NICE National Institute for Health and Care Excellence

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

ID900

Fourth Appraisal Committee meeting

12 April 2017

For public

Appraisal history

Committee meeting	Action
1st Committee meeting (April 2016)	• ACD issued • Complex patient access scheme (PAS) • Nivolumab not recommended
2nd Committee meeting (June 2016)	• No documentation issued • Following the committee meeting, the company that markets nivolumab (Bristol-Myers Squibb), requested to make a further submission including a revised PAS • NICE has agreed that the appraisal can be referred 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 non-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 non-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 patient 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 careful consideration, the DSU choice of curve was the committee-preferred hybrid KM/exponential approach 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 choice of curve. The company provided an updated company submission/ACD2 response for the <u>whole non-squamous NSCLC population</u> comparing nivolumab with docetaxel as follows: • Accounting for the DSU choice of curve, long-term survival extrapolations, a ‘ company intermediary worst case’ curve and a ‘new company base-case’ curve • 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 non-squamous NSCLC ID900, 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 vs docetaxel?
- What is the most plausible ICER with revised proposed PAS for nivolumab vs nintedanib?
- 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)

- Non-squamous NSCLC causes distressing symptoms and has few treatment options – important unmet need
- Nivolumab is clinically-effective compared with docetaxel (CheckMate-057)
- Plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression. Data collection to demonstrate the clinical effectiveness of nivolumab in people with at least a 10% PD-L1 expression would be valuable
- Committee was uncertain of the application of a clinical stopping rule
- The ICER calculated with the committee' preferred modelling assumptions were above £80,000 per QALY gained for nivolumab compared with docetaxel and remained above £50,000 with the 2-year stopping rule.
- For the comparison with nintedanib plus docetaxel, the most plausible ICER for nivolumab was above £150,000 per QALY gained

Minded not to recommend non-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 mixed exponential curves to extrapolate beyond the available trial data from CheckMate-057. For the comparison with nintedanib plus docetaxel, use more mature LUME-Lung 1, with exponential curve to extrapolate (ERG assumption)
  - Company preferred using the log-normal curve
- **Modelling progression free survival**
  - Use 24 month progression-free survival data for modelling health state costs and QALYs and time to treatment discontinuation data for modelling treatment costs and AEs. Use exponential curve for extrapolation
  - Company preferred using time to treatment discontinuation data
- **Utility values**
  - Utility value of 0.713 for the progression-free health state and between 0.657 and 0.480 for the progressed-disease health state
  - Company used PF=0.739 and PD=0.657; ERG used PF=0.713 and PD=0.5685
- **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
  - Joint submission from National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, Royal College of Radiologists, British Thoracic Oncology Group
  - Royal College of Pathologists
  - Roy Castle Lung Cancer Foundation
- Web comments received from
  - Patients, family members 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 ACD1, 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)
  - The impact on laboratory resources will also need to be taken into consideration if the recommendation will be restricted to PD-L1 ≥10%
- 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 an 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)
- New evidence updated overall survival (OS) year supporting data for OS curve
- Revised PAS
- 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*"

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 non-squamous indication, the available evidence (2 years data from CheckMate-057 and 4 year data from CheckMate-003), not supportive of the use of a decreasing hazards function, therefore the ERG and committee-preferred exponential function should be used 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

- Log-normal curve (company stated log-logistic) applied for overall survival extrapolation, because it provides a better statistical fit to the model.
- 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 (TA428)
- Wider benefits of the simple PAS for the NHS included in scenario analysis as a PAS credit and excluded from the company base-case on NICE request
- Additional 3 year overall survival data from CheckMate-057
- PFS modelling should be reconsidered based on 3-year data

New evidence

- Additional 3 year overall survival data from CheckMate-057
- Additional 5 year data from CheckMate-003

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

CheckMate-057: Overall survival

36 month analyses

Additional 3 year overall survival data from CheckMate 057, which shows a [redacted] and therefore suggests that the log-logistic extrapolation curve is plausible.

