particular to study the impact of subsequent therapies. A direct head-to-head study of nivolumab versus routine surveillance with patients staged according to the AJCC 8th edition would also be useful to help validate the efficacy from the ITCs conducted in the CS.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

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 **2pm on 6 August 2018** 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 committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 ERG base case and scenarios from Markov option 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Having reviewed the ERG's amended version of the company's previous model and recreated the ERG's base case and scenarios, the company believes that these have been incorrectly applied and suggest a change in application would ensure robust results. These are in relation to the scenarios created using 'Markov option 2' and changing the proportion of patients who receive subsequent treatments upon a distant recurrence. The ERG has produced these scenarios by changing the subsequent treatment data source on the 'Controls' sheet from 'trial 238' to 'Manual input' and then manually changing the placeholder %'s in columns L and M on the 'Subsequent TX' sheet. This is incorrect for the following reasons: • The placeholder values that were left in the company model were not designed to replicate the base case should the 'Manual inputs' option be	The company suggests that in order to apply these scenarios correctly, the applicable changes should be made on the calculation cells instead of the manual input cells in the 'Subsequent TX' sheet. The following describes how these can be applied: 1. Create two switches relating to scenarios for the nivolumab arm and the scenarios relating to the routine surveillance arm. For the purpose of example calculations these switches will be named 'ERG_scen_nivo' and 'ERG_scen_RS', respectively. 2. The switches should have four options; a. No scenario: company base case b. Scenario 1: 100% of patients receive nivolumab (after routine surveillance in ERG_scen_RS) or ipilimumab (after nivolumab in ERG_scen_nivo) c. Scenario 2: 50% of patients receive dabrafenib+trametinib (other 50% have either nivo or ipi depending which arm this applies to) d. Scenario 3: 100% of patients receive dabrafenib+trametinib 3. On sheet 'Subsequent TX' in cells P75:94 amend the formula to include an IF statement at the beginning: *=IF(ERG_scen_nivo="scenario 1",0,IF(ERG_scen_nivo="scenario 2",0,IF(ERG_scen_nivo="scenario 3",0,…[original formula]…)))* Apply this to all cells ensuring that in cell P81 the value is '1' for scenario 1 and '0.5' for scenario 2. In cell P83	The company believes that the corrections make the incremental cost-effectiveness ratios (ICERs) estimated by the ERG scenario more robust for the intended scenario explored. To aid the corrections in the model, the company has provided a version of the ERG's model that implements these scenarios. In sheet 'Subsequent TX' cells Q62 and Q63, the switches for the scenarios relating to nivolumab arm and routine surveillance arm have been added, respectively. Cells highlighted in orange, with white text indicate cells where the company have amended the formula to apply these scenarios.	The ERG thanks the company for highlighting this inaccuracy and providing an updated model. The ERG has made changes to the report accordingly.

selected (cells L29:49, N29:49, L75:94 and N75:94) and are simply placeholders taken from the distribution of the total 1L and 2L records combined. • Consequently, the distribution of subsequent treatments, which informs the post-recurrence survival (PRS) for nivolumab and routine surveillance, changes from just using the 1L distribution to the total 1L and 2L distribution. Hence, applying the scenario to the routine surveillance arm only also changes the nivolumab PRS from the base case. The 1L distribution is used to inform the weighted curves used in Markov 2, and the total 1L and 2L distribution is used to inform the costs of subsequent therapies. • Additionally, the calculation of the subsequent treatment costs using the manual inputs differs from using the trial data,	the value is '0.5' for scenario 2 and '1' for scenario 3. In cells Q75:94 amend the formula to include an IF statement at the beginning: *=IF(ERG_scen_RS="scenario 1",0,IF(ERG_scen_RS="scenario 2",0,IF(ERG_scen_RS="scenario 3",0,…[original formula]…)))* Apply this to all cells ensuring that in cell Q87 the value is '1' for scenario 1 and '0.5' for scenario 2. In cell Q83 the value is '0.5' for scenario 2 and '1' for scenario 3. These changes will ensure the correct % is shown in each scenario and the original % base case stay when no scenario is selected. 4. In sheet 'Subsequent TX' cell L110, change the formula to include an IF statement at the beginning: *=IF(ERG_scen_nivo="no scenario",L107*CHOOSE(P22,$E68,$H68,1),L107)* And in cell N110 change to: *=IF(ERG_scen_RS="no scenario",N107*CHOOSE(P22,$D68,$G68,1),N107)* This means that the cost applied does not inflate with the trial patient records vs patient numbers but costs stay the same if 'no scenario' is applied. Therefore, the cost is only based on all patients having nivolumab/ipilimumab and not inflated to account for that fact that patients received more than one subsequent therapy relative to how many patients were in each arm. 5. In sheet 'Subsequent TX' change the formula in cells L123:133 to include an IF statement at the beginning: *=IF(ERG_scen_nivo="scenario 1",0,IF(ERG_scen_nivo="scenario 2",0,IF(ERG_scen_nivo="scenario 3",0,…[original*		

and therefore these change for the local/regional costs, which we do not believe was not intended for the ERG scenario.	*formula]…)))* Apply this to all cells ensuring that in cell L125 the value is '1' for scenario 1 and '0.5' for scenario 2. In cell L127 the value is '0.5' for scenario 2 and '1' for scenario 3. In cells N123:133 amend the formula to include an IF statement at the beginning: *=IF(ERG_scen_RS="scenario 1",0,IF(ERG_scen_RS="scenario 2",0,IF(ERG_scen_RS="scenario 3",0,…[original formula]…)))* Apply this to all cells ensuring that in cell N130 the value is '1' for scenario 1 and '0.5' for scenario 2. In cell N127 the value is '0.5' for scenario 2 and '1' for scenario 3. This will ensure that the %s informing the PRS are correct for the scenario applied.		
As per above, the following ICERs need correcting in the ERG report: Page 22: *"…from £18,685 to £161,658 per QALY. Another scenario was conducted that also applied ipilimumab to all distant recurrence patients after adjuvant nivolumab. This ICER was also much greater than the company's base case at £34,925 per QALY…"* Page 25, Table A Page 121: *"All other subsequent treatments were kept the*	*Page 22:* *"…from £18,685 to £96,443 per QALY. Another scenario was conducted that also applied ipilimumab to all distant recurrence patients after adjuvant nivolumab. This ICER was also much greater than the company's base case at £31,663 per QALY"* Page 25, Table A – please correct the reported costs/QALYs/LYs and ICERs based on the corrections to the scenarios. Page 121: *"All other subsequent treatments were kept the same. This increased the ICER from £18,685 per QALY to £96,443 per QALY."* Page 122: *"using data from the metastatic NMA with fractional polynomial models, resulted in ICERs of £324,108 per QALY"* Page 151, Table 66 – Please correct the reported	Corrections in these values reflect the updates in the formulas above which implement correctly the scenarios the ERG originally intended to explore.	As per the above, these changes have now been made.

same. This increased the ICER from £18,685 per QALY to £161,658 per QALY." Page 122: *"using data from the metastatic NMA with fractional polynomial models, resulted in ICERs of £589,557 per QALY"* Page 151, Table 66 Page 152, Table 67 Page 153, Table 68 *ERG base case £36,135* *Scenario 1 £17,045* *Scenario 2 £250,633* *Scenario 3 £37,891*	costs/QALYs/LYs and ICERs based on the corrections to the scenario. Page 152, Table 67 – Please correct the reported costs/QALYs/LYs and ICERs based on the corrections to the scenario. Page 153, Table 68 - Please correct the reported costs/QALYs/LYs and ICERs based on the corrections to the scenario. *ERG base case £32,758* *Scenario 1 £15,245* *Scenario 2 £238,154* *Scenario 3 £34,354*		

