For projector and public observers - redacted

Lead team presentation

Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy

Cost effectiveness

1st Appraisal Committee meeting

Committee D, 27 September 2017

Lead team: Matt Bradley

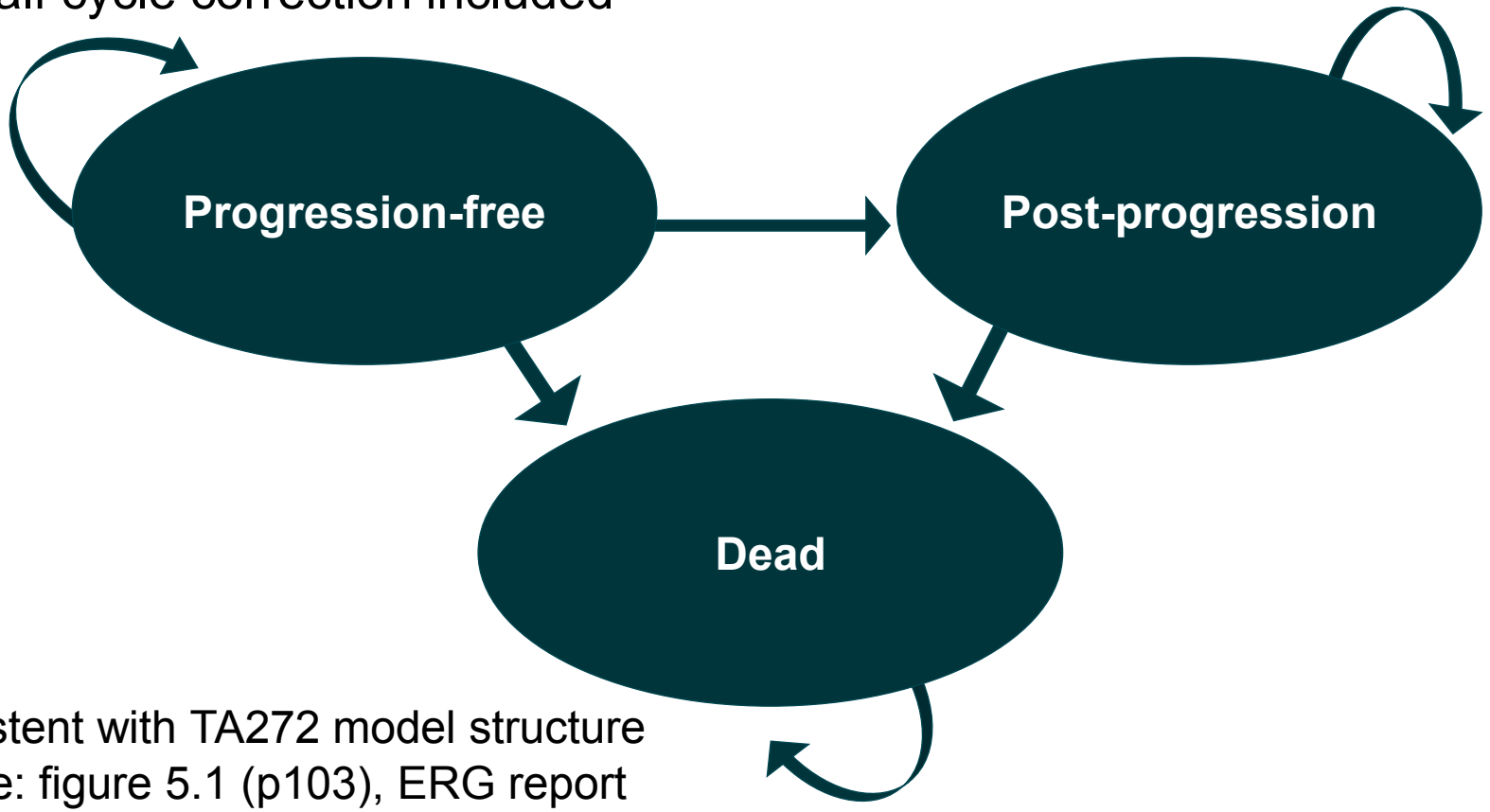
Company: Bristol-Myers Squibb Pharmaceuticals Limited

Chair: Gary McVeigh

Evidence review group: Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Economic model

- De novo economic model using a cohort-based partition survival model
- 3 mutually exclusive states
- Movement between states occurs at the end of each cycle (4 weeks)
- Half cycle correction included



Consistent with TA272 model structure
Source: figure 5.1 (p103), ERG report

Company's economic model

Population	• Consistent with the CheckMate 275 & 032 trials • Age, gender, weight and body surface area (BSA) included in the model
Comparators	• Paclitaxel: 80mg/m^2 Q3W of a four-week cycle • Docetaxel: 75mg/m2 Q3W • Best supportive care (BSC)
Perspective	NHS+PSS (England and Wales)
Time horizon	Life time horizon
Cycle length	4 weeks to account for length of treatment cycles
Discounting	3.5% per year for cost and utilities
Stopping rule	• None (base-case) • 75% of those still on treatment discontinue after 2 years (scenario)
Utilities source	CheckMate275

