NICE National Institute for Health and Care Excellence

Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer

ID811

Fourth Appraisal Committee meeting

12 April 2017

For Public

Appraisal history

Committee meeting	Action
1st Committee meeting (November 2015)	• ACD issued • List price • Nivolumab not recommended
2nd Committee meeting (February 2016)	• FAD issued to C&Cs only • List price • The appraisal was suspended at appeal stage; the FAD was withdrawn, not published and remains confidential. • The company requested to make a further submission including a patient access scheme. • In recognition of the exceptional nature of this request, NICE agreed to refer it back to the appraisal committee.
3rd Committee meeting (August 2016)	• A simple discount PAS proposed by the company to DH • ACD2 was issued

Committee consideration (1)

12 April 4th meeting

Recommen-dation from ACD2 at 3rd ACM	• Nivolumab is not recommended for treating locally advanced or metastatic squamous non-small-cell lung cancer after chemotherapy in adults with a PD-L1 expression of less than 10%. • The Appraisal Committee is minded not to recommend nivolumab as an option for treating locally advanced or metastatic squamous non-small-cell lung cancer after chemotherapy in adults with a PD-L1 expression of at least 10%. The committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund.
Company response to ACD2	• The company did not submit a CDF proposal for the PD-L1 subgroup, instead continued to pursue an alternative proposal with new evidence and analyses in order to address some of the committee uncertainties in the appraisal for the whole population for committee's consideration

Committee consideration (2)

12 April 4th meeting

Other responses to ACD2	• Responses were received from a number of patients and professional organisations, as well as 2 petitions • Comments related to the recommendation, subgroups, CDF, fairness and access
NICE response and commission of the DSU	Reviewed the company proposal and commissioned the NICE decision support unit (DSU) to: • Explore the goodness of fit for all OS extrapolation curves (company ACD2 response 'intermediary', committee-preferred ACD2 and company original, curves) relative to the clinical OS outcome data • Explore rationales for a 2 year stopping rule and uncertainty of the long-term treatment effect • Propose a DSU-preferred OS curve-fit (chosen from the company ACD2 response 'intermediary', the committee-preferred ACD2 or company original curves), and reasons for the choice

Committee consideration (3)

12 April 4th meeting

DSU report	• After carefully reviewing the evidence, the DSU prefers to use the company's 'intermediary' curve to extrapolate OS.

NICE response and submission table	• NICE defined an updated company submission table, including
	  • the committee-preferred ACD2 assumptions and scenarios.
	  • the approach to continued treatment effect be consistent with what has been explored in the final guidance of TA428 pembrolizumab for NSCLC (paragraphs 4.8 and 4.12, in particular).
	  • NICE finally specified that the company did not include the impact of wider benefit to the NHS in the company base case (i.e. melanoma and renal cell cancer 'credit' omitted from the base case: reference NICE methods).
	• NICE requested probabilistic sensitivity analysis results for the different scenarios in the submission table and the corresponding incremental cost and QALY results for all of the scenarios be provided.

Committee consideration (4)

12 April 4th meeting

Company response	The company took account of the DSU findings. The company provided an updated company submission/ACD2 response for the <u>whole squamous NSCLC marketing authorisation population</u> comparing nivolumab with docetaxel as follows: • Accounting for the DSU choice of curve, long-term survival extrapolations, a ' company intermediary' curve and a 'new company base case' curve were presented • New supporting clinical evidence – updated 3 year OS data to support the company choice of curve • Updated PAS discount • 2 year stopping rule implemented • Scenarios with melanoma and renal cell cancer 'credit' included

The committee is being asked to consider the new evidence and analyses presented and make recommendations for <u>the whole population</u> for nivolumab in squamous NSCLC ID811, as the CDF route is no longer appropriate

Key issues for consideration

Whole population under consideration

- What is the most plausible method for overall survival extrapolation?
- Should treatment duration be limited? Is it plausible to assume that patients continue to benefit from nivolumab after stopping treatment at 2 years? If so for how long?
- Should the committee's consideration on progression-free survival be reconsidered based on additional evidence from company?
- What is the most plausible ICER with revised proposed PAS for nivolumab?
- Does the committee consider nivolumab to be an innovative therapy?
- Is the committee satisfied that all the end-of-life criteria have been met?