There issues with the consistency of presentation and plausibility of the ERG's preferred base case and presented scenarios. 1. A number of contradictory statements are presented on what the ERG consider to be the most plausible estimate of OS, for example Section 5.4.5.4.3, page 122: *"Based on the data available, the ERG considers it preferable to assume OS for nivolumab is equivalent to ipilimumab, and to use the Markov Option 2 structure to apply subsequent therapy costs and survival outcomes reflective of treatments expected to be received in the UK."* 2. Section 6.3: The ERG base case uses Markov 2 and assumes that all patients who have a distant recurrence after routine surveillance receive nivolumab and all patients after adjuvant nivolumab	1. Please clarify whether the ERG prefers the assumption that nivolumab OS is the same as ipilimumab OS or prefers to use Markov 2 to explore differences in PRS. 2. The company requests that the ERG select a base case where subsequent therapies represent clinical practice and the decision problem within the submission as outlined in the Final Scope Issued by NICE. 3. The company asks the ERG to refer to a more plausible ICER throughout the report or to highlight the inappropriateness of this scenario with each mention. 4. The company requests the ERG to remove this scenario altogether from the report or provide justification for considering it as plausible to present.	Given the current evidence available, the company agrees with the ERG that the scenario assuming that nivolumab OS is the same as ipilimumab OS is a plausible assumption, and the company provided scenarios to address these (company submission, Section B3.8 page 177 and response to clarification questions B1). However, the use of Markov 2 does not align with this assumption which is stated. Therefore, the ERG cannot agree to that assumption and use Markov 2 as this explores differences in OS with two specific treatment sequences. Whilst the company agrees with the ERG that the impact of subsequent therapy is a key uncertainty within the model and submitted Markov 2 to explore such scenarios it is not within the scope of this submission to consider specific sequences as is currently done within the ERG base case. This would be within the scope of an MTA rather than an STA. We would therefore request that only clinically valid scenarios are presented to provide the Committee with reasonable ICER ranges. It is fundamentally not plausible to assume that all patients receive the same	The issue raised by point 1, relating to text on page 122, has been resolved as follows: *"Based on the data available, the ERG considers it preferable to assume OS for nivolumab is equivalent to ipilimumab for the PSM, and for the Markov Option 2 structure, to apply subsequent therapy costs and survival outcomes reflective of treatments expected to be received in the UK. The latter will form the ERG's preferred base case."* The ERG does not consider points 2 and 4 to be factual errors.

receive ipilimumab. This does not address the decision problem presented by NICE which is to assess whether nivolumab should be used as an alternative to routine surveillance or not and instead addresses the issues of the cost-effectiveness of different sequences of treatments. 3. The ERG refers to a scenario where they only assume all patients in the routine surveillance arm who have a distant recurrence receive nivolumab, and the resulting ICER (£161k per QALY – corrected ICER £96K per QALY) is referred to five times throughout the report. The company feels that it is mis-leading to refer to this scenario as it is not presented in the ERG scenarios in Section 6.3.1, and as the ERG state, it is not clinically plausible: Page 156 *"However, this analysis does actually cause the resulting OS curves to*		treatment post recurrence; as the ERG states *"subsequent therapies can vary depending on the patient and the provider"*. NICE was originally set up to reduce this variation and indeed the majority of subsequent treatments used in the CheckMate-238 study have been recommended by NICE in are therefore available. A more plausible option would be to assume a sensible mix of treatments such as Scenario 1 presented in Section 6.3.1 considering the use of BRAF/MEK inhibitors – although this still has a simplistic approach, it acknowledges the reality that not all patients receive the same treatment upon recurrence. Additionally, there is evidence in the Prescription Cost Data that dabrafenib and trametinib are being used (Hospital Pharmacy Audit Index 26,877.9 and 12,698.11 for dabrafenib and trametinib respectively)[1] so ignoring this use in the ERG base case does not appear justified. Additionally, comparing the base case ICER to an implausible ICER (£161k) throughout the report without clarity of the implausibility of this scenario is mis-leading and does not represent a reasonable range of	

cross, which may be implausible but this merely highlights the lack of robust and reliable OS modelling available to inform the economic analysis. The results should, therefore, be considered with serious caution." 4. Section 6.3.1: The ERG presents a scenario (Scenario 2) that assumes that all patients after nivolumab who have a distant recurrence receive dabrafenib+trametinib contrary to the incidence statistics for BRAF mutations.		uncertainty. Lastly for the purposes of presenting valid scenarios, Scenario 2 in Section 6.3.1 along with suffering from the same issue of not addressing the decision problem is impossible as of the patients with known BRAF status in CheckMate 238 only 48.1% were BRAF +VE (eligibility criteria for dabrafenib+trametinib).	
Further clarification of the limitations of Markov option 2 required – Section 5.4.5.4.2, page 121: *"The ERG emphasises the fact that this analysis uses a range of potentially disparate sources of evidence to inform PRS, so it is unlikely that the estimates of PRS and the applicability to the population on which the ITC was formed is robust and reliable. However, even if the analysis was considered reliable, the range of ICERs*	*"The ERG emphasises the fact that this analysis uses a range of potentially disparate sources of evidence to inform PRS, so it is unlikely that the estimates of PRS and the applicability to the population on which the ITC was formed is robust and reliable. Additionally, it assumes that adjuvant treatment has no effect on PRS and constant HRs are applied to derive some survival curves. However, even if the analysis was considered reliable, the range of ICERs resulting from explored scenarios demonstrates the potentially serious uncertainty that currently exists within the results."* The company additionally requests that these limitations are reiterated in Section 6.3 as the ERG uses this model as its	Markov option 2 was provided to explore an alternative means to estimate overall survival (OS) given the lack of OS data at the time of the submission from CheckMate-238. However, we agree with the ERG that the robustness of this option is limited, having highlighted a number of limitations in the company submission, as it uses a variety of different sources and assumptions to produce the individual treatment survival curves and also assumes that	The ERG does not consider this to be a factual error.

resulting from plausible scenarios demonstrates the potentially serious uncertainty that currently exists within the results."	preferred base case.	adjuvant treatment has no effect on treatment post recurrence. The company did not choose this as the base case due to these limitations. During the post submission process, [redacted] Therefore, the need for Markov option 2 is not as imperative, [redacted]	

Issue 2 Applicability of CheckMate 238 subsequent treatments to UK practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statements made in Section	As the statements are contradictory, the company requests that the ERG amend	Subsequent treatment data present a key uncertainty within the evidence	The ERG does not consider this to

5.4.5.4.1, page 120: *"This issue is that the subsequent treatments received by patients in the two trials are not reflective of current UK clinical practice, according to clinical expert advice sought by the ERG."* And Section 5.4.8.5.1, page 136: *"Clinical expert opinion sought by the ERG suggests that these data are not reflective of UK clinical practice."* Is contradictory to previous statements made in Section 1.2 page 17 *"…ERG's clinical experts reported that the types of subsequent therapies given in CheckMate 238 were likely to be generally more consistent with the types used in UK clinical practice."* And Section 4.2.1 page 45 and 46*:* *"However, they considered that the subsequent therapies used in CheckMate 238 were reasonable and that the difference in subsequent immunotherapy use between the CheckMate 238 study arms could be explained by the drugs mechanisms of actions…"* *"The ERG's clinical experts did, however, report that the types of subsequent therapies given in CheckMate 238 were likely to be generally consistent with the types used in UK clinical practice although BRAF + MEK combination is now used more frequently than single agent BRAF."*	their statements regarding actual views of clinical experts on subsequent therapies to be consistent throughout the document, and to be clear whether clinical experts view the subsequent treatments as reflective of UK or not reflective of UK practice.	base and are a key driver of the ERG's base case assumptions. Therefore, it should be clear within the report where the ERG's assumptions have come from.	be a factual error.

Issue 3 Surrogate relationship between RFS and OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, page 19: "*The ERG also has concerns that the majority of studies used in the surrogacy analysis to inform the OS estimate in CheckMate 238 are based on interferon (12 out of 14 studies), which unlike nivolumab and ipilimumab, is not an immunotherapy*"	The company asks the ERG to reconsider the wording around this statement as interferons (IFNs), and other cytokines such as interleukin-2 (IL-2) are known to aid in communication of the immune system and data has been presented validating the surrogacy equation based upon IFNs with the data available for ipilimumab.	Firstly, IFN and IL-2 are both types of cytokines that stimulate the immune system, encouraging killer T-cells and other cells to attack cancerous cells.[2-4] In this way, IFN does have some immunotherapeutic properties. Secondly, and as acknowledged by the European Medicines Agency (EMA) and presented within the aggregate level analysis within the submission, similar measures of association between recurrence-free survival (RFS) and OS, as judged by the parameters of the linear regression equation, are found across immune-oncology and interferon-based trials to those found with interferon-based trials alone. Finally, the survival profiles with regard to the shape of KM survival curves between immune-oncology and cytokine therapies are similar, with both showing a survival plateau typically associated with immunotherapies (based on nivolumab and ipilimumab[5], and interleukin data[6]). It is therefore reasonable to assume that survival profiles (and surrogacy relationships) between immune-oncology and cytokine therapies, including IFN, are similar.	The ERG does not consider this to be a factual error.

Further information required in statement - Section 5.4.4.1 page 102: *"The proportion of patients in the death state at any given cycle was informed by a surrogate relationship between RFS and OS that had previously been estimated using interferon trials in the adjuvant setting."*	*"The proportion of patients in the death state at any given cycle was informed by a surrogate relationship between RFS and OS that had previously been estimated using interferon trials in the adjuvant setting* [redacted]	To make clear that the surrogacy relationship used in this analysis in the base case did not use only interferon trials [redacted]	Text has been amended to: "…using *predominantly* interferon trials…".
Re-clarify paragraph – Section 5.4.5.1 page 106: *"To estimate OS from the RFS data in the CheckMate 238 trial, the company used a published study that predicted an OS HR from an RFS HR. The equation was derived from a regression analysis using PLD, which used predominantly interferon trials in the adjuvant setting. The company used the HRs from this study, along with HRs from the CA184-029 trial and the recently published COMBI-AD trial, which compared dabrafenib in combination with trametinib against placebo, as adjuvant treatment for melanoma, and performed a regression analysis to predict an OS HR from an RFS HR."*	*"To estimate OS from the RFS data in the CheckMate 238 trial, the company used a new study that predicted an OS HR from an RFS HR.[30] The new study was based on a published study which used regression analysis using PLD from predominantly interferon trials in the adjuvant setting.[29] The new study derived a predictive* [redacted] *, as adjuvant treatment for melanoma, and performed a regression analysis to predict an OS HR from an RFS HR.[30]"*	The amendment makes clear that the OS and RFS relationship used in the company base case is based on the new study [redacted]	The ERG does not consider this to be a factual error.