ERG comment:

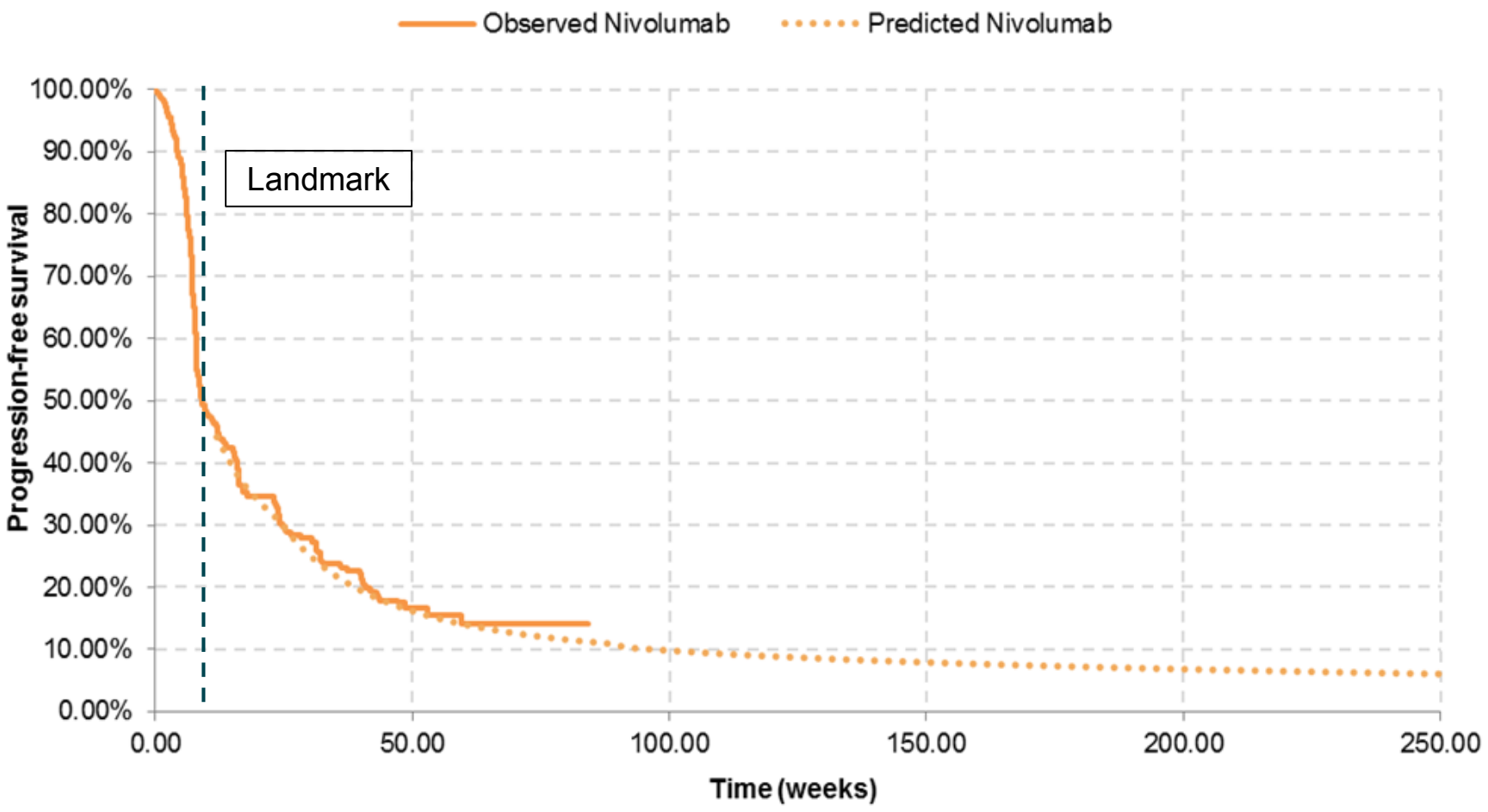
- Partitioned survival model has limitations
  - Transition probabilities are not estimated for each possible transition
  - Survival functions are modelled independently even though there are dependencies (e.g. progression is prognostic of mortality)

Survival analysis

- Standard models unsuitable for nivolumab's mechanism of action
  - Fails to capture changes in hazard overtime associated with long and durable response to treatment observed in some patients
- A response-based modelling approach was adopted
  - Fit parametric survival curves to the responders and non-responders separately to more accurately characterise hazard and survival
- Landmark analysis was undertaken to overcome immortal time bias
  - OS and PFS of responders and non-responders is estimated together until a specified landmark point – 8 weeks
  - Until the landmark, Kaplan-Meier estimates for the whole group (pooled)
  - After the landmark, generalised gamma was selected for OS and PFS
- The separated curves are then combined again for modelling purposes, weighted based on patients measured as being progression-free and alive at 8-weeks