Nivolumab

- Mechanism of Action
  - Nivolumab is an inhibitor of PD-1, part of the immune checkpoint pathway
- Marketing Authorisation – received in April, 2016
  - Indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults
  - Before the MA was granted, nivolumab was available through MHRA's Early Access to Medicines Scheme (EAMS)
  - MHRA awarded nivolumab a Promising Innovative Medicine (PIM) designation
- Dosage and Administration
  - 3 mg/kg every 2 weeks, by intravenous infusion over 60 minutes
- Cost
  - List price: £439.00 per 40-mg vial - The company have submitted a revised patient access scheme to DoH. The size of the discount is confidential
- Recent guidance
  - Pembrolizumab recommended as an option for or treating locally advanced or metastatic PD-L1-positive NSCLC (NICE TA428)

Committee considerations and preliminary recommendations in ACD2 (ACM3)

- Squamous NSCLC causes distressing symptoms and has few treatment options – important unmet need
- Nivolumab is a clinically effective treatment option – gains in OS and PFS
- Using an exponential curve for OS and PFS extrapolation was more appropriate (2 knot spline hazards model for OS)
- A utility value of 0.693 for the progression-free health state and a utility value of 0.509 in the progressed-disease health state is appropriate (company preferred 0.750 for PF and 0.592 for PD)
- ERG's approaches to treatment costs were mostly appropriate
- Innovative treatment
- End-of-life criteria were met
- Most plausible ICER for nivolumab compared with docetaxel with PAS was £73,500 per QALY gained (company base case £66,100 per QALY gained)

Minded not to recommend squamous NSCLC with a PD-L1 expression of at least 10%. Company invited to submit a proposal for the Cancer Drugs Fund

ACD, appraisal consultation document; ICER, incremental cost-effectiveness ratio; NSCLC, non-small-cell lung cancer; QALY, quality adjusted life years

Committee's preferred assumptions

From ACD2

- **Modelling overall survival**
  - Use the exponential curve to extrapolate OS data from CheckMate-017, in line with the ERG suggestions.
- **Modelling progression free survival**
  - Use the exponential curve after 2.2 months to extrapolate PFS data from CheckMate-017, in line with the ERG suggestions.
- **Utility values**
  - Utility value of 0.693 for the progression-free health state and a utility value of 0.509 for the progressed-disease health state
- **PD-L1**
  - nivolumab might have a different level of clinical effectiveness according to the level of PD-L1 expression, but it did not have the cost-effectiveness evidence to consider these subgroups
- **Stopping rule –** A stopping rule should not be applied to the economic modelling
- **End of life –** The committee concluded that nivolumab met the end-of-life criteria

ACD2 consultation comments

- Comments received from consultees:
  - Bristol-Myers Squibb (company)
  - British Thoracic Society (BTS)
  - Joint submission from National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Physicians (RCP), Royal College of Radiologists (RCR), British Thoracic Oncology Group (BTOG)
  - Roy Castle Lung Cancer Foundation (RCLCF)
- Web comments received from
  - Patients, relatives of patients with breast cancer, members of the public, NHS professionals

ACD2 consultation comments themes

- Subgroup based on PD-L1 expression:
  - Inappropriate to make recommendations for nivolumab based on PD-L1 expression (company)
  - Inconsistency with previous ACD, where the committee concluded that there is no evidence that suggests that a subgroup based on PD-L1 expression level can be defined (NCRI, ACP, RCP, RCR, BTOG [joint submission])
  - The 10% threshold is arbitrary (NCRI, ACP, RCP, RCR, BTOG)
  - PD-L1 is a heterogeneous biological marker (NCRI, ACP, RCP, RCR, BTOG, clinical expert)
  - Patients with less than 10% of PD-L1 expression also experienced OS benefits and less toxicity with nivolumab compared to docetaxel (NCRI, ACP, RCP, RCR, BTOG)
- Stopping rule:
  - A 2-year stopping rule is applicable, clinicians are willing to adhere (Company, NCRI, ACP, RCP, RCR, BTOG)

ACD2 consultation comments themes (2)

- Docetaxel is the only relevant comparator in these populations (company comments)
- Nivolumab has been approved in Scotland – equality of access (Web comments, Petition comments)
- Some of the consultees supported the idea of including nivolumab on the cancer drugs fund (Web comments, RCLCF comments)
- Some raised concerns about the feasibility of data collection in CDF (NCRI, ACP, RCP, RCR, BTOG comments [joint submission],
- Nivolumab showed more tolerable toxicity profile in clinical trial than docetaxel (company comments, NCRI, ACP, RCP, RCR, BTOG comments [joint submisison], Petition comments)
- Consultees are urging NICE, BMS and NHS England to reach consensus and ensure that cost issues and issues of uncertainty are addressed (Web comments, RCLCF comments)

