NICE National Institute for Health and Care Excellence

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Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy [ID1585] *(CDF review of TA490)*

Lead team presentation

2nd Appraisal Committee Meeting - 17th June 2021 (virtual)

Chair: Lindsay Smith
ERG: Kleijnen Systematic Reviews Ltd
Technical team: Nigel Gumbleton, Hannah Nicholas, Linda Landells
Company: BMS

Key issues

- Should the ITT population or docetaxel subgroup be used for decision making?
- Are programmed death-ligand 1 (PD-L1) subgroups suitable for decision making?
- Are the company extrapolation methods for TTD suitable for the docetaxel subgroup?
- Is no or 5-year treatment waning effect most appropriate for decision making?
- Is no; 2 year; or 5 year stopping rule most appropriate for decision making?
- Which utility values are most appropriate for decision making?
- Does nivolumab meet the life extending element of the End of Life criteria?

Topic history [1]

TA490 – original appraisal (guidance published November 2017)

Nivolumab is recommended in the Cancer Drugs Fund (CDF) for treating **squamous cell carcinoma of the head and neck**, only if:

- the disease has progressed within 6 months of having chemotherapy
- nivolumab is stopped at 2 years of uninterrupted treatment
- the conditions in the managed access agreement are followed

ID1585 – CDF review (ACM1 – 3 December 2020)

Nivolumab is not recommended, within its marketing authorisation, for treating recurrent or metastatic squamous cell carcinoma of the head and neck in adults whose disease has progressed during or after platinum-based chemotherapy.

Topic history [2]

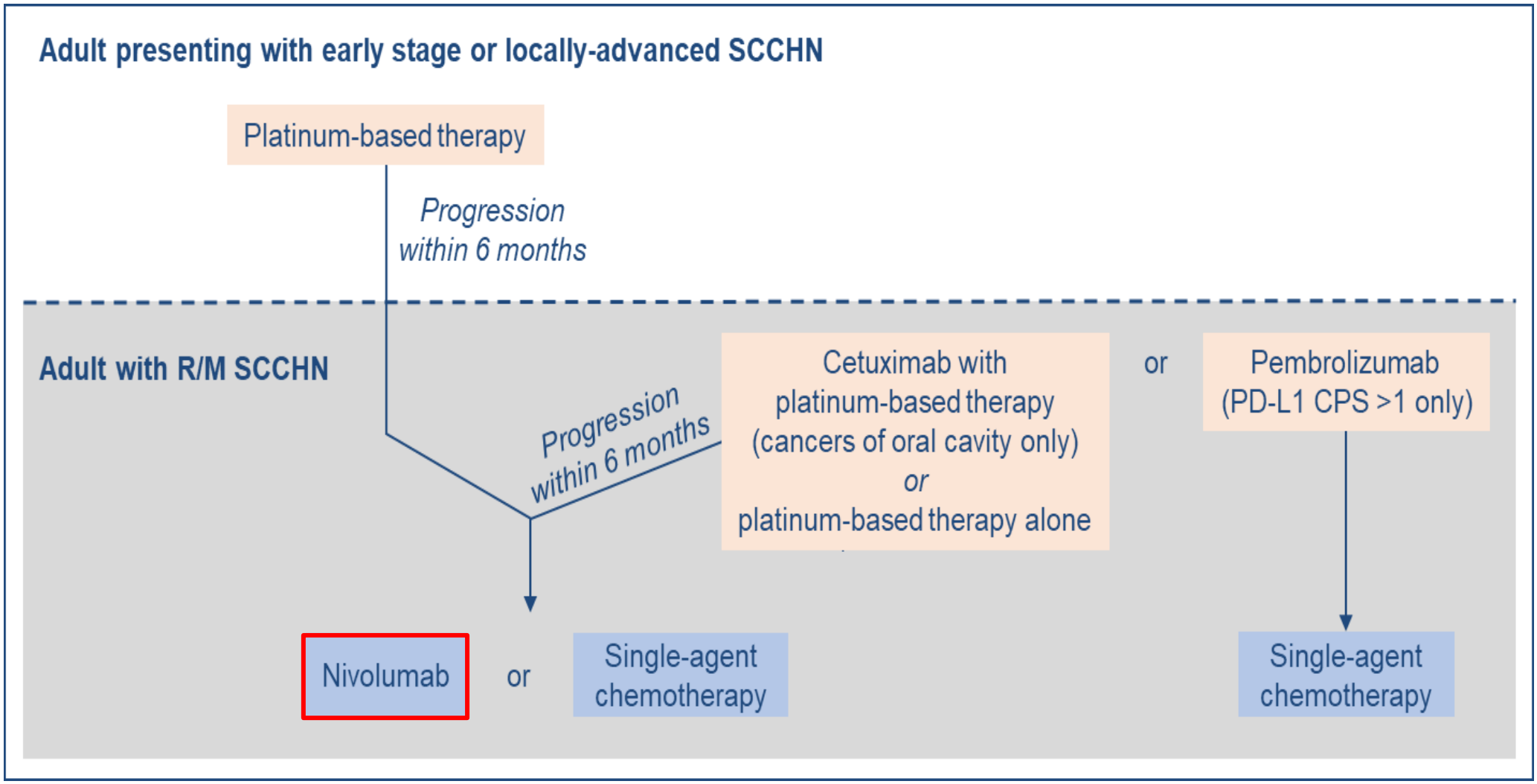
Nivolumab marketing authorisation: treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based chemotherapy.