Survival analysis: progression free survival

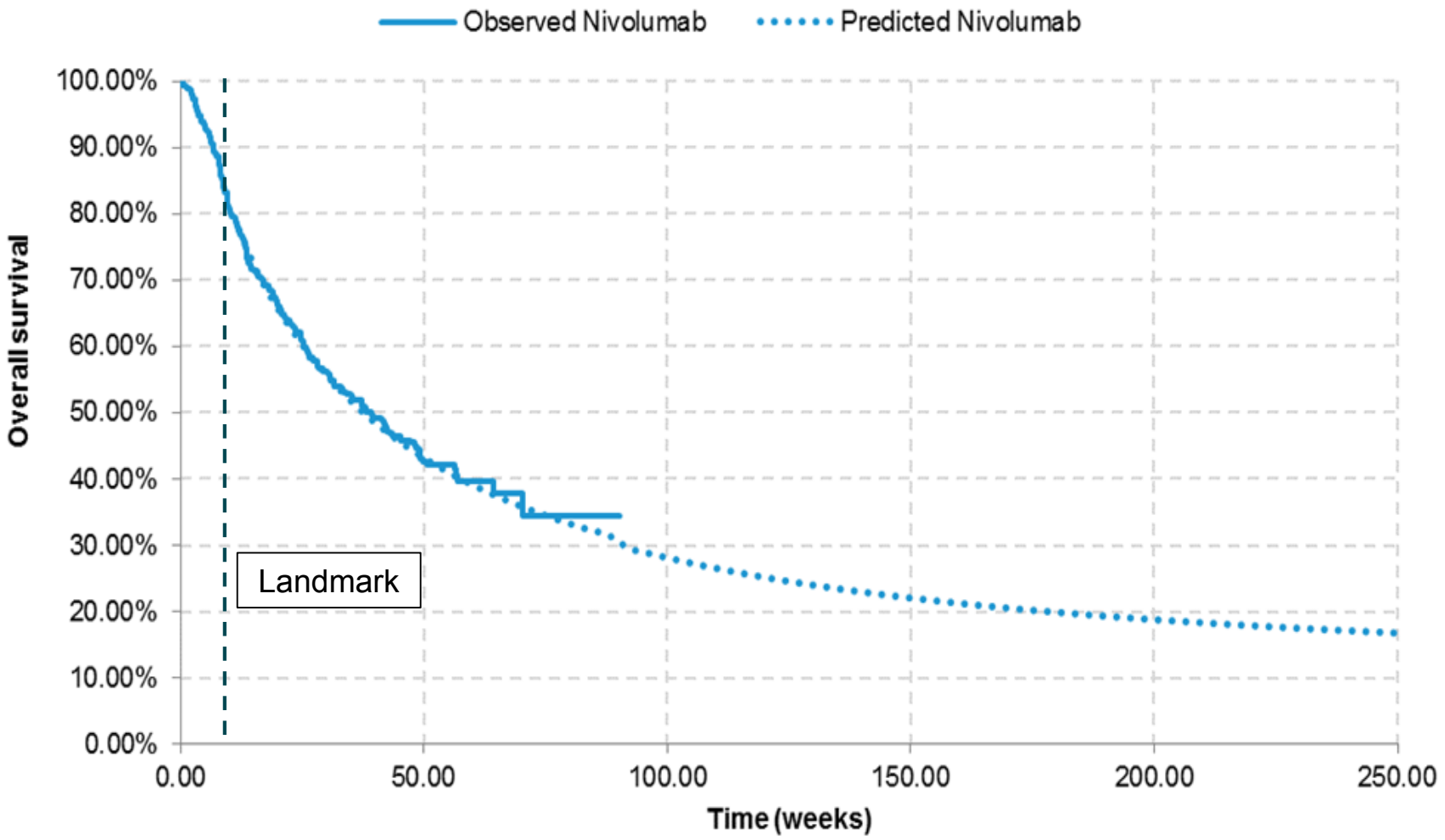
Company approach: response-based model - combined curve