Petitions

- Petition submitted by 2 members of the public
- Signed by 95,632 and 174,083 people
- Asking NICE to make lung cancer wonder drug, nivolumab available in England and Wales

ACD2 company new evidence proposal

For whole population nivolumab vs docetaxel
as of January 2017

- An intermediary generalised gamma curve should be applied for overall survival extrapolation (based on 4-year data from CheckMate 003 it is a plausible assumption)
- 2-year stopping rule should be applied
- Revised PAS: confidential simple discount
- 2-year stopping rule should be applied (Pembrolizumab TA248 – stopping rule accepted implementation supported by clinicians)

  "*NHS England commented during consultation that it was confident that a 2-year stopping rule would be acceptable to both patients and clinicians and would be implementable*" - Section 4.8

DSU commissioned by NICE

DSU specification

NICE commissioned the NICE decision support unit (DSU) to:

- Explore the goodness of fit for all OS extrapolation curves (company ACD2 response 'intermediary', committee-preferred ACD2 and company original, curves) relative to the clinical OS outcome data
- Explore rationales for a 2 year stopping rule and uncertainty of the long-term treatment effect
- Propose a DSU-preferred OS curve-fit (chosen from the company ACD2 response 'intermediary', the committee-preferred ACD2 or company original curves), and reasons for the choice

DSU findings

- Overall survival: For the squamous indication, the available evidence (2 years data from CheckMate-057 and 4 year data from CheckMate-003), seems to support the use of a decreasing hazards function, therefore the company 'intermediary' curve, a generalised gamma curve is plausible for OS extrapolation
- 2-year stopping rule: A stopping rule might be possible to apply. However there is no evidence to support that a continuous treatment effect is sustained after stopping treatment with nivolumab. Assuming that patients will experience the same benefit after treatment discontinuation is unreasonably optimistic.

Company's final revised modelling approach and new evidence

Modelling approach

- Committee's preferred utility values used in the modelling
- 2-year stopping rule applied
- For consistency with other appraisals a declining treatment effect after stopping treatment was assumed as a request by NICE
- Wider benefits of the simple PAS for the NHS included in scenario analysis as a PAS credit – requested by NICE
- PFS modelling should be reconsidered based on 3-year data
- Overall survival curve using the log-logistic extrapolation

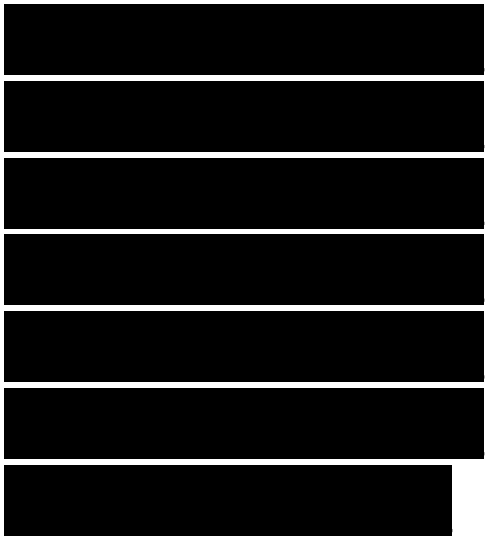
New evidence

- Additional 3 year overall survival data from CheckMate-017
- Additional 5 year data from CheckMate-003

Company was also asked to present corresponding ICERs to the DSU's preferred assumptions

CheckMate-017: Overall survival

36 month analyses



Overview of overall survival results

CheckMate 017

	Median OS		Hazard ratio
	Nivolumab	Docetaxel	
12 months analysis	9.2 (CI 7.3 to 13.3)	6.0 (CI 5.1 to 7.3)	0.59 (CI 0.44 to 0.79)
24 months analysis (used in the CE model)	9.23 (CI 7.33 to 12.62)	6.01 (5.29 to 7.39)	0.62 (0.47 to 0.80)
36 months analysis (not used in the CE model)	9.23 (CI 7.33 to 12.62)	6.01 (CI 5.13 to 7.33)	-
	OS rate		
12 months analysis	42.2%	24.1%	
18 months analysis	28.1 %	12.4%	
24 months analysis	23.0 %	8.0%	
36 months analysis	[redacted]	5.8 %	