Issue 4 Use of ITT population versus 1-year censored population for ipilimumab in CA184-029

Description of problem	Description of proposed	Justification for amendment	ERG response

	amendment		
Page 17: "*The company conducted additional analyses in their clarification response using data where ipilimumab patients who were treated beyond one-year were censored at one year which the ERG considers to be a more conservative estimate of the benefit of nivolumab compared to placebo as opposed to the over-optimistic results provided by the ITT ipilimumab population*." Page 24: "*The ERG, therefore, considers the analysis provided by the company where ipilimumab patients continuing treatment beyond one-year are censored in CA184-029 to be a more robust analysis and results in a more conservative estimate of the benefit of nivolumab compared to placebo as opposed to the over-optimistic results provided by the use of the ITT ipilimumab CA184-029 population*" Page 118: "*This analysis indicates that the RFS treatment effect estimates from the ITC using the ITT population are potentially overestimated*."	The strength of wording in the ERG report (i.e. "over-optimistic") could be misleading. It is not possible to state whether the intention-to-treat (ITT) ipilimumab data or the 1-year censored ipilimumab data are closer to what would have happened in this trial had treatment been curtailed at 1 year by design.	Figure 32 (page 119) in the ERG report shows the potential effect of informative censoring when censoring patients due to treatment duration. When placebo patients continuing beyond 1 year are censored at that point, the difference between that curve and the ITT placebo curve is dramatic – clearly demonstrating informative censoring on a feature directly related to the outcome. The fact that the difference between the ITT curve and 1-year censored curve for ipilimumab is so small (in comparison) is encouraging and could be seen as supportive for the ITT analysis. It also demonstrates how well patients who stop treatment at one year perform relative to those who are well enough to receive more treatment.	The ERG does not consider this to be a factual error.

Issue 5 Clarification of use of trial covariate in the PLD ITC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Page 17: "*For the PLD ITC the company included covariates for Gender, age, stage and trial, with the rationale for including a trial covariate being, "it will account for all unobserved differences between trials, thus maintaining randomisation". The ERG is unclear as to exactly what these differences addressed by the trial level covariate are as the company has described them as "unobserved*" Page 75: "*The ERG is unclear as to exactly what differences are addressed by the trial level covariate*" Page 91: "*The ERG is unclear as to exactly what these differences addressed by the trial level covariate are*" Page 155: "*Co-variate analyses were applied to account for some differences between the studies, but the ERG is unclear as to exactly what factors the trial covariate is adjusting for in the patient level data (PLD) meta-regression analyses*."	No amendment to ERG report is required. This point about use of the trial covariate was not raised during ERG clarifications, and this response is therefore to aid clarity and potentially be of help for the committee presentation and ACM.	The trial covariate was included in the PLD ITC for form the bridge between trials in the ITC, in turn making ipilimumab the common comparator. Including the trial covariate in the PLD analyses as a fixed effect has a similar effect to using ipilimumab as the common comparator in a normal Bucher ITC of aggregate data. It assumes that the differences between the ipilimumab outcomes between the trials can be explained by differences between the trials, but it also assumes the trial effect applies equally to both treatments within that trial (again, the same assumption we would make in a Bucher ITC). The fact that additional covariates were included in the PLD ITC allows a better estimation of the effects of key characteristics on the outcomes and therefore 'removes' these effects (e.g. gender, age) from the trial effect (hence the phrase 'unobserved differences'). The company submission made a brief reference to this (see below), but we appreciate more detail could have been provided. Page 63 of CS: "However, the inclusion of a trial covariate is analogous to performing a traditional ITC on summary data using ipilimumab as a common comparator because the trial effect will account for all unobserved differences between trials, thus maintaining randomisation."	The ERG does not consider this to be a factual error.

Issue 6 Comparative effectiveness data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5.2, page 24: "*The ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment although data were provided for these outcomes for nivolumab versus ipilimumab*" And Section 3.4, page 36 and Section 4.5.1, page 93: "*The ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment*" And Section 1.1, page 15: "*As a result of the requirement for the ITC, the ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment as the data for these outcomes in CheckMate 238 and CA184-029 were unsuitable for combining in an ITC*" And Section 4.5, page 89: "*However, as a result of the requirement for the ITC, the ERG considers no*	*"The ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, as this outcome was not thought of relevance to the economic model, or AEs of treatment because this outcome was unsuitable for combining in an ITC"* Regarding comparative HRQoL data, this was presented in Appendix O.2 and in Section B.3.4.	To aid clarity around data presentation in the CS.	The ERG does not consider this to be a factual error.

suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment although the ERG notes that the company reported the data for these outcomes in CheckMate 238 and CA184-029 were unsuitable for combining in an ITC"			

Issue 7 Missing redactions from the report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the ERG report, values pertaining to the proportion of patients continuing Ipilimumab ([redacted]) treatment beyond 1 year from CA184-029 study are not marked as AIC: Section 1.2, page 17 Section 3.3, page 34 Section 4.4.1.1. page 66 Section 4.5, page 91 Section 5.4.5, page 113	Please mark the % of patients continuing ipilimumab treatment beyond 1 year from CA184-029 study as AIC throughout the text on pages indicated. As such values should be amended to [redacted] on pages indicated.	Data not available in public domain	The ERG thanks the company for highlighting this issue. The proposed amendments will be made.
Table 6 presenting subsequent treatments, section 4.2.1, page 46 (adapted from table 17 of main submission)	Please mark all data as AIC with the exception of the top row (i.e. patients receiving any subsequent therapy) as no other data has been made available in the public domain. This was a mistake made in the	Data not available in public domain.	The ERG thanks the company for highlighting this issue. The proposed amendments will be made.

	company submission.		
Section 5.4.5.1, page 104: *"The resulting HR was [redacted] and this was applied to the KM data"*	*"The resulting HR was [redacted] and this was applied to the KM data"*	The HR is a result of unpublished analysis and should be marked 'academic in confidence' (AIC) as per the company submission.	The ERG thanks the company for highlighting this issue. The proposed amendments will be made.
Section 5.4.5.1, page 107: *"This was then multiplied by the OS HR for ipilimumab compared to placebo from the CA184-029 trial to produce an OS HR for nivolumab versus placebo. The resulting HR was [redacted]. … To estimate the long-term survival for the nivolumab group, the OS HR ([redacted]) derived from the predictive surrogacy equation was applied to this placebo survival curve."*	*"This was then multiplied by the OS HR for ipilimumab compared to placebo from the CA184-029 trial to produce an OS HR for nivolumab versus placebo. The resulting HR was [redacted]. … To estimate the long-term survival for the nivolumab group, the OS HR ([redacted]) derived from the predictive surrogacy equation was applied to this placebo survival curve."*	The HR is a result of unpublished analysis and should be marked 'academic in confidence' as per the company submission.	The ERG thanks the company for highlighting this issue. The proposed amendments will be made.
Section 5.4.5.1, page 110 – Figure 25 Section 5.4.5.1, page 111 – Figure 26 Section 5.4.5.2, page 112 – Figure 27 Section 5.4.5.2, page 113 – Figure 28 Section 5.4.5.3, page 115 – Figure 29 Section 5.4.5.3, page 116 – Figure 30 Section 5.4.5.3, page 116 – Figure 31	Mark the figures as AIC.	Figures contain unpublished data relating to the survival analysis and cost-effectiveness analysis and should be marked AIC as per the company submission.	The ERG thanks the company for highlighting this issue. The proposed amendments will be made.

Section 5.4.5.4.1, page 120: *"Although the company do not have the PLD required to provide an adjusted ITC for OS, the ERG considers it reasonable, based on Figure 33 to assume equal efficacy."*	*"Although the company do not have the PLD required to provide an adjusted ITC for OS [redacted]."*	This information relates to the unplanned interim OS analysis, and any description or discussion of this should be marked 'commercial in confidence' (CIC), as per the justifications provided in the 'Checklist of confidential information' from the response to ERG clarification questions.	
Section 6.2.1.1, page 148: *"The company used the trial effect coefficient estimated from the RFS ITC; however, the ERG noted that this did not align the survival models with the KM data from the CheckMate 238 trial."* Figure 37 & Figure 38	*"The company used the trial effect coefficient estimated from the RFS ITC; [redacted]* Mark the figures as CIC.	This information relates to the unplanned interim OS analysis, and any description or discussion of this should be marked CIC as per the justifications provided in the 'Checklist of confidential information' from the response to ERG clarification questions. Figures show confidential OS KM data from CheckMate 238.	The ERG thanks the company for highlighting this issue. The proposed amendments will be made.