Source: Figure 36 (page 93), company submission

Survival analysis: overall survival

Company approach: response-based model - combined curve



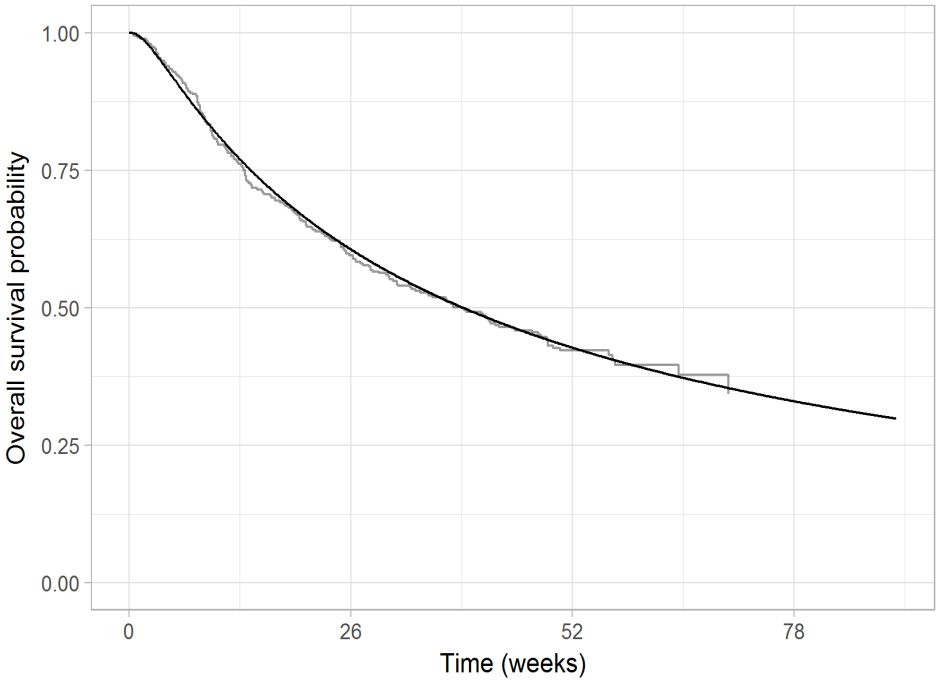
Source: Figure 37 (page 94), company submission

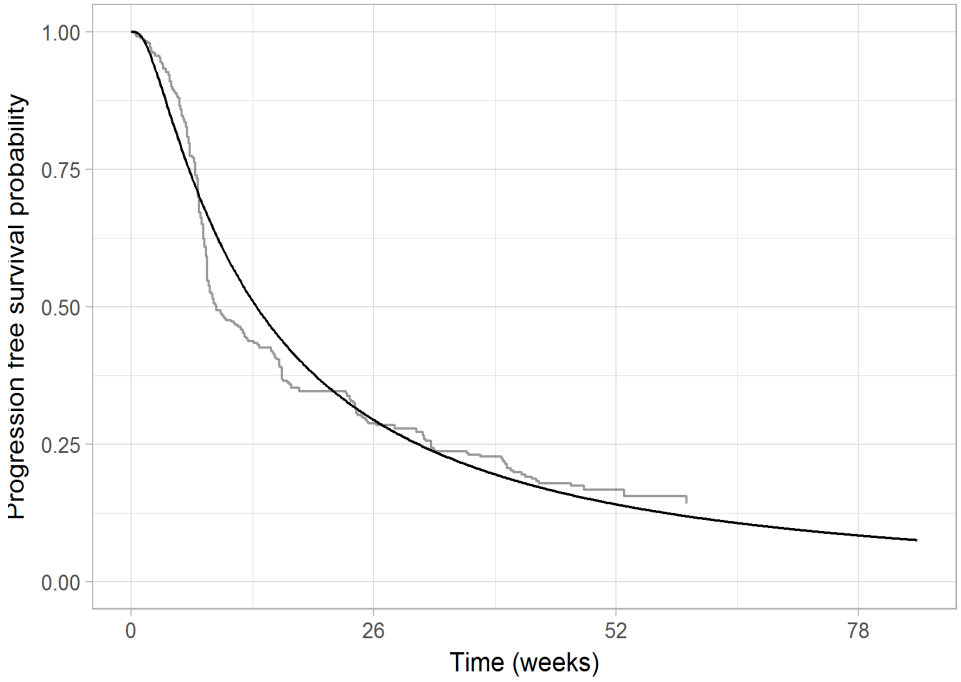
Survival analysis

ERG approach: conventional parametric time-to-event

ERG Comment:

- Standard models provided a good fit for OS and a reasonable fit for PFS
  - Response-based model not shown to be better





Source: company appendix L, OS (figure 114) and PFS (figure 120)

Survival analysis
ERG comment

- Responders and non-responders are combined for the indirect comparison, reducing the benefit achieved with a response-based model
- Prefer to use parametric time-to-event model to the estimate survival to the landmark point to avoid the problem of overfitting
- Additional assumptions in response-based model add uncertainty
  - Choice of landmark point has an unpredictable effect on results
  - Only data after the landmark point is used
- Response-based analysis biases results towards responders
  - 2.8 life years (response-based) v 1.84 life years (conventional)
- Limited expert consultation in the choice and validation of the model
- Unrealistic to assume a constant weighting of responder groups

Time to treatment discontinuation

- Nivolumab should be administered as long as clinical benefit is observed or until treatment is no longer tolerated by the patient
- Time-to-treatment discontinuation (TTD) was estimated through a parametric time-to-event model – generalised gamma
- TTD of the comparators was based on PFS
- Treatment with paclitaxel was assumed to stop after 6 (model) cycles
- Assumed that all BSC patients receive this treatment until death
- Scenario analysis where (25%) remain on nivolumab after 2 years