CheckMate-003 Overall survival

(5-year data)

Enrolled all types of NSCLC, both squamous and non-squamous

Company suggest the new data in combination with the 36 month Checkmate 017 are supportive of the log-logistic curve for OS extrapolation

Proposed patient access scheme

- Simple discount confidential PAS (level of discount is commercial in confidence)
- Revised proposed PAS

Company cost-effectiveness results

- Assumptions used in the cost-effectiveness model:
  - Utility values:
    - progression-free health state: 0.693;
    - progressed-disease health state: 0.509
  - PFS extrapolation: exponential curve after 2.2 months
  - OS extrapolation: log-logistic or generalised gamma curve
  - Revised PAS applied
  - Wider NHS PAS benefit **not** included in base case but presented in scenario analysis

ICER results: Company new base case

Whole population, no PAS credit, vs docetaxel

Log-logistic OS curve

Table 4 of company submission	Continued treatment effect over lifetime for patient after 2 years stopping rule applied	Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £35,248 Inc. QALYs: 0.58 **ICER: £60,165**	Inc. Costs: £35,042 Inc. QALYs: 0.57 **ICER: 61,470**	Inc. Costs: £34,086 Inc. QALYs: 0.54 **ICER: 64,038**	Inc. Costs: £32,714 Inc. QALYs: 0.51 **ICER: £64,635**
25% continue treatment after 2 years	Inc. Costs: £30,295 Inc. QALYs: 0.58 **ICER: £51,896**	Inc. Costs: £30,102 Inc. QALYs: 0.57 **ICER: £53,361**	Inc. Costs: £29,387 Inc. QALYs: 0.54 **ICER: £54,475**	Inc. Costs: £28,591 Inc. QALYs: 0.51 **ICER: £56,312**
9% continue treatment after 2 years	Inc. Costs: £29,173 Inc. QALYs: 0.58 **ICER: £50,009**	Inc. Costs: £28,982 Inc. QALYs: 0.57 **ICER: £50,937**	Inc. Costs: £28,322 Inc. QALYs: 0.54 **ICER: £52,841**	Inc. Costs: £27,657 Inc. QALYs: 0.51 **ICER: £54,123**
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £28,645 Inc. QALYs: 0.58 **ICER: £49,171**	Inc. Costs: £28,456 Inc. QALYs: 0.57 **ICER: £50,112**	Inc. Costs: £27,821 Inc. QALYs: 0.54 **ICER: £51,633**	Inc. Costs: £27,217 Inc. QALYs: 0.51 **ICER: £54,178**

ICER results: DSU's suggested method

Whole population, no credit, nivolumab vs docetaxel

Generalised gamma OS curve

Table 5 of company submission	**Continued treatment effect over lifetime for patient after 2 years stopping rule applied**	**Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect**
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £32,383 Inc. QALYs: 0.43 **ICER: £71,7630**	Inc. Costs: £32,303 Inc. QALYs: 0.43 **ICER : £73,737**	Inc. Costs: £31,719 Inc. QALYs: 0.42 **ICER : £74,026**	Inc. Costs: £30,643 Inc. QALYs: 0.40 **ICER £74,400**
25% continue treatment after 2 years	Inc. Costs: £27,431 Inc. QALYs: 0.43 **ICER : £61,613**	Inc. Costs: £27,363 Inc. QALYs: 0.43 **ICER £62,023**	Inc. Costs: £27,020 Inc. QALYs: 0.42 **ICER : £62,995**	Inc. Costs: £26,520 Inc. QALYs: 0.40 **ICER : £65,023**
9% continue treatment after 2 years	Inc. Costs: £26,308 Inc. QALYs: 0.43 **ICER: £59,632**	Inc. Costs: £26,244 Inc. QALYs: 0.43 **ICER: £58,947**	Inc. Costs: £25,955 Inc. QALYs: 0.42 **ICER: £60,702**	Inc. Costs: £25,586 Inc. QALYs: 0.40 **ICER: £62,195**
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £25,780 Inc. QALYs: 0.43 **ICER : £58,043**	Inc. Costs: £25,717 Inc. QALYs: 0.43 **ICER :£58,043**	Inc. Costs: £25,454 Inc. QALYs: 0.42 **ICER : £59,426**	Inc. Costs: £25,146 Inc. QALYs: 0.40 **ICER : £60,882**