Issue 8 Minor changes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Minor typo – Section 1.5.2, page 24: *"…meaning that the OS estimate for nivolumab versus routine surveillance generated from the ITC is potentially underestimated."*	*"…meaning that the OS estimate for nivolumab versus routine surveillance generated from the ITC is potentially overestimated."*	To aid clarity as this is what we think was meant.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.

Minor typo – Section 5.4.5.2, page 111: *"However, to estimate the probability of remaining in the PF state and the probability of transitioning to death from the PF state, the composite RFS measure needed to be "split" to separate out the rates of recurrence and the rates of death."*	*"However, to estimate the probability of remaining in the RF state and the probability of transitioning to death from the RF state, the composite RFS measure needed to be "split" to separate out the rates of recurrence and the rates of death."*	To be clear that the ERG is referring to the recurrence-free (RF) health states.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.
Further information required - Section 5.4.5.3, page 113: *"For patients with a local/regional recurrence, the survival curves that were fitted to data from the CA184-029 trial were used."*	*"For patients with a local/regional recurrence, the survival curves that were fitted to local/regional recurrence data from the CA184-029 trial were used."*	Added clarity that the data used to inform the local/regional recurrence patients were taken from CA184-029 using survival data from patients who had a local/regional recurrence in that trial.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.
Unreported ICER – Section 5.4.5.4.3, page 122: *"However, the ERG considers the company's analyses to be no less certain than the ERG's scenario that resulted in an ICER greater than £300k per QALY, hence, emphasising the potential impact of the uncertainty."*	The company asks the ERG to remove reference to a scenario of £300k per QALY or be clear what this scenario is.	The ERG did not present a scenario which resulted in an ICER of £300k per QALY and did not provide any details of what scenario this referred to or whether it was plausible. The company has also corrected the scenarios implemented from the ERG report, it is therefore imperative for the ERG to be clear as to what these scenarios are.	The ERG thanks the company for highlighting this issue. The text "greater than £300k" has been amended to include the correct ICER "of £324,108".
Further information required – Section 5.4.6, page 123: *"For the proportions of immune-related AEs and diarrhoea in the routine surveillance group, the risk of AEs from the placebo group of CA184-029 was adjusted for the difference in risks across the ipilimumab groups of the two trials."*	*"For the proportions of immune-related AEs and diarrhoea in the routine surveillance group, the risk of AEs from the placebo group of CA184-029 was adjusted for the difference in risks across the ipilimumab groups of the two trials with the exception of 'Other grade ≥3' AEs which were assumed to be the same as nivolumab due to implausible results from adjustment."*	Requested change to make clear that the adjustment was not applied to all AE categories in the base case.	The ERG does not consider this to be a factual error.
Further clarification required – Section	*"The company apply the same utilities*	The company applies the same utility	The ERG thanks the company for

5.4.7.4, page 129: *"The company apply the same utilities and same utility decrements to each treatment group so there is no benefit in capturing the differences between treatments."*	*per treatment arm and same utility decrements per AE to each treatment group so there are small differences between treatments."*	decrement per AE to each treatment arm. However, these are then multiplied by the percentage of patients who had an AE in each arm and the duration of AEs; therefore, a different overall disutility is applied to the two treatment arms (-0.009 for nivolumab and -0.006 for routine surveillance).	highlighting this issue. The proposed amendment has been made.
Incorrect statement – Section 5.4.8.3, page 132: *"As discussed in Section 5.4.6, the company included costs associated with any grade of immune-related disorders, diarrhoea grade ≥2, and other AEs grade ≥3, which occurred in at least 5% of patients."*	*"As discussed in Section 5.4.6, the company included costs associated with any grade of immune-related disorders, diarrhoea grade ≥2, and other AEs grade ≥3."*	The 'other grade ≥3' category did not have a cut off of 5%. Therefore, this sentence should be removed.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.
Incorrect statement – Section 5.4.8.3, page 132: *"The proportion of patients treated for AEs in an inpatient or outpatient setting was not recorded in either the CA184-029 or CheckMate 238 trials."*	*"The proportion of patients treated for AEs in an inpatient setting was recorded in CheckMate 238 however the number of hospitalization days was not recorded. The proportion of patients treated for AEs in an outpatient setting was not recorded in either the CA184-029 or CheckMate 238 trials."*	The proportion of patients who were hospitalised for AEs from CheckMate 238 were presented in Table 30 of the company submission. Only the average number of hospitalisation days per AE were collected from Oxford outcomes.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.
Further clarity required – Section 5.4.8.5.1 page 136: *"The most important of these issues concerns the application of subsequent therapy costs. However, the appropriateness of this application of subsequent therapies needs to be considered in parallel with the appropriateness of the treatment effectiveness measures and the impact of subsequent therapies on post-*	Further clarification is required on what the issues with the application of subsequent therapy costs were and how these relate to appropriateness of treatment effectiveness.	The ERG does not specify what the issues relating to the application of subsequent therapy costs; thus, the company requests that this is clarified.	The ERG does not consider this to be a factual error.

progression survival."			
Further clarity required – Section 1.2, page 16, Section 4.3.6, page 62 and Section 4.5, page 90: "*the AEs were more frequently deemed to be treatment-related with ipilimumab (95.8%) compared to nivolumab (85.2%) and to lead to treatment discontinuation (ipilimumab 41.7% compared to nivolumab 7.7%)*."	"*Treatment-related AEs were more frequent with ipilimumab (95.8%) compared to nivolumab (85.2%). In addition, treatment-related AEs leading to treatment discontinuations were more frequent with ipilimumab (41.7%) compared to nivolumab (7.7%).*"	Provides clarity of data presented.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.
Minor typo – Section 1.2, page 17: "*the only difference was that RFS was assessed by the investigator in CheckMate whereas in CA184-029 it was assessed by an independent panel*"	"*the only difference was that RFS was assessed by the investigator in CheckMate 238 whereas in CA184-029 it was assessed by an independent panel*"	Provides clarity.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.
Minor typo – Section 1.2, page 18: [redacted]	[redacted]	The drug name was spelt incorrectly.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.
Incorrect statement – Section 4.2.1, page 43 and Section 4.2.4, page 50: "*Based on the May 2017 data-cut, 275 patients in the nivolumab arm had discontinued study drug*"	"*Based on the May 2017 data-cut, 177 patients in the nivolumab arm had discontinued study drug*"	Correctly presents data for patient discontinuation at the May 2017 data-cut.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.
Minor typo: Section 1.2, page 17: *"The ERG also noted that the subsequent therapies differed between CheckMate 238 and CA8184-029 and the…"* And Section 4.5, page 91,	Section 1.2, page 17: *"The ERG also noted that the subsequent therapies differed between CheckMate 238 and CA184-029 and the…"* And Section 4.5, page 91, *" The ERG also noted that the*	The study number was spelt incorrectly.	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.

" The ERG also noted that the subsequent therapies differed between CheckMate 238 and CA8184-029 and the…"	*subsequent therapies differed between CheckMate 238 and CA184-029 and the…"*		
Minor typo: Section 4.4.1.1, page 66 *"… although the range was wider for CA184-029 (range: 1–16) compared to CheckMate 238 (range: 1-7)."*	*"… although the range was wider for CA184-029 (range: 3–8) compared to CheckMate 238 (range: 1-7)."*	The range provided in the ERG report is incorrect.	The ERG does not consider this to be a factual error.

References

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3. Lasfar A, Gogas H, Zloza A, et al. IFN-λ cancer immunotherapy: new kid on the block. *Immunotherapy*. 2016; 8(8):877-88.
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6. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. 1999; 17(7):2105-16.