	Decision problem (N.B. same scope used in TA490 and CDF review)	Notes

Population	• Adults with recurrent or metastatic squamous-cell carcinoma of the head and neck who have previously received platinum-based chemotherapy	• TA490: recommended only if disease progressed within 6 months of chemotherapy (trial population)
		• Subgroups also considered:
		  • PD-L1 ≥1% and PD-L1 <1% (TA490 and CDF review)
		  • Docetaxel subgroup (CDF review only)

Comparators	• Docetaxel • Paclitaxel • Methotrexate	• TA490: docetaxel most appropriate comparator for people fit enough to have it
Outcomes	• Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	• N/A

Head and neck cancer patient treatment pathway



Source: Figure 1, company response to ACD.

CPS: combined positive score; PD-L1: programmed death-ligand 1; R/M: recurrent or metastatic; SCCHN: squamous cell carcinoma of the head and neck.

Additional data collection versus data seen in TA490 + SACT cohort study

	CheckMate 141 – primary evidence source	SACT – supportive evidence
Study design	Multicentre, open-label, phase III randomised controlled trial	Cohort study
Population	• Histologically confirmed recurrent or metastatic squamous cell carcinoma of the head and neck • Stage III/IV • Not amenable to local therapy with curative intent [a] • Disease progressed within 6 months of last dose of platinum-based chemotherapy	
Intervention	• Nivolumab 3mg/kg intravenous injection every 2 weeks	• Nivolumab (weight-based or a flat dose)
Data cut-off	20th September 2016 (TA490) 15th October 2019 (CDF review)	12th May 2019
Comparator	Investigator's choice of chemotherapy, from: • Docetaxel • Methotrexate • Cetuximab	Not applicable
Outcomes	• OS, PFS, TTD • Overall and by PD-L1 status	• OS, TTD • Overall and by PD-L1 status

Source: Table 4 company submission. [a]Surgery or radiation therapy with or without chemotherapy.

PD-L1: programmed death-ligand 1; PFS: progression free survival; SACT: systemic anti-cancer therapy; TTD: time to treatment discontinuation