ICER results: Committee's assumptions

Exponential OS curve, whole population, no credit, vs docetaxel

Table 6 of company submission	**Continued treatment effect over lifetime for patient after 2 years stopping rule applied**	**Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect**
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £31,378 Inc. QALYs: 0.38 **ICER: £81,940**	Inc. Costs: £31,358 Inc. QALYs: 0.38 **ICER: £82,013**	Inc. Costs: £30,988 Inc. QALYs: 0.38 **ICER: £81,725**	Inc. Costs: £30,075 Inc. QALYs: 0.37 **ICER: £80,712**
25% continue treatment after 2 years	Inc. Costs: £26,425 Inc. QALYs: 0.38 **ICER: £69,344**	Inc. Costs: £26,419 Inc. QALYs: 0.38 **ICER: £68,934**	Inc. Costs: £26,289 Inc. QALYs: 0.38 **ICER: £69,337**	Inc. Costs: £25,952 Inc. QALYs: 0.37 **ICER: £69,791**
9% continue treatment after 2 years	Inc. Costs: £25,302 Inc. QALYs: 0.38 **ICER: £65,959**	Inc. Costs: £25,299 Inc. QALYs: 0.38 **ICER: £66,277**	Inc. Costs: £25,224 Inc. QALYs: 0.38 **ICER: £66,654**	Inc. Costs: £25,018 Inc. QALYs: 0.37 **ICER: £67,177**
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £24,774 Inc. QALYs: 0.38 **ICER: £64,947**	Inc. Costs: £24,772 Inc. QALYs: 0.38 **ICER: £64,533**	Inc. Costs: £24,723 Inc. QALYs: 0.38 **ICER: £65,375**	Inc. Costs: £24,578 Inc. QALYs: 0.37 **ICER: £66,060**

- The company did not apply the ERG's amendments to overall survival and progression-free survival modelling appropriately
- The ERG corrected for these errors and recalculated the results. ICERs were slightly different but all within £1500 of company's calculated estimates

ICER results: Company scenario

Whole population, including PAS credit, vs docetaxel

Generalised Gamma OS curve

Table 8 of company submission	**Continued treatment effect over lifetime for patient after 2 years stopping rule applied**	**Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect**
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £30,001 Inc. QALYs: 0.43 **ICER: £67,198**	Inc. Costs: £29,921 Inc. QALYs: 0.43 **ICER: £67,915**	Inc. Costs: £29,337 Inc. QALYs: 0.42 **ICER: £68,700**	Inc. Costs: £28,261 Inc. QALYs: 0.40 **ICER: £68,686**
25% continue treatment after 2 years	Inc. Costs: £25,049 Inc. QALYs: 0.43 **ICER: £56,510**	Inc. Costs: £24,981 Inc. QALYs: 0.43 **ICER: £56,672**	Inc. Costs: £24,638 Inc. QALYs: 0.42 **ICER: £57,502**	Inc. Costs: £24,138 Inc. QALYs: 0.40 **ICER: £58,654**
9% continue treatment after 2 years	Inc. Costs: £23,926 Inc. QALYs: 0.43 **ICER: £53,698**	Inc. Costs: £23,862 Inc. QALYs: 0.43 **ICER: £54,216**	Inc. Costs: £23,573 Inc. QALYs: 0.42 **ICER: £55,267**	Inc. Costs: £23,204 Inc. QALYs: 0.40 **ICER: £56,627**
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £23,398 Inc. QALYs: 0.43 **ICER: £52,284**	Inc. Costs: £23,335 Inc. QALYs: 0.43 **ICER: £52,752**	Inc. Costs: £23,072 Inc. QALYs: 0.42 **ICER: £53,841**	Inc. Costs: £22,764 Inc. QALYs: 0.40 **ICER: £55,002**

Extrapolation of progression-free survival

Whole population, including PAS credit, generalised gamma OS curve, vs docetaxel

PFS extrapolation curve	ICER results (£/QALY) (all results include wider PAS benefit)
Weibull	£50,399
Gamma	£51,026
Log-normal	£47,342
Average ICER	**£49,589**

Key issues for consideration

- What is the most plausible method for overall survival extrapolation?
- Should treatment duration be limited? Is it plausible to assume that patients continue to benefit from nivolumab after stopping treatment at 2 years? If so for how long?
- Should the committee's consideration on progression-free survival be reconsidered based on additional evidence from company?
- What is the most plausible ICER with revised proposed PAS for nivolumab?
- Does the committee consider nivolumab to be an innovative therapy?
- Is the committee satisfied that all the end-of-life criteria have been met?