Nivolumab for adjuvant treatment of resected stage III and IV melanoma

ERRATA

This report was commissioned by the NIHR HTA Programme as project number 17/156/02

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the company'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
17	'CheckMate' amended to 'CheckMate 238', and 'CA8184-029' amended to 'CA184-029'
18	Spelling of the word 'nivolumab' amended
22	ICERs updated after corrections to the ERG model
24	Word 'underestimated' amended to 'overestimated
25-26	Table A results updated after correction to the ERG model
43	275 amended to 177
50	275 amended to 177
91	'CA8184-029' amended to 'CA184-029'
102	The word "predominantly" added to highlight that not only interferon trials were used in the surrogacy analysis.
111	"PF" corrected to "RF"
113	Text amended to clarify that local/regional recurrence data were used.
121-122	Minor edits to text and ICERs updated after corrections to the ERG model
129	Text on utility decrements per AE amended
132	Erroneous text about inclusion of AEs removed. Text about inpatient and outpatient data from trials amended.
151-153	Results updated after corrections to the ERG model
Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; RF, recurrence-free;	

regional lymph node surgical removal. The ERG's clinical experts reported that the baseline characteristics for CA184-029 appear broadly consistent with those of CheckMate 238, although the ERG notes that median age of patients in CA184-029 is slightly younger compared to CheckMate 238 and patients in CheckMate 238 included patients with a more advanced disease stage (Stage IV) that were excluded from CA184-029. In addition, approximately 20% of the patients in CA184-029 had Stage IIIa disease and Stage IIIa patients were excluded from CheckMate 238. The ERG notes that the company applied co-variate adjustments in the ITC analyses to adjust for these differences in Stage and age. There were also comparability issues in terms of the RFS definitions used in CheckMate 238 and CA184-029 although the ERG considers the resulting analyses conducted by the company mean that the only difference was that RFS was assessed by the investigator in CheckMate 238 whereas in CA184-029 it was assessed by an independent panel. The ERG considers this difference in outcome assessment is likely result in a conservative estimate of the efficacy of ipilimumab versus placebo.

The ERG also noted that there was a difference in the maximum duration of ipilimumab treatment between CheckMate 238 and CA184-029; in CheckMate a maximum of one-years treatment was allowed whereas in CA184-029 ipilimumab treatment could continue for upto three-years and approximately [redacted] of patients continued ipilimumab treatment beyond one year. The company conducted additional analyses in their clarification response using data where ipilimumab patients who were treated beyond one-year were censored at one year which the ERG considers to be a more conservative estimate of the benefit of nivolumab compared to placebo as opposed to the over-optimistic results provided by the ITT ipilimumab population.

The ERG also noted that the subsequent therapies differed between CheckMate 238 and CA184-029 and the ERG's clinical experts reported that the types of subsequent therapies given in CheckMate 238 were likely to be generally more consistent with the types used in UK clinical practice. The ERG notes that part of the reason for the differences in subsequent therapy is likely to be related to advances in clinical practice since CA184-029. The ERG also notes that due to the outcome censoring selected for the ITC analyses, these differences in subsequent therapies will have the largest impact in the analysis of OS.

In terms of the ITC, the company conducted analyses for RFS using patient level data (PLD) meta-regression and parametric survival models; and also conducted a Bucher adjusted indirect comparison. For the PLD ITC the company included covariates for Gender, age, stage and trial, with the rationale for including a trial covariate being, "it will account for all unobserved differences between trials, thus

maintaining randomisation". The ERG is unclear as to exactly what these differences addressed by the trial level covariate are as the company has described them as "unobserved". The resulting parametric curves from the log-logistic meta-regression model (that was deemed to be the best-fitting model) suggest that for the matched population (CheckMate 238 and CA184-029), nivolumab is associated with the longest RFS compared to both ipilimumab and placebo.

The Bucher ITC analyses for RFS using the full ITT populations of CheckMate 238 and CA182-029 were conducted with and without covariate adjustments for age, gender and stage. [redacted] The CA184-029 data suggests that the ipilimumab censored at one-year population has a slightly shorter RFS compared to the ITT population beyond approximately 18 months; although this analysis is likely to be biased against ipilimumab as the censored patients are likely to be those who will have the best prognosis at 1 year. The HRs estimated by the Bucher ITC for nivolumab versus placebo were numerically [redacted] higher when the ipilimumab censored at one-year data were used rather than the full ipilimumab dataset, [redacted]

The ERG requested the company conduct a re-analysis of the clinical data from CheckMate 238 and CA184-029, re-staging patients into the new AJCC 8th edition disease stages for melanoma, and an analysis by baseline PD-L1 status, although the company reported that they were unable to conduct these analyses due to insufficient PLD being available from CA184-029. The ERG nevertheless considers them both to be potential subgroups of interest.

OS for nivolumab versus routine surveillance for use in the economic model was estimated using a surrogacy analysis. The ERG requested [redacted]

A further issue relating to OS is that the subsequent treatments received in the CA184-029 trial have generally been superseded by more effective drugs such as immunotherapies in current UK clinical practice. Therefore, the more effective immunotherapies are likely to improve OS for patients after disease recurrence for those who receive routine surveillance and the relative benefit of adjuvant nivolumab may not be a great as the company's analyses suggest.

If the use of the OS data identified in the metastatic setting is robust and reliable, this approach potentially resolves the issue of subsequent treatments, or at least allows for the exploration of alternative estimates of PRS by varying the proportions of subsequent treatments in the model. The ERG conducted a scenario that used nivolumab as the subsequent therapy for all distant recurrence after routine surveillance and this increased the incremental cost-effectiveness ratio (ICER) substantially from £18,685 to £96,443 per QALY. Another scenario was conducted that also applied ipilimumab to all distant recurrence patients after adjuvant nivolumab. This ICER was also much greater than the company's base case at £31,663 per QALY; above the upper £30k per QALY threshold.

There were also some minor issues with excess resources use for imaging, whereby the majority of patients in the model were assumed to receive regular CT and PET scans of the chest and abdomen. Clinical experts suggested that it is unlikely for both to be given in UK clinical practice. The ERG assessed the impact of removing the PET scan costs from the model and this had a negligible effect on the results. A similar issue was noted with the use of both CT and MRI for the head. The ERG found the impact of this to be minimal also.

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

Clinical

- The data for nivolumab is based on evidence from an international phase III, double-blind, high-quality RCT (CheckMate 238), which is closely aligned with the NICE final scope requested population, intervention and outcomes.

- The company's statistical approach was generally appropriate and well described.

The company conducted a comprehensive SLR to identify clinical effectiveness evidence of relevance to the decision problem in the NICE final scope.

- The ERG considers the validity and generalisability of the results of the ITC to be questionable based on differences in the ipilimumab treatment duration between the CheckMate 238 and CA184-029 studies (upto 1 year in CheckMate 238 and upto 3 years in CA184-029). The ERG, therefore, considers the analysis provided by the company where ipilimumab patients continuing treatment beyond one-year are censored in CA184-029 to be a more robust analysis and results in a more conservative estimate of the benefit of nivolumab compared to placebo as opposed to the over-optimistic results provided by the use of the ITT ipilimumab CA184-029 population.

- The ERG considers no suitable clinical effectiveness data were presented in the CS for the comparison of nivolumab versus routine surveillance for the outcomes of DMFS, HRQoL or AEs of treatment although data were provided for these outcomes for nivolumab versus ipilimumab.

- The ERG is concerned about the use of non-standard methods for the surrogacy analysis which was reported to be a first-step 'statistical exercise' to estimate OS for nivolumab versus routine surveillance. In addition, the surrogacy relationship was based on predominantly interferon studies which is potentially unreliable when applied to data for an immunotherapy, and used trial-level data rather than the PLD which was used in the methods which the surrogacy analysis is based on ([redacted].

- Data for nivolumab, and in particular for the outcome of OS [redacted] and ongoing nature of the CheckMate 238 study. [redacted]

- The ERG is also concerned that the subsequent therapies in CA184-029 do not reflect clinical practice in the UK. Following routine surveillance, a larger proportion of patients are likely to receive more effective subsequent immunotherapies than in the CA184-029 trial, meaning that the OS estimate for nivolumab versus routine surveillance generated from the ITC is potentially overestimated.

Economic

- The key weakness in the company's economic analysis is the lack of mature PLD OS data to inform nivolumab. This prevented the use of an indirect comparison between the CheckMate 238 and CA184-029 trials, which could have been adjusted for, including adjustments for subsequent treatments, to provide a potentially more reliable analysis.

- The changing pathway in recent years has also made the OS data from the CA184-029 trial less applicable, given that more effective treatments are now available for use as subsequent treatments for advanced melanoma. Adding to this, the CA184-029 trial also used a different treatment duration for the ipilimumab group, making the ITC between the trials potentially unreliable. However, this was explored for RFS with the use of censored data.

- The use of a surrogate relationship to estimate OS from RFS, which the company describe as being derived in an exploratory analysis, is not reliable enough to be considered for the base case analysis. The alternative structures with alternative OS data sources for subsequent treatments demonstrate the extent of the potential uncertainty in OS estimates with ICER increasing substantially, meaning that the company's base case analysis cannot be confidently relied upon for decision making.

- The company apply multiple estimates of effect using HRs, where the assessment of PH has not been appropriately assessed, such as the estimation of PRS from OS and the long-term prediction of RFS from OS. The company also apply HRs to survival models that do not support the use of PH, which is methodologically flawed.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The ERG's preferred base case results are given in Table A, showing the impact of using the censored RFS ITC and changing the subsequent treatments. This base case used the company's alternative Markov Option 2 model as its foundation.