Recap: CDF review TA490 – Key clinical evidence in ITT population

CheckMate 141 has 37 months of additional data

Outcome	TA490		CDF review		
	CheckMate 141 September 2016		CheckMate 141 October 2019		SACT October 2019
	Nivolumab (ITT) (n=240)	IC (ITT) (n=121)	Nivolumab (ITT) (n=240)	IC (ITT) (n=121)	Nivolumab (n=506)
Deaths, n (%)	[redacted]	[redacted]	218 (90.8)	118 (97.5)	335/506 (66.2)
Median OS, months (95% CI)	[redacted]	[redacted]	7.72 (5.68, 8.74)	5.06 (4.04, 6.24)	6.5 (5.6, 7.6)
HR	0.70 (97.73% CI: 0.51, 0.96)		0.69 (95% CI: 0.55, 0.86)		NA
Survival rate, % (95% CI)					
12-month	[redacted]	[redacted]	33.4 (27.5, 39.5)	19.4 (12.9, 26.9)	34 (29, 38)
18-month	[redacted]	[redacted]	22.1 (17.0, 27.6)	8.4 (4.3, 14.3)	NA
24-month	[redacted]	[redacted]	16.8 (12.3, 21.9)	5.9 (2.6, 11.1)	NA
36-month	[redacted]	[redacted]	10.3 (6.8, 14.7)	2.5 (0.7, 6.6)	NA
48-month	[redacted]	[redacted]	8.0 (4.9, 12.0)	1.7 (0.3, 5.4)	NA

Source: Table 5 from company submission, table 3.4 from the ERG report

HR: hazard ratio; IC: investigator choice; ITT: intention to treat population; NA: not available; OS: overall survival; SACT: Systemic anti-cancer therapy

ACD Consultation comments

Comments received from:

- Bristol Myers Squibb (company)
- Clinical expert
- Head And Neck Cancer UK (patient group) – ACD accurately reflects committee discussion

Themes of consultation comments from clinical expert:

- Considerable unmet need for innovative treatments that offer a meaningful extension to life.
- Significant improvement in ability to treat patients over the existing treatment options.
- Well-tolerated treatment, extends survival and first treatment to show a survival benefit in those progressed after platinum chemotherapy.

Issues discussed at ACM1

Issue	Committee judgement in ACD
1) Data source – ITT or docetaxel subgroup	The docetaxel subgroup is most appropriate data source because it was most relevant to NHS clinical practice.
2) PD-L1 expression subgroups	Evidence that nivolumab is clinically beneficial for tumours with a PD-L1 score of 1% and above but the benefit for those with a low PD-L1 score was less certain.
4) TTD extrapolation	Company used 2-spline normal distribution for nivolumab arm, [redacted] for IC arm. ERG preferred generalised gamma distribution for both arms. Company method in docetaxel subgroup uncertain as no evidence of goodness of fit presented.
5) Stopping rule and duration of treatment effect	A 2-year stopping rule is not appropriate. Plausible that nivolumab's treatment effect matches that of standard care at 5 years after treatment started.
6) Utility values	Use both treatment-dependent and treatment-independent values in the base-case analysis.
7) End of Life criteria	It is unclear whether nivolumab meets the end-of-life criteria for extending life when compared with docetaxel.

IC: investigator choice ITT: intention to treat population; PD-L1: programmed death-ligand 1; TTD: time to treatment discontinuation

Most appropriate data source [1]

ACD: docetaxel subgroup should be used instead of ITT population

Background

- Comparator in CheckMate: investigator's choice of docetaxel, methotrexate or cetuximab.
- Original appraisal (TA490): ITT population from CheckMate used as data source.
- Committee conclusion: uncertainty about relevance of comparator arm to UK practice.
- CDF review, ACM1: company presented scenario analysis using docetaxel subgroup data.

ACD conclusion: Docetaxel subgroup was the most appropriate data source for this guidance review because it was most relevant to NHS clinical practice

Company's consultation comments

- ITT population most appropriate and consistent with original appraisal.
- Use of docetaxel subgroup data inconsistent with clinical feedback and not area of uncertainty identified in CDF Exit process.
- Treatment effect in ITT population and docetaxel subgroup similar.
- Outcomes in SACT cohort reflective of CheckMate.
  - more similar to outcomes for the ITT population than docetaxel subgroup.
- Docetaxel is most relevant comparator, but best supportive care also a relevant comparator

NICE ITT, intention-to-treat; SACT, systemic anti-cancer therapy.

Most appropriate data source [2]

Clinical experts prefer ITT population; ERG prefers docetaxel subgroup

Clinical expert consultation comments

- ITT population is relevant → reflects clinical practice.
- Docetaxel poorly tolerated and not considered to result in survival benefit.