ERG comment:

- TTD was not estimated like OS and PFS – no justification
- Selective use of response-based modelling when it favours nivolumab
- Use of generalised gamma was justified by the lack of clinical plausibility of alternatives, without the support of clinical expert opinion
- Using alternative parametric distributions increased the ICER
- ERG analyses adopted a conventional, non-response based approach, using generalised gamma distribution for estimating TTD

Other issues

Relative effectiveness

- Assumed HRs for BSC and cisplatin plus gemcitabine for PFS
- Predicted survival curves for the comparators often underestimate survival when compared with the available trial data, because the STC accounts for differences in characteristics between studies

ERG comment:

- HRs used to estimate PFS for BSC and cisplatin plus gemcitabine were based on assumptions, and not supported by clinical evidence

Adverse events

- All-cause grade 3 or 4 AEs were included if the incidence was ≥5% and the impact on costs and utilities were front-loaded in the model

ERG comment:

- Nausea/vomiting, diarrhoea, and ALT increase have an incidence <5% for all treatments included in the cost effectiveness model. The ERG removed these adverse events from its analyses

Utility values

State	Utility/disutility value: mean (standard error)	95% CI	Source
Pre-progression	Imputed value: 0.718 (0.016) Observed value: 0.713 (0.017)	Imputed value: 0.686 to 0.75 Observed value: 0.679 to 0.747	Imputed from Checkmate 275
Change in utility – pre-progression to post-progression	Imputed value: -0.115 Observed value: -0.061	Imputed value: -0.143 to -0.087 Observed value: -0.123 to -0.055	Imputed from Checkmate 275
Post-progression	Imputed value 0.603 (N/A) Observed value: 0.623 (N/A)	N/A	Checkmate 275
Neutropenia	-0.18	NR	Attard et al. (2014)
Anaemia	-0.09	-0.13, -0.06	Beusterien et al. (2010)
Thrombocytopenia	-0.18	NR	Attard et al. (2014)
Asthenia/Fatigue	-0.12	NR	Attard et al. (2014)
Nausea/vomiting	-0.05	-0.08,-0.02	Nafees et al. (2008)
Diarrhoea	-0.29	NR	Attard et al. (2014)
ALT increase	-0.05	-0.07, -0.03	NICE TA347 (2015)
Leukopenia	-0.09	NR	Frederix et al. (2013)

Source: Table 35 company evidence submission

Health-related quality of life (HRQoL)
ERG comment

- Inconsistencies in the number of reported observations
  - Interpolated, imputed and valid observations don't sum to the total
- The exclusion of CheckMate 032 utilities, is inconsistent with the pooling of other outcomes
- The imputation of immature trial data is inappropriate as none of the immature observations will be censored due to death of patients
- There was no justification for using multiple imputation in favour of a mixed model to adjust for missing data
- Lack of justification for not using time-dependent utilities
- Dis-utilities for adverse events were inconsistent with a previous nivolumab appraisal (H&K), they were derived from the literature
  - It was unclear how the studies were selected – not from the SLR

Company base-case results

Deterministic

Technologies	Total		Pairwise vs. Nivolumab			ICER: Incremental (£/QALY)*
	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER (£/QALY)	
BSC	£9,052	0.64	[redacted]	[redacted]	£38,302	-
Docetaxel	£13,913	0.92	[redacted]	[redacted]	£44,996	£17,361
Paclitaxel	£14,430	0.76	[redacted]	[redacted]	£37,643	Dominated
Nivolumab	[redacted]	[redacted]				£44,996

Source: adapted from table 30 (page 92) company response to clarification

*Fully incremental ICERs generated by the NICE team

Probabilistic sensitivity analysis

- Patient age, weight and BSA, costs, resource use, utilities, TTD, PFS and OS were varied
- Incremental costs increased and incremental QALYs decreased compared to the deterministic results