Table A. ERG base case ICER

Results per patient	Nivolumab	Routine surveillance	Incremental value
Company's alternative model (Markov Option 2)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Lys	[redacted]	14.08	[redacted]
ICER			**£18,685**
RFS using censoring at one-year of treatment continuation			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Lys	[redacted]	14.19	[redacted]
ICER (compared with company ICER)			**£18,960**
ICER with all changes incorporated			**£18,960**

Nivolumab as subsequent therapy for distant recurrence after routine surveillance			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Lys	[redacted]	17.05	[redacted]
ICER (compared with company ICER)			**£96,443**
ICER with all changes incorporated			**£107,787**
Ipilimumab as subsequent therapy for distant recurrence after adjuvant nivolumab			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Lys	[redacted]	17.05	[redacted]
ICER (compared with company ICER)			**£10,202**
ICER with all changes incorporated			**£32,758**
Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; LY, life-year; QALYs, quality-adjusted life years; RFS, recurrence-free survival.			

Other outcomes used in the economic model/specified in the scope	DMFS, determined based on the first date of distant metastasis provided by the investigator and was defined as the time between the date of randomisation and the date of first distant metastasis or death, whatever the cause.[a] AEs according to the CTCAE v4.0. Immune-mediated AEs were determined on the basis of a prespecified list of terms from the MedDRA. HRQL according to the EORTC QLQ-C30 and the EQ-5D. HRQL was assessed at baseline, Weeks 5, 7, 11, 17, 25, 37 and 49, and then at two follow-up visits.
Abbreviations: AEs, adverse events; AJCC, American Joint Committee on Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DMC, data monitoring committee; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30; HRQL, health-related quality of life; IVRS, interactive voice response system; MRI, magnetic resonance imaging; RFS, recurrence-free survival; VEGF, vascular endothelial growth factor; WBC, white blood cell.	

4.2.1 Trial conduct

CheckMate 238 was an international randomised, double-blind, phase III trial of nivolumab compared with ipilimumab as adjuvant therapy in patients with completely resected Stage IIIB, IIIC or IV melanoma.[1] The company reported that CheckMate 238 was conducted at 130 centres in 25 countries, including 9 sites in England and Wales.

Patients were enrolled in CheckMate 238 between 30 March 2015 and 30 November 2015 and were required to be a minimum of 15 years old and to have Stage IIIB, IIIC or IV melanoma, according to the 2009 classification of the American Joint Committee on Cancer (AJCC) 7th edition.[1] However, as discussed in Section **Error! Reference source not found.**, only patients aged 18 or over were actually enrolled into the trial and the AJCC classification has recently been updated to the 8th edition[12] which means some Stage IIIA patients were enrolled.

Patients in CheckMate 238 were randomised 1:1 to nivolumab or ipilimumab study arms using an interactive voice response system (IVRS). The randomisation was stratified according to disease stage and programmed death receptor ligand-1 (PD-L1) status. The company focused their report in the CS on the 18-month follow-up data-cut of May 2017, although some results using [redacted]-month follow-up data from [redacted] were also provided. The ERG reports only the latter data-cut, although in some instances the [redacted] data were not provided in the CS and so the May 2017 data-cut is used by the ERG where necessary. The Consolidated Standards of Reporting Trials (CONSORT) diagram provided in Appendix D of the CS indicates that, at the interim data-cut in May 2017, a total of 906 patients had undergone randomisation resulting in 453 patients in each of the nivolumab and ipilimumab groups. As discussed in Section **Error! Reference source not found.**, there was an imbalance in the reasons for discontinuation from study drug between the two study arms. Based on the May 2017 data-cut, 177 patients in the nivolumab arm had discontinued study drug with the most common reasons for discontinuation being disease recurrence (121 patients) and study drug toxicity (41 patients). In the ipilimumab arm, 331 patients discontinued with the most common reason being study drug toxicity (208 patients) and the second most common reason was disease recurrence (101 patients).

4.2.4 Summary statement

In summary, CheckMate 238, an international randomised, double-blind, phase III trial of nivolumab compared with ipilimumab as adjuvant therapy in patients with completely resected Stage IIIB, IIIC or IV melanoma provided the clinical effectiveness evidence for adjuvant nivolumab in the CS.[1] CheckMate 238 was conducted at 130 centres in 25 countries, including 9 sites in England and Wales. The ERG considers CheckMate 238 addressed the population, intervention and outcomes requested in the NICE final scope although it was for the comparison of nivolumab versus ipilimumab and not the required comparison of nivolumab versus routine surveillance. However, the company also conducted an ITC to enable estimates of nivolumab versus routine surveillance to be presented in the CS (discussed in Section **Error! Reference source not found.**).

A total of 906 patients were randomised in CheckMate 238, resulting in 453 patients in each of the nivolumab and ipilimumab groups; study drug treatment in both groups was continued up to a maximum of one year. The ERG notes that the median treatment duration was [redacted] for the nivolumab group compared to [redacted] for the ipilimumab group.[22] Based on a May 2017 data-cut, 177 patients in the nivolumab arm had discontinued study drug with the most common reason for discontinuation being disease recurrence (121 patients). In contrast, in the ipilimumab arm, 331 patients had discontinued by the May 2017 data-cut with the most common reason being study drug toxicity (208 patients). The ERG's clinical experts reported that these differences in reasons for study drug discontinuations were not unexpected given the known toxicity profile of ipilimumab.

The baseline characteristics for each trial arm in CheckMate 238 appear to be well balanced and the company response to clarification suggests that approximately 50% of randomised patients in CheckMate 238 were from Western Europe sites although less than 10% of the randomised patients were from UK sites. The ERG's clinical experts reported that the baseline characteristics of patients in CheckMate 238 were generally in keeping with those expected of the equivalent patients in the UK although the ERG notes that only Stage IIIB, IIIC or IV melanoma patients were enrolled in CheckMate 238 when defined using the AJCC 7th edition.[1] However, the AJCC classification has recently been updated to the 8th edition[12] which means some Stage IIIA patients were also enrolled.

At the [redacted] data-cut, a total of [redacted] patients ([redacted]) from the nivolumab group and [redacted] patients ([redacted]) from the ipilimumab group had received subsequent melanoma anti-cancer therapies. The ERG's clinical experts reported that they were unsure as to what treatments would routinely be used following disease progression in patients who have received adjuvant nivolumab, as adjuvant therapy is not currently given in the UK. However, they considered that the subsequent therapies used in CheckMate 238 were reasonable. For the outcomes of RFS and DMFS, patients who received

approximately [redacted] of patients continued ipilimumab treatment beyond one year). The company conducted additional analyses in their clarification response using data where ipilimumab patients who were treated beyond one-year were censored at one year, which the ERG considers to be a more conservative estimate of the benefit of nivolumab compared to placebo, as opposed to the over-optimistic results provided by using the ITT ipilimumab population of CA184-029.

- The ERG also noted that the subsequent therapies differed between CheckMate 238 and CA184-029 and the ERG's clinical experts reported that the types of subsequent therapies given in CheckMate 238 were likely to be generally more consistent with the types used in UK clinical practice. The ERG notes that part of the reason for the differences in subsequent therapy is likely to be related to advances in clinical practice since CA184-029. The ERG also notes that due to the outcome censoring selected for the ITC analyses, these differences in subsequent therapies will have the largest impact in the analysis of OS.

- The company conducted an ITC analysis for RFS using PLD meta-regression and parametric survival models. For the PLD ITC the company included covariates for gender, age, stage and trial, with the rationale for including a trial covariate being, "it will account for all unobserved differences between trials, thus maintaining randomisation". The ERG is unclear as to exactly what these differences addressed by the trial level covariate are. The resulting parametric curves from the log-logistic meta-regression model (that was deemed to be the best-fitting model) suggest that for the matched population (CheckMate 238 and CA184-029), nivolumab is associated with the longest RFS compared to both ipilimumab and placebo.

- The company also conducted a Bucher adjusted indirect comparison for RFS using the full ITT populations of CheckMate 238 and CA182-029. This was conducted with and without covariate adjustments for age, gender and stage. [redacted] The HRs estimated by the Bucher RFS ITC for nivolumab versus placebo were numerically [redacted] higher when the ipilimumab censored at one-year data were used rather than the full ITT ipilimumab dataset, [redacted].

- The ERG requested the company conduct a re-analysis of the clinical data from CheckMate 238 and CA184-029, re-staging patients into the new AJCC 8th edition disease stages for melanoma, and an analysis by baseline PD-L1 status although the company reported that they were unable to conduct these analyses due to insufficient PLD. The ERG nevertheless considers them both to be potential subgroups of interest.

between the two is the proportion in the PR state. Appropriate costs and utility values are applied in each health state, which are described in Section 5.4.8 and Section 5.4.7, respectively.

This approach is a simple application of the key outcome data relating to disease-free survival and mortality that is often collected in cancer drug trials. For this reason, it is a common approach taken to model the cost effectiveness of cancer drugs for NICE technology appraisals, and generally considered appropriate.