ERG comments

- Docetaxel subgroup most appropriate.
- Similar treatment effect in ITT population and docetaxel subgroup not a reason to change opinion.
- Comparison with SACT data does not help inform size of relative treatment effect between nivolumab and docetaxel.
- Unclear whether best supportive care a relevant comparator
  - Terms of engagement: people not eligible for docetaxel likely have methotrexate.

Should the ITT population or docetaxel subgroup be used for decision making?

NICE ITT, intention-to-treat; SACT, systemic anti-cancer therapy.

PD-L1 subgroups [1]

ACD: benefit in PD-L1 < 1% subgroup uncertain

Background

- Original appraisal (TA490): nivolumab beneficial in ≥1% PD-L1. Benefit unclear in <1% PD-L1.
- CDF review, ACM1: company presented scenario analysis using PD-L1 subgroups.
- Clinical expert: availability of PD-L1 status at initiation limited + not good predictor of outcomes.
- Committee noted:
  - PD-L1 testing routine now pembrolizumab is recommended ≥1% PD-L1
  - nivolumab likely to be used in people with low PD-L1 score
  - uncertainty with PD-L1 subgroup results → small number of people included

Outcome	CDF review			
	CheckMate 141 – October 2019			
	PD-L1 <1%		PD-L1 ≥1%	
	Nivolumab (n=76)	IC (n=40)	Nivolumab (n=96)	IC (n=61)
Deaths (n)	72/76 (94.7)	40/40 (100)	87/96 (90.6)	60/61 (98.4)
Median OS, months (95% CI)	6.51 (4.37, 11.73)	5.45 (3.68, 8.54)	8.15 (6.67, 9.53)	4.60 (3.81 5.78)
HR (95% CI)	0.74 (0.50 to 1.10; p=0.138)		0.54 (0.39 to 0.76; p<0.001)	

Source: tables 8 and 9 company submission

ACD conclusion: Benefit for those with a low PD-L1 score is uncertain

NICE CI: confidence interval; PD-L1: programmed death ligand 1; IC: investigator choice

PD-L1 subgroups [2]

ACD: benefit in PD-L1 < 1% subgroup uncertain

Company's consultation comments

- In original appraisal (TA490) PD-L1 subgroup results not suitable for decision making. Conclusion in ACM1 contradicts this, despite no change in the data.
- CheckMate 141 not powered to detect a difference between treatment arms in PD-L1 subgroups → PD-L1 status not quantified in 24% of ITT population.
- High proportion of people don't have PD-L1 status determined, these people might be losing out on effective treatment despite evidence in ITT population indicating benefit
- Analysis by PD-L1 subgroups does not address decision problem outlined in the final scope.

Clinical expert consultation comments

- Nivolumab would not be reserved for PD-L1 <1% patients. Would be used for patients with all levels of PD-L1, with a large majority PD-L1 ≥1%.

ERG comments

- Results using PD-L1 status need to be interpreted with caution.
- Appears PD-L1 status impacts effectiveness of nivolumab and more so in the docetaxel subgroup.

Are programmed death-ligand 1 (PD-L1) subgroups suitable for decision making?

TTD Extrapolation docetaxel subgroup [1]

ACD: Most plausible extrapolation method for TTD in docetaxel subgroup is uncertain

Background

- CDF review ACM1: Extrapolation methods for ITT population;

	TTD	
	Nivolumab	**IC**
Company	2-spline normal	[redacted]
ERG	Generalised gamma distribution	

- CDF review ACM1: Company applied same assumptions for ITT population to docetaxel subgroup without providing evidence of goodness of fit to docetaxel subgroup data.

ACD: the extrapolation of TTD for the docetaxel subgroup was uncertain

Company's consultation comments

- CE results for variety of extrapolation methods for TTD have also been presented. In line with ERG preferences, generalised gamma model was explored for extrapolation of TTD.
- ERG preference versus company preference has small impact on ICER.

Are the company extrapolation methods for TTD suitable for the docetaxel subgroup?