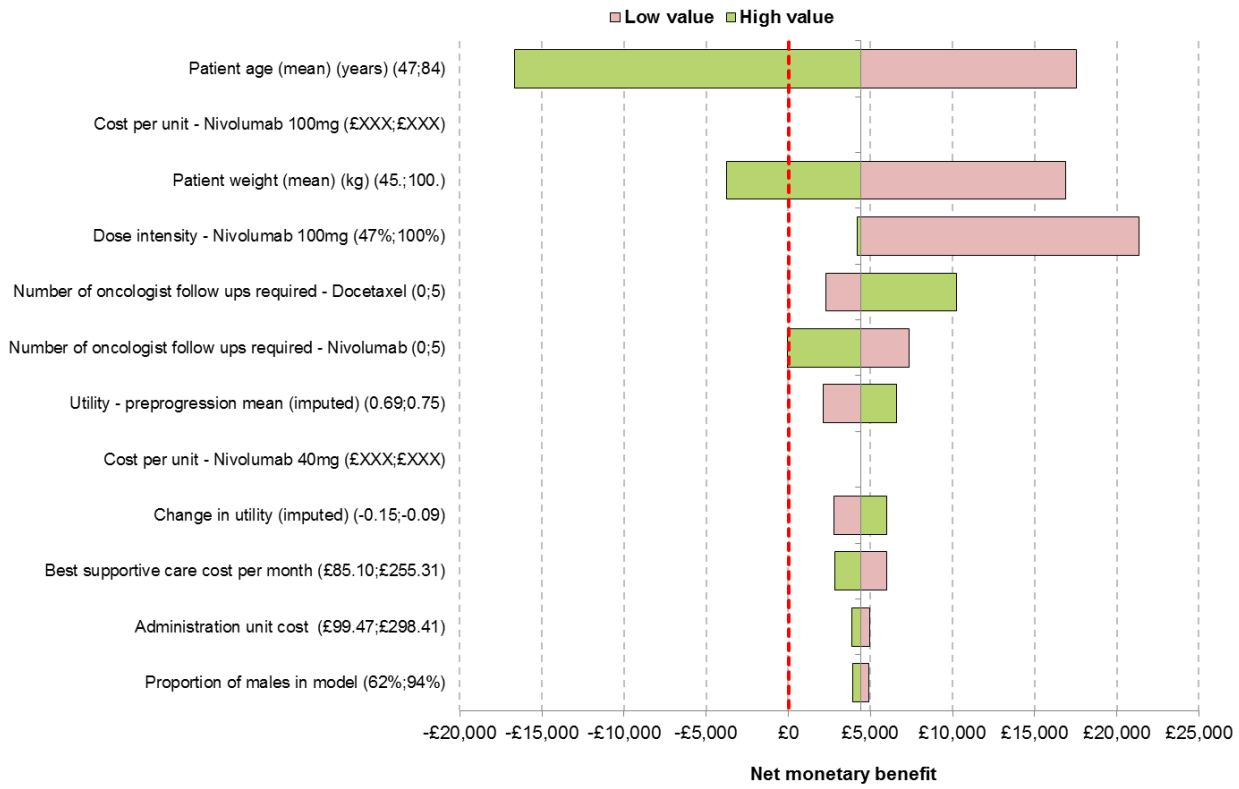
Nivolumab vs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Probability of cost effectiveness[a]
Paclitaxel	[redacted]	[redacted]	£46,209	72.10%
Docetaxel	[redacted]	[redacted]	£54,220	49.00%
BSC	[redacted]	[redacted]	£44,698	76.30%
Company scenario analysis				
Cis+gem	[redacted]	[redacted]	£103,568	6.9%

[a]The probability of nivolumab being cost-effective vs the stated comparator at a CE threshold of £50,000/QALY.
Abbreviations: Cis+gem: cisplatin plus gemcitabine; BSC: best supportive care, ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years
Sources: Table 46 (page 116) company submission and table 5.18 (page 125), ERG report

Deterministic sensitivity analysis

Nivolumab v docetaxel

- DSA results show that the model results are robust to changes to the majority of parameters; only 4 parameters causing direction of ICER to markedly change; patient age, cost per unit of nivolumab, patient weight*, and nivolumab dose intensity



Tornado diagram for nivolumab v docetaxel

*Patient weight had a lesser impact on the ICER when comparing nivolumab with paclitaxel or BSC

Deterministic scenario analysis

Scenario	Scenario info	ICER vs. Paclitaxel	ICER vs. Docetaxel	ICER vs. BSC
Base case*	Gen. gamma	£37,647	£44,960	£38,164
1 Survival curves	Landmark 8 weeks			
	Weibull	£101,994	£114,823	£91,372
	Gompertz	£49,010	£59,858	£50,201
	Lognormal	£52,900	£72,044	£53,634
	Log-logistic	£58,279	£78,063	£59,695
	Exponential	£57,998	£70,582	£59,564
	Landmark 26 weeks			
	Gen. Gamma	£34,541	£40,246	£34,774
	Weibull	£50,060	£62,866	£51,378
	Gompertz	£35,655	£41,933	£35,269
	Lognormal	£38,834	£48,610	£38,192
	Log-logistic	£42,475	£54,235	£43,097
	Exponential	£60,279	£76,786	£61,389

Sources: Tables 48 – 54 company submission
***Original base-case before minor corrections. Updated ICERs presented in slide 12**

Deterministic scenario analysis

Scenario	Scenario info	ICER vs. Paclitaxel	ICER vs. Docetaxel	ICER vs. BSC
Base case*	Generalised gamma	£37,647	£44,960	£38,164
2 Fractional polynomial model[a]	p1=1, p2=1	£56,073	£59,504	£43,554
3 Exponential piecewise model	Piecewise exponential at 8 weeks	£53,616	£65,450	£55,597
	Piecewise exponential at 26 weeks	£55,681	£71,147	£57,293
4 Vial sharing	Inclusion of vial sharing	£35,651	£42,630	£36,333
5 Stopping rule[b]	Stopping rule included	£31,561	£37,781	£32,743
6 Alternative TTD parametric curves	Weibull	£33,562	£40,141	£34,525
	Gompertz	£183,467	£216,984	£168,053
	Lognormal	£61,810	£73,465	£59,688
	Log-logistic	£61,994	£73,683	£59,851
	Exponential	£28,331	£33,971	£29,866