For this appraisal, RFS was informed by an indirect treatment comparison (ITC) between the CA184-029 trial, which compared ipilimumab with placebo, and the CheckMate 238 trial, which compared nivolumab with ipilimumab. The ipilimumab groups of the two trials provides the link to indirectly form the desired comparison of nivolumab and placebo.[1, 21] This is discussed further in Section 4.4.

The proportion of patients in the death state at any given cycle was informed by a surrogate relationship between RFS and OS that had previously been estimated using predominantly interferon trials in the adjuvant setting. The implementation of this and the estimation of long term treatment effects is discussed further in Section 5.4.5.

5.4.4.2 Markov model (alternative scenario analyses)

The company's economic model also includes an alternative Markov structure, which was used to test structural uncertainty and to provide a range of scenario analyses that enabled the modelling of alternate assumptions for long term treatment effectiveness. The Markov structure has the same health states and the same time horizon as the PSM but the key differences lie in application of the effectiveness data.

In contrast to the PSM, the Markov model relies on transition probabilities between each of the states, which are applied at each cycle to determine the proportion of patients in a particular health state at a particular time. This structure allows for alternative data sources to inform post-progression survival, which, in a PSM, would be inherently determined for the time horizon of the model by survival models used to inform the analysis.

5.4.4.3 ERG critique

The ERG considers the company's PSM and Markov structures used in the base case analysis and scenarios to be suitable structures for the decision problem. The model is generally well constructed and the ERG did not identify any errors in the functioning of the model.

The model contains relevant health states to capture the key changes in the natural history of the disease; namely, recurrence-free, disease recurrence and death. The time horizon is long at 60 years but the ERG considers this to be appropriate given that patients as young as 18 are included in the population. The

[redacted]

[redacted]5.4.5.2 Markov model (Option 1)

The Markov model uses the same RFS modelling from the ITC as per the PSM. However, to estimate the probability of remaining in the RF state and the probability of transitioning to death from the RF state, the composite RFS measure needed to be "split" to separate out the rates of recurrence and the rates of death. This was approximated by weighting the RFS curves by the proportion of patients from the CheckMate 238 trial who had disease recurrence and who died, from those patients who had experienced an event. This split was used up to 10 years after which the proportion of patients used to determine the weights was taken from the Agarwala *et al*. 2017 trial; a longer-term trial comparing interferon with routine surveillance in the adjuvant setting.[46]

Post-recurrence survival (PRS) uses the same OS data as in the PSM. To estimate PRS transition probabilities from the OS data, Cox PH models were fitted to the data in the CA184-029 trial to estimate treatment specific HRs for PRS compared with OS. The resulting HRs, which were applied to the OS modelling used in the PSM, were [redacted] and [redacted] for ipilimumab and placebo, respectively, which were used to estimate PRS for nivolumab and routine surveillance, respectively.

The resulting health-state partitions for the company's Markov scenario (Option 1), demonstrating the proportions of patients in each health-state across the time horizon of the model, are depicted in Figure 27 and Figure 28, for nivolumab and routine surveillance, respectively.

[redacted]

[redacted]

5.4.5.3 Markov model (Option 2)

The company also provided a second Markov option in the model, which used the same approach as the first option in terms of RFS, but had differences to the approach for estimating PRS.

The OS estimates for this modelling approach were derived from numerous data sources. For patients with a local/regional recurrence, the survival curves that were fitted to the local/regional recurrence data from the CA184-029 trial were used. For patients with distant recurrence, a range of data sources, including Kaplan–Meier (KM) data from drug trials for advanced and/or metastatic melanoma, and registry data, were used to fit survival curves, which were then weighted to produce estimates expected to be reflective of the relevant population.

These curves were weighted by the subsequent treatments as per the treatments assessed in each of the data sources, and were assumed to apply up to 10 years. Beyond 10 years, registry data were used to estimate the proportion of patients alive at each cycle, and again, general population mortality data were used to impose a minimum mortality rate.

For patients in either the CheckMate 238 or CA184-029 trial who received nivolumab, ipilimumab or a combination of the two as a subsequent therapy, PRS was determined by the OS in the relevant group of the CheckMate 067 trial.[49]

5.4.5.4.2 Markov structure (ERG critique)

The first modelling option within the company's Markov structure (Option 1) provides an alternative to the surrogacy relationship to estimate OS; however, this alternative brings with it, different issues that do not necessarily mitigate the uncertainty in the results.

This Markov model structure avoids the requirement for the surrogate relationship to predict the OS benefits based on the RFS benefits, by using alternative data sources to estimate PRS transition probabilities. However, a key concern that the ERG has is with the application data used to inform PRS and the assumptions made in the application.

In particular, the ERG is uncertain that the assumption of a constant relative effect on the OS hazard, regardless of the applicability in the Agarwala *et al.* 2017 study, may not be a reliable measure of estimating PRS.[46] However, the company also provide a scenario analysis using the CA184-029 trial, which may be preferable given that it is a trial assessing an immunotherapy in the adjuvant setting rather than interferon. This modelling approach does not, however, resolve the issue of inappropriate subsequent therapies influencing OS outcomes.

The alternative modelling approach provided by the company using the Markov structure (Option 2) allows for the issues of inappropriate subsequent treatments to be explored. The data sources used are from various trials of different drugs used in the post-recurrence setting, meaning that both of these issues can be explored by applying a suitable proportion of patients to the subsequent treatments as used in UK clinical practice. The validity of applying the OS data from these alternative sources also needs to be considered, which is discussed later in this section.

The ERG sought clinical expert opinion to inform the expected proportions of subsequent therapies in order to assess the potential impact on OS and on the ICER. The experts suggested that a greater use of immunotherapies such as pembrolizumab and ipilimumab would be used in clinical practice. A key point that the experts raised is that nivolumab would be used in a metastatic setting following routine surveillance, and may in fact have the same efficacy as using nivolumab in the adjuvant setting. The ERG conducted a scenario using the Markov Option 2 model, which set all patients in the routine surveillance group who had a distant recurrence to receive subsequent nivolumab. All other subsequent treatments were kept the same. This increased the ICER from £18,685 per QALY to £96,443 per QALY.

The ERG emphasises the fact that this analysis uses a range of potentially disparate sources of evidence to inform PRS, so it is unlikely that the estimates of PRS and the applicability to the population on which the ITC was formed is robust and reliable. However, even if the analysis was considered reliable, the range of ICERs resulting from plausible scenarios demonstrates the potentially serious uncertainty

that currently exists within the results. The ERG considers it difficult to fully account for this uncertainty without an OS ITC using the CheckMate 238 trial data, with appropriate adjustments for subsequent treatments.

A scenario assuming all patients with a distant recurrence in the routine surveillance group receive subsequent nivolumab using data from the metastatic NMA with fractional polynomial models, resulted in an ICER of £324,108 per QALY. This merely acts to reiterate the uncertainty, as the applicability of these data is not certain, nor has it fully been justified by the company. Further to this, the company applied the underlying time-varying HRs to an exponential model for dacarbazine. This is methodologically flawed as it breaks the transitivity between survival models in the NMA and, hence, breaks the applicability of the relative treatment effect. The company should have instead fitted a fractional polynomial with parameters P1=0 and P2=1 to the dacarbazine data in order to retain the transitivity of the treatment effect across the network.

5.4.5.4.3 Summary of critique

Overall, the ERG considers there to be a large degree of uncertainty remaining in the analysis, although it appears difficult to mitigate this uncertainty without the availability of PLD from the CheckMate 238 trial to form an adjusted ITC for OS. Based on the data available, the ERG considers it preferable to assume OS for nivolumab is equivalent to ipilimumab for the PSM, and for the Markov Option 2 structure, to apply subsequent therapy costs and survival outcomes reflective of treatments expected to be received in the UK. The latter will form the ERG's preferred base case. The ERG acknowledges that this is still a very uncertainty analysis and only partially mitigates the uncertainty in the company's analysis. However, the ERG considers the company's analyses to be no less certain than the ERG's scenario that resulted in an ICER of £324,108 per QALY, hence, emphasising the potential impact of the uncertainty.

5.4.6 Adverse events

Adverse events (AEs) were included in the economic analysis to account for resources required to management those that occur in patients who receive nivolumab. The company included immune-related AEs of any grade, diarrhoea of grade 2 or above, and any other AE of grade 3 or above.

The company noted that previous metastatic melanoma NICE submissions of immunotherapies had applied a similar approach, using endocrine disorders instead of immune-related AEs. The company considered immune-related AEs to be more appropriate given that the comparator is routine surveillance, making the broader inclusion of AEs a potentially more important factor.

For nivolumab, data were taken directly from the all-cause data in the CheckMate 238 trial. For the proportions of immune-related AEs and diarrhoea in the routine surveillance group, the risk of AEs

trial.[60] They are applied as a one-off impact at the start of the model, with immune-related AEs and other AEs weighted by inpatient visits to apply the appropriate toxicity decrement.