CE: cost-effectiveness; IC: investigator choice; ITT: intention to treat; TTD: time to treatment discontinuation; ICER: incremental cost-effectiveness ratio

Stopping rule and treatment waning [1]

ACD: no stopping rule, 5-year treatment waning plausible

Background

Stopping rule

- Original appraisal, TA490: Analyses without a stopping rule are more appropriate for decision-making. 2-year stopping rule only accepted in Cancer Drugs Fund.
- CDF review, ACM1 – no new evidence presented:
  - No stopping rule included in CheckMate141. Stopping rule included in pembrolizumab (TA661) trial.
  - Stopping rules have been accepted in previous appraisals, regardless if stopping rule included in the trial. Committee concluded that a 2-year stopping rule was not appropriate.

Treatment waning

- Original appraisal (TA490): plausible nivolumab treatment benefit continued up to 5 years.
- CDF review, ACM1:
  - Smoothed hazard-rates plot for OS in ITT population for nivolumab and investigator choice → hazard rates met at 5 years.
  - Crossover from IC arm to nivolumab may bias against nivolumab (see 'Other issues')

ACD: no stopping rule and 5-year treatment waning most appropriate for decision making

Stopping rule and treatment waning [2]

ACD: no stopping rule, 5-year treatment waning plausible

Company's consultation comments

Stopping rule

- Stopping rule in line with pembrolizumab for same indication (TA661) and nivolumab in other indications.

Treatment waning

- Difference between treatment arms in change in hazards over time observed at end of the follow-up period for CheckMate 141 → hazard rates were not converging.
- Not appropriate that hazard in nivolumab arm becomes equal to IC arm - consistent with TA490 Committee preference for use of piecewise models to extrapolate OS.
- Given maturity of CheckMate 141 data and piecewise models used to extrapolate OS, applying treatment waning assumption where no stopping rule employed is counterintuitive.
- Base case includes 5-year stopping rule and no treatment waning.

ERG comments

- ACD → exclude stopping rule. 5-year stopping rule inconsistent with clinical evidence.
- Stopping rule should not be an argument against the 5-year treatment waning assumption.

Is no or 5-year treatment waning effect appropriate for decision making? Is no; 2 year; or 5 year stopping rule most appropriate for decision making?

Utility Values [1]

ACD: treatment-dependent and independent estimates in base case

Background

- Experts: QoL similar for different treatment options and diminishes in last months of life.
- Original appraisal (TA490): most appropriate utility estimates lie between the treatment-dependent utilities and treatment-independent utilities.
- CDF review, ACM1: no new evidence, maintain approach used in TA490.

ACD: utility values lie between treatment-dependent & independent estimates

Company consultation comments

- Agree most appropriate values lie between treatment-dependent and independent.
- Updated base case: utility values derived from regression model that included progression status and treatment arm (known as 'Model 1').
- Argue true utility values may lie closer to treatment-dependent values than independent.

ERG comments

- Model 1 is a plausible treatment-dependent utilities alternative.
- The difference in utilities is substantially larger for the PF off treatment state for Model 1 (favouring nivolumab).
- Key question - how long off-treatment utility gains for nivolumab should be extrapolated.

Utility Values [2]

ACD: treatment-dependent and independent estimates in base case

			Model 6	Model 7	Model 1
		Used in:	Company base case (pre-consultation)	ERG base case	Company base case (post-consultation)
		Treatment dependent / independent?	Dependent	Independent	Dependent scenario
PF	**Nivolumab**	**On treatment**	[redacted]	[redacted]	[redacted]
		Off treatment			[redacted]
	IC	**On treatment**	[redacted]		[redacted]
		Off treatment			[redacted]
PD	**Nivolumab**	**On treatment**	[redacted]	[redacted]	[redacted]
		Off treatment			[redacted]
	IC	**On treatment**	[redacted]		[redacted]
		Off treatment			[redacted]

Which utility values are most appropriate for decision making?

NICE IC: investigator's choice; PD: progressed disease; PF: progression-free.