[a] Second-best fitted fractional polynomial model
[b] Stopping rule applied where after 2 years treatment, 75% of patients still receiving treatment will discontinue treatment
Sources: Tables 48 – 54 company submission
***Original base-case before minor corrections. Updated ICERs presented in slide 12.**

ERG base-case

#	Amendment from company analysis
Fixing errors	
1	Error in the use of UK life tables and conversion of background mortality rate to probability
2	Apply dose intensity after calculating the number of vials per weight category, instead of before
Fixing violations	
3	Added cisplatin plus gemcitabine to the base-case and fully incremental analysis in the PSA
4	Used OS to calculate the responder and non-responder proportions used for response-based TTD - avoiding double counting of patients
5	Removed adverse events with an incidence <5% from the analysis
6	Used the pooled utility estimates from CheckMate275 and CheckMate032
7	Used the pooled weight from CheckMate 275 and 032
8	Removed patient characteristics and comparator treatment costs from the PSA
Matters of judgement	
9	Using conventional survival analysis, not response-based analysis
10	Assumed only doses delayed by 7 days or more to be missed doses

ERG base-case

Amendment	Technologies	Total costs	Total QALYs	Δ costs	Δ QALYs	Nivolumab ICER* (£/QALY)	Δ ICER^ v company base-case
Fixing errors (1) and (2)	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,744	0.82	[redacted]	[redacted]	£50,974	-£3,246
	Paclitaxel	£14,155	0.71	[redacted]	[redacted]	£42,715	-£3,494
	BSC	£8,813	0.58	[redacted]	[redacted]	£42,532	-£2,166
Proportions of responders based on OS for TTD (4)[b]	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,779	0.82	[redacted]	[redacted]	£50,889	-£3,331
	Paclitaxel	£14,162	0.71	[redacted]	[redacted]	£42,644	-£3,565
	BSC	£8,819	0.58	[redacted]	[redacted]	£42,435	-£2,263
Removing AEs with incidence < 5% (5)[b]	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,810	0.82	[redacted]	[redacted]	£51,023	-£3,197
	Paclitaxel	£14,205	0.71	[redacted]	[redacted]	£42,870	-£3,339
	BSC	£8,858	0.58	[redacted]	[redacted]	£42,566	-£2,132
Utilities from pooled CheckMate studies (6)[b]	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,803	0.84	[redacted]	[redacted]	£49,613	-£4,607
	Paclitaxel	£14,204	0.73	[redacted]	[redacted]	£41,605	-£4,604
	BSC	£8,849	0.59	[redacted]	[redacted]	£41,406	-£3,292

(b) Conditional on the fixing errors adjustment (1) and (2)

Source: Table 6.1 ERG report *ICERs provided following factual accuracy check ^probabilistic ICERs

ERG base-case

Amendment	Technologies	Total costs	Total QALYs	Δ costs	Δ QALYs	Nivolumab ICER (£/QALY)	Δ ICER^ v company base-case
Weight from pooled CheckMate studies (7)[b]	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,763	0.82	[redacted]	[redacted]	£52,682	-£1,538
	Paclitaxel	£14,165	0.71	[redacted]	[redacted]	£44,199	-£2,010
	BSC	£8,819	0.58	[redacted]	[redacted]	£43,780	-£918
Excluding parameters from PSA (8)[b]	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,763	0.82	[redacted]	[redacted]	£51,149	-£3,071
	Paclitaxel	£14,178	0.71	[redacted]	[redacted]	£42,868	-£3,341
	BSC	£8,829	0.57	[redacted]	[redacted]	£42,632	-£2,066
Conventional instead of response-based analysis (9)[b]	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,507	0.72	[redacted]	[redacted]	£84,193	+£29,973
	Paclitaxel	£13,894	0.61	[redacted]	[redacted]	£65,302	+£19,093
	BSC	£8,736	0.55	[redacted]	[redacted]	£66,951	+£22,253
Missed doses when delayed > 7days (10)[b*]	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,894	0.82	[redacted]	[redacted]	£54,053	-£167
	Paclitaxel	£14,197	0.71	[redacted]	[redacted]	£45,372	-£837
	BSC	£8,844	0.58	[redacted]	[redacted]	£44,704	+£6

(b) Conditional on the fixing errors adjustment (1) and (2)
Source: Table 6.1 ERG report *ICERs provided following factual accuracy check ^Probabilistic ICERs