The company acknowledge that there may be some double counting with adverse events experienced in CheckMate 238, but they consider the impact likely to be low given that the utilities are assumed to be equal across treatment groups. A scenario analysis was also conducted to assess the impact of potential double counting and this is provided in Section 5.5.

5.4.7.4 ERG critique

The ERG considers the company's approach to utility estimation within the economic analysis to be generally sound. The company appropriately applied EQ-5D-3L values from the trial informing the treatment effectiveness where data were available, i.e. CheckMate 238 trial for nivolumab. Where evidence was not available, i.e. for routine surveillance, the company's approach to estimating utilities by applying a mapping algorithm was suitable and they provided a clear justification for the selection of the mapping study used. The company also considered the use of published utilities from other studies to assess the potential uncertainty in this data. The ERG considers the company's approach to be thorough and appropriate.

However, for the impact of AEs, the ERG considers inclusion of AE decrements using an external source to be unnecessary. The company apply the same utilities per treatment arm and same utility decrements per AE to each treatment group so there are small differences between treatments. Further to this, the impact of AEs would already be captured within the trial data itself, so the purpose of applying these utility decrements is unclear. The ERG considers a more plausible approach would be to attempt to remove the impact of AEs from the health-state utility values (HSUVs) by adding the decrements to the utility values for the routine surveillance group. However, the ERG considers this to be unlikely to affect the results of the cost-effectiveness analysis.

5.4.8 Resources and costs

The company conducted a SLR to identify evidence relating to resource use and costs to be unnecessary, given that they had access to PLD for both the CheckMate 238 and CA184-029 trials that inform the treatment effectiveness within the economic analysis. The company also considered that the treatment pathways in the metastatic setting have changed considerably in recent years making it unlikely that relevant and up-to-date evidence would be publicly available.

5.4.8.1 Drug costs

The unit cost of nivolumab per vial based on the list price and the current agreed patient access scheme (PAS) are given in Table 38. There are two vial sizes available; 4ml and 10ml, both with a concentration of 10mg/ml, providing a dose per vial of 40mg and 100mg, respectively.

5.4.8.3 Resource use for adverse reactions

As discussed in Section 5.4.6, the company included costs associated with any grade of immune-related disorders, diarrhoea grade ≥2, and other AEs grade ≥3. For nivolumab, this data was taken from the CheckMate 238 trial, which also collected data for the number of hospitalisations required for treatment of AEs. For routine surveillance, AEs were based on the relative difference between the ipilimumab and placebo groups of the CA184-029 trial and the ipilimumab and nivolumab groups of the CheckMate 238 trial, with the exception of "other" AEs, which were assumed to be the same as nivolumab in the base case analysis because of an implausible difference making AEs higher for the placebo group.

The model captures the different resources expected to be incurred by inpatient and outpatients. Costs for inpatients were calculated using the weighted non-elective excess bed day unit costs for endocrine disorders, and for other AEs, the total HRG excess bed day cost was used; both from NHS reference costs 2016-17. These costs are summarised in Table 41.

Table 41. Adverse event inpatient costs (CS, page 157, Table 45)

Treatment	Hospital cost (£)	Type of stay	Reference
Hospital bed day (immune-related)	£297.41	Non-elective excess bed days	Weighted average between KA08A, DZ29H and FD01C- NHS reference costs 2016/17[64]
Hospital bed day (other AEs)	£305.85	Total HRGs - Non-elective inpatients	Excess bed days - NHS reference costs 2016/17[64]

Abbreviations in table: AE, adverse events; HRG, healthcare resource group; NHS, National Health Service.
Note: Endocrine disorders used as costs for immune-related disorders.

The proportion of patients treated for AEs in an inpatient setting was recorded in CheckMate 238; however, the number of hospitalisation days was not recorded. The proportion of patients treated for AEs in an outpatient setting was not recorded in either the CA184-029 or CheckMate 238 trials. To inform this, the company used a study by Oxford Outcomes,[66] which was designed to estimate resource use associated with advanced melanoma in the UK, Italy, Sweden, Spain and Portugal. The UK resource estimates were used to inform the model and these were inflated to 2016-17 prices using the PSSRU inflation indices.[65]

Table 42. Adverse event outpatient costs (CS, page 158, Table 46)

Outpatients and unit costs	Value	Reference
% Treated as outpatient (immune-related disorders)	24.2%	Oxford Outcomes. Table 91
Unit outpatient cost (immune-related disorders)	£428.08	Oxford Outcomes. Table 17
% Treated as outpatient (diarrhoea)	19.2%	Oxford Outcomes. Table 91
Unit outpatient cost (diarrhoea)	£649.85	Oxford Outcomes. [66] [27] Table 17
% Treated as outpatient (other Grade 3+ AEs)	21.7%	Oxford Outcomes. Table 91
Unit outpatient cost (other Grade 3+ AEs)	£403.68	Oxford Outcomes. Table 16/17

Abbreviations in table: AE, adverse events.

The results of these scenario analyses are given in Table 66 along with the company's results of their preferred analysis for the Markov Option 2 model.

Table 66. Scenario analyses for Markov Option 2 model

	Results per patient	NIvolumab (1)	Routine surveillance (2)	Incremental value (2-1)
0	**Company's Markov Option 2**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Lys	[redacted]	14.08	[redacted]
	ICER			**£18,685**
1	**RFS using censoring ipilimumab at one-year**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Lys	[redacted]	14.19	[redacted]
	ICER (compared with base case)			**£18,960**
2	**Nivolumab as subsequent therapy for distant recurrence after routine surveillance**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Lys	[redacted]	16.89	[redacted]
	ICER (compared with base case)			**£96,443**
3	**Nivolumab after routine surveillance; ipilimumab after adjuvant nivolumab (distant recurrence only)**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Lys	[redacted]	16.89	[redacted]
	ICER (compared with base case)			**£31,663**
	Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.			

6.3 ERG base case ICER

The ERG's preferred base case is based on the company's alternative model; the Markov Option 2. The ERG made three key changes to the company's preferred assumptions for this model, outlined in the following bullets:

- RFS based on the ITC analysis that used censoring for patients who received treatment beyond one year in the ipilimumab group of the CA184-029 trial;
- nivolumab applied as subsequent therapy for patients with a distant recurrence after routine surveillance;
- ipilimumab applied as subsequent therapy for patients with a distant recurrence after adjuvant nivolumab.

Although subsequent therapies can vary depending on the patient and the provider, the ERG considered a simplistic approach to assume that all patients within a particular treatment group have the same subsequent treatments following a distant recurrence.

The chosen therapies are both recommended in the metastatic setting by NICE and, therefore, represent a cost-effective use of resource. Clinical experts suggested that nivolumab is the most effective and should be the first choice; however, they were uncertain as to whether it should be used following adjuvant nivolumab. The clinicians considered ipilimumab to be an appropriate immunotherapy that could be used after adjuvant nivolumab as it is a different class of drug.

The results of the ERG's preferred base case ICER are given in Table 67.

Table 67. ERG base case ICER

Results per patient	Nivolumab	Routine surveillance	Incremental value
Company's alternative model (Markov Option 2)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Lys	[redacted]	14.08	[redacted]
ICER			**£18,685**
RFS using censoring at one-year of treatment continuation			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Lys	[redacted]	14.19	[redacted]
ICER (compared with company ICER)			**£18,960**
ICER with all changes incorporated			**£18,960**

Nivolumab as subsequent therapy for distant recurrence after routine surveillance			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Lys	[redacted]	17.05	[redacted]
ICER (compared with company ICER)			**£96,443**
ICER with all changes incorporated			**£107,787**
Ipilimumab as subsequent therapy for distant recurrence after adjuvant nivolumab			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Lys	[redacted]	17.05	[redacted]
ICER (compared with company ICER)			**£10,202**
ICER with all changes incorporated			**£32,758**
Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; LY, life-year; QALYs, quality-adjusted life years; RFS, recurrence-free survival.			

6.3.1 Scenarios using ERG's preferred base case

The ERG conducted a range of scenario analyses using the ERG's preferred base case as a basis. The results are presented in Table 68.

Table 68. Scenario analyses using ERG's preferred base case

	Results per patient	Nivolumab (1)	Routine surveillance (2)	Incremental value (2-1)
0	**ERG's preferred base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Lys	[redacted]	17.05	[redacted]
	ICER			**£32,758**
1	**50% of patients with distant recurrence in each group receive dabrafenib+trametinib**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Lys	[redacted]	14.21	[redacted]
	ICER (compared with base case)			**£15,245**
2	**All patients with distant recurrence in the nivolumab group receive dabrafenib+trametinib**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Lys	[redacted]	17.05	[redacted]
	ICER (compared with base case)			**£238,154**
3	**Using metastatic fractional polynomial-based NMA to inform PRS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	Lys	[redacted]	15.16	[redacted]
	ICER (compared with base case)			**£34,354**
	Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PRS, post-recurrence survival; QALYs, quality-adjusted life years.			