End-of-life criteria [1]

ACD: uncertainty whether life-extending criterion met

Background

- Original appraisal (TA490): committee accepted life expectancy <24 months & nivolumab extends life by >3 months → met end-of-life criteria.
- CDF review, ACM1:
  - Short life-expectancy criterion met.
  - Docetaxel subgroup: uncertain would extend life by >3 months compared with NHS standard care → uncertain nivolumab meets end-of-life criteria compared with docetaxel.
  - PD-L1 subgroups: uncertainty in clinical evidence for PD-L1 <1% subgroup, committee concluded it is uncertain life-extending criterion was met.

ACD: Nivolumab meets the short-life expectancy criterion, however there is uncertainty whether nivolumab meets the life-extending criterion when compared with docetaxel and for tumours with a PD-L1 score less than 1%.

Company consultation comments

- End-of-life not identified as area of uncertainty in original appraisal (TA490)
- Data from ITT population shows nivolumab meets the end-of-life criteria
- Presented mean survival for docetaxel and PD-L1 subgroups: >3 months survival benefit for all scenarios. durability across a range of extrapolation methods confirms nivolumab meets end-of-life criteria.

NICE ITT: intention to treat; PD-L1: programmed death-ligand 1

End-of-life criteria [2]

ACD: uncertainty whether life-extending criterion met

Extrapolation method used in company and ERG base case

Extrapolation method for OS	Mean survival (months)		Survival benefit for nivolumab (months)
	Nivolumab	IC/ docetaxel	
Intended for docetaxel subgroup			
Piecewise lognormal 96-week cut-off	[redacted]	[redacted]	[redacted]
Piecewise lognormal 48-week cut-off	[redacted]	[redacted]	[redacted]
Fully parametric lognormal	[redacted]	[redacted]	[redacted]
Fully parametric loglogistic	[redacted]	[redacted]	[redacted]
PD-L1 <1% subgroup			
Piecewise lognormal 48-week cut-off	[redacted]	[redacted]	[redacted]
Fully parametric lognormal	[redacted]	[redacted]	[redacted]
Fully parametric loglogistic	[redacted]	[redacted]	[redacted]

Source: company response to ACD, table 5. Estimated survival benefit for nivolumab for a variety of extrapolation methods

Does nivolumab meet the life extending element of the end of life criteria?

NICE IC: investigator choice; PD-L1: programmed death-ligand 1

Other issues

Issue	Summary
Effect of switching from comparator to nivolumab unknown	**ACD:** • People in investigator-choice arm could have had nivolumab in extension phase of trial. • Company did not provide data on how many people switched. • Effect of switching on overall survival unclear - could bias results against nivolumab. **Company response:** • [redacted] (ITT population, n=121; intended for docetaxel population, n = [redacted] patients crossed over from IC arm to nivolumab treatment (15th October 2019). • These patients had received docetaxel → greater uncertainty in survival estimates for intended for docetaxel subgroup relative to the ITT population. **ERG response:** • Unlikely that any bias because of this would be substantial. • Difficult to predict what the combined effect of subsequent therapy might have been.
OS extrapolation	As per the Committee's preferred approach in TA490 and in alignment with the additional analysis presented by the Company at Technical Engagement, the piecewise method was used.

Key issues

- Should the ITT population or docetaxel subgroup be used for decision making?
- Are programmed death-ligand 1 (PD-L1) subgroups suitable for decision making?
- Are the company extrapolation methods for TTD suitable for the docetaxel subgroup?
- Is no or 5-year treatment waning effect most appropriate for decision making?
- Is no; 2 year; or 5 year stopping rule most appropriate for decision making?
- Which utility values are most appropriate for decision making?
- Does nivolumab meet the life extending element of the End of Life criteria?

CE results (deterministic): Company base case and committee preferred assumptions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]	-	-	-
Docetaxel	10,561	0.35	[redacted]	[redacted]	**£40,069**

Source: company response to ACD

Issue	Committee preferred assumption from ACD	Assumption included in company base case?
Data source	Include data from the docetaxel subgroup only	✗ - Intention to treat
Stopping rule	Exclude the stopping rule.	✗ - 5-year stopping rule
Treatment waning	Assume no treatment benefit for nivolumab 5 years after start of treatment	✗ - No treatment waning
Utility values	Include treatment-dependent and treatment-independent utility values	✗ - utility values from an alternative treatment dependent model (Model 1).
Utility values	Exclude the estimated utility decrements related to time before death	✓ - time-to-death utility decrements not applied