Nivolumab ICERs v cisplatin plus gemcitabine all over £91,000 or dominated

ERG base-case

Combined adjustments 1-10

Pairwise – Probabilistic results					
Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab	[redacted]	[redacted]			
Docetaxel	£12,540	0.74	[redacted]	[redacted]	£86,030
Paclitaxel	£13,905	0.63	[redacted]	[redacted]	£67,205
BSC	£8,741	0.56	[redacted]	[redacted]	£68,348

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year
Source: Table 5.22 ERG report *ICERs provided following factual accuracy check

- Cisplatin plus gemcitabine dominated nivolumab
- Nivolumab has a probability of being cost-effective of 0% and 0% at thresholds of £30,000 and £50,000 per QALY gained

Deterministic ERG base-case ICERs

- £82,028, £64,298 and £66,161 per QALY gained for nivolumab (with PAS) versus docetaxel, paclitaxel and BSC respectively
- Cisplatin plus gemcitabine dominated nivolumab

ERG exploratory analysis

- The ERG presented 8 exploratory analysis based on their base-case (conventional survival analysis) - all resulted in ICERs above £50,000 per QALY for nivolumab versus any relevant comparator
- Additional exploratory analysis based on ERGs base-case assumptions but using response-based modelling approach was also presented

Exploratory analyses on ERG base-case using response-based model for OS, PFS, TTD	
1	Maintaining the company's base-case choice of parametric time-to-event models
2	Responder OS & PFS (generalised gamma), non-responder OS & PFS (Weibull) based on best fit AIC/BIC, maintaining CS base-case TTD (generalised gamma)
3	Responder OS & PFS (generalised gamma), non-responder OS & PFS (Weibull) based on best fit AIC/BIC, responder TTD (lognormal) and non-responder TTD (Gompertz)
4	Use of 26-week landmark instead of 8-week landmark

ERG exploratory analysis

Analysis on ERG base case using response-based model

Amendment	Technology	Total costs	Total QALYs	Δ costs	Δ QALYs	Nivolumab ICER* (£/QALY)	Δ ICER^ v company base-case
Response-based analysis using ERG base-case (1)	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,919	0.85	[redacted]	[redacted]	£53,937	-£283
	Paclitaxel	£14,198	0.73	[redacted]	[redacted]	£45,466	-£743
	BSC	£8,838	0.6	[redacted]	[redacted]	£44,600	-£98
Response-based analysis alternative OS and PFS (2)	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,516	0.74	[redacted]	[redacted]	£122,716	+£68,496
	Paclitaxel	£13,891	0.63	[redacted]	[redacted]	£96,836	+£50,627
	BSC	£8,718	0.56	[redacted]	[redacted]	£94,964	+£50,266
Response-based analysis alternative OS, PFS and TTD (3)	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£12,507	0.77	[redacted]	[redacted]	£75,916	+£21,696
	Paclitaxel	£13,978	0.68	[redacted]	[redacted]	£66,008	+£19,799
	BSC	£8,699	0.55	[redacted]	[redacted]	£62,998	+£18,300
Response-based analysis using 26-week landmark (4)	Nivolumab	[redacted]	[redacted]				
	Docetaxel	£10,711	0.5	[redacted]	[redacted]	£77,167	+£22,947
	Paclitaxel	£13,681	0.52	[redacted]	[redacted]	£73,309	+£27,100
	BSC	£8,043	0.35	[redacted]	[redacted]	£62,903	+£18,205

Source: Table 6.1 ERG report *ICERs provided following factual accuracy check ^probabilistic ICERs

Nivolumab ICER v cisplatin plus gemcitabine are at least £87,000

End of life

Criterion	Data available
Short life expectancy, less than 24 months	• No studies in the literature review provided evidence of OS estimates for this patient population that approached 24 months • Highest median modelled OS of any of the comparators was 10.5 months (Gemcitabine+Cisplatin) (95% CI 3 to 22.9)

Treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Company model predicted mean life years (LY) with nivolumab 2.78 years (33.36 months)
	• Predicted mean LY from company model for comparators:
	  • Paclitaxel = 1.19 years (14.28 months)
	  • Docetaxel = 1.40 years (16.80 months)
	  • BSC = 1.01 years (12.12 months)
	• Company state that the survival gains offered by nivolumab represent a significant extension to life

ERG comment: the company's argument is,

- based on a lack of evidence to argue that there is no evidence of life expectancy over 24 months, and
- weak evidence from the economic model based on a comparison of single arm studies to show an extension to life of at least 3 months

Key points for consideration

- Quality of evidence
  - No comparative nivolumab trial data
  - Generalisability of nivolumab studies to UK practice
  - Reliability of simulated treatment comparison. Are all important prognostic factors accounted for?
  - Reliability of network meta-analysis. Are the included studies sufficiently homogeneous?
- Effectiveness of nivolumab
- Evidence for PD-L1 subgroups recommendations
- The company excluded gemcitabine and cisplatin from its base case. Is this appropriate?
- Approach to model survival. Company used a response-based analyses. ERG preferred conventional approach.
- Most plausible ICER
- Any significant health benefits not captured in the model
- End of life