NICE [redacted]

CE: cost-effectiveness; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

Company base case and scenario analyses

Scenario	Assumptions used	Deterministic ICER (change vs. base case)	
	Company base-case: • ITT population • OS: Kaplan-Meier for 96 weeks + log-normal • TTD: 2-point spline normal for nivo.; [redacted] • Updated utility values from 'Model 1' • Time-to-death utility decrements not applied • 5 year stopping rule, no treatment waning	£40,069	
Company scenarios			
1	Data source: use intended for docetaxel subgroup	£47,577	+£7,508
2	OS: fully parametric log-normal curve to extrapolate	£43,853	+£3,784
3	TTD: generalised gamma to extrapolate	£39,362	-£707
4	Utility values: use treatment independent (TI) & treatment dependent (TD)	TI: £45,245 TD: £38,496	+£5,176 -£1,573
5a	No stopping rule, no treatment waning	£44,922	+£4,853
5b	5-year stopping rule, 5-year treatment waning	£47,530	+£7,461

Source: company response to ACD appendix 2

Company base case and technical team scenario analyses

Scenario	Assumptions used	Deterministic ICER (change vs. base case)	
	Company base-case: • ITT population • OS: Kaplan-Meier for 96 weeks + log-normal • TTD: 2-point spline normal for nivo.; [redacted] • Updated utility values from 'Model 1' • Time-to-death utility decrements not applied • 5 year stopping rule, no treatment waning	£40,069	
Technical team scenarios [a]			
6	Utility values: use treatment independent (TI) & treatment dependent (TD) + TTD: generalised gamma to extrapolate	TI:£44,995 TD:£38,282	+£4,926 -£1,787
7a	No stopping rule 5-year treatment waning TTD: generalised gamma to extrapolate	£47,291	+£7,222
7b	7a + Treatment independent (TI) and treatment dependent (TD) utilities	TI: £55,841 TD: £46,460	+£15,772 +£6,391

• [a] Calculated by NICE technical team, validated by ERG.

ERG scenario analyses: docetaxel population

Scenario	Assumptions used	Deterministic ICER (change vs. base case)	
	Company base-case: • ITT population • OS: Kaplan-Meier for 96 weeks + log-normal • TTD: 2-point spline normal for nivo.; [redacted] • Updated utility values from 'Model 1' • Time-to-death utility decrements not applied • 5 year stopping rule, no treatment waning	£40,069	
ERG scenarios			
8	**Intended for docetaxel population** 5 year treatment waning No stopping rule TTD: generalised gamma to extrapolate	£60,625	+£20,556
9	8 + use treatment independent utility values	£75,171	+£35,102

 ITT: intention to treat; OS: overall survival; TTD: time to treatment discontinuation; ERG: evidence review group

Scenario analyses based on PD-L1 subgroups

Scenario	Assumptions used	Deterministic ICER (change vs. base case)	
	Company base-case: • ITT population • OS: Kaplan-Meier for 96 weeks + log-normal • TTD: 2-point spline normal for nivo.; [redacted] • Updated utility values from 'Model 1' • Time-to-death utility decrements not applied • 5 year stopping rule, no treatment waning	£40,069	
11a	PD-L1 ≥ 1% subgroup only [b]	£38,822	- £1,247
11b	PD-L1 < 1% subgroup only [b]	£44,890	+£4,821
12a	PD-L1 ≥ 1% subgroup only + docetaxel subgroup	Not able to calculate using the model	
12b	PD-L1 < 1% subgroup only + docetaxel subgroup		
13a	PD-L1 ≥ 1% + no stopping rule + 5 year treatment waning OS: piecewise log-normal 48-week to extrapolate TTD: generalised gamma to extrapolate Treatment dependent utilities [c]	£48,006	+£7,937
13b	13a + treatment independent utilities [c]	£54,772	+£14,703

- [b] calculated by company. [c] calculated by ERG.

ITT: intention to treat; OS: overall survival; TTD: time to treatment discontinuation; ERG: evidence review group