Overall survival results CheckMate-057

	Median OS		Hazard ratio
	Nivolumab	Docetaxel	
12 months analysis	12.2 months (CI 9.7 to 15.0)	9.4 months (CI 8.1 to 10.7)	0.73 (CI 0.59 to 0.89), p = 0.002
18 months analysis	-	-	0.72 (CI 0.60 to 0.88), p=0.001
24 months analysis	12.9 (CI 9.7 to 15.1)	9.5 (CI 8.1 to 10.7)	0.75 (CI 0.63 to 0.92)
36 months analysis	12.21 (CI 9.66 to 15.08)	9.49 (CI 8.11 to 10.74)	-
	OS rate		
12 months analysis	51% (CI 45 to 56)	39% (CI 33 to 45)	
18 months analysis	39% (CI 34 to 45)	23% (CI 19 to 28)	
24 months analysis	28.7%	16.1%	
36 months analysis	[redacted]	9.4%	

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

Cost-effectiveness results

- Assumptions used in the cost-effectiveness model:
  - Utility values:
    - progression-free health state: 0.713;
    - progressed-disease health state: 0.5685
  - PFS extrapolation: exponential curve
  - 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-normal OS curve

Table 4 of company new submission Log-normal OS curve applied All ICER results are probabilistic	**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: £26,012 Inc. QALYs: 0.46 **ICER: £57,204**	Inc. Costs: £25,842 Inc. QALYs: 0.45 **ICER: £58,026**	Inc. Costs: £25,262 Inc. QALYs: 0.41 **ICER: £61,371**	Inc. Costs: £24,686 Inc. QALYs: 0.38 **ICER: £65,021**
25% continue treatment after 2 years	Inc. Costs: £24,957 Inc. QALYs: 0.46 **ICER: £54,731**	Inc. Costs: £24,786 Inc. QALYs: 0.45 **ICER: £55,443**	Inc. Costs: £24,207 Inc. QALYs: 0.41 **ICER: £58,693**	Inc. Costs: £23,643 Inc. QALYs: 0.38 **ICER: £62,535**
9% continue treatment after 2 years	Inc. Costs: £24,731 Inc. QALYs: 0.46 **ICER: £54,195**	Inc. Costs: £24,561 Inc. QALYs: 0.45 **ICER: £55,439**	Inc. Costs: £23,982 Inc. QALYs: 0.41 **ICER: £58,229**	Inc. Costs: £23,421 Inc. QALYs: 0.38 **ICER: £62,252**
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £24,605 Inc. QALYs: 0.46 **ICER: £53,793**	Inc. Costs: £24,435 Inc. QALYs: 0.45 **ICER: £54,929**	Inc. Costs: £23,855 Inc. QALYs: 0.41 **ICER: £58,107**	Inc. Costs: £23,296 Inc. QALYs: 0.38 **ICER: £61,457**

ICER results: Company alternative

Whole population, no credit, nivolumab vs docetaxel

Generalised gamma OS curve

Table 5 of BMS new submission Generalised-gamma intermediary OS curve applied All ICER results are probabilistic	**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: £25,464 Inc. QALYs: 0.42 **ICER: : £60,145**	Inc. Costs: £25,314 Inc. QALYs: 0.41 ICER: £61,998	Inc. Costs: £24,802 Inc. QALYs: 0.38 **ICER: £66,097**	Inc. Costs: £24,267 Inc. QALYs: 0.35 **ICER: £71,438**
25% continue treatment after 2 years	Inc. Costs: £24,408 Inc. QALYs: 0.42 **ICER: £58,206**	Inc. Costs: £24,259 Inc. QALYs: 0.41 **ICER: £60,141**	Inc. Costs: £23,747 Inc. QALYs: 0.38 **ICER: £63,596**	Inc. Costs: £23,224 Inc. QALYs: 0.35 **ICER: £67,939**
9% continue treatment after 2 years	Inc. Costs: £24,183 Inc. QALYs: 0.42 **ICER: £58,244**	Inc. Costs: £24,034 Inc. QALYs: 0.41 **ICER: £58,813**	Inc. Costs: £23,522 Inc. QALYs: 0.38 **ICER: £62,818**	Inc. Costs: £23,002 Inc. QALYs: 0.35 **ICER: £67,962**
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £24,056 Inc. QALYs: 0.42 **ICER: £57,421**	Inc. Costs: £23,907 Inc. QALYs: 0.41 **ICER: £58,219**	Inc. Costs: £23,395 Inc. QALYs: 0.38 **ICER: £61,455**	Inc. Costs: £22,877 Inc. QALYs: 0.35 **ICER: £67,210**

ICER results: Committee's assumptions / DSU recommendation

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

Table 6 of Company new	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: £23,187 Inc. QALYs: 0.29 **ICER: £79,813**	Inc. Costs: £23,187 Inc. QALYs: 0.29 **ICER: £79,823**	Inc. Costs: £23,162 Inc. QALYs: 0.29 **ICER: £80,120**	Inc. Costs: £23,070 Inc. QALYs: 0.28 **ICER: £81,018**
25% continue treatment after 2 years	Inc. Costs: £22,132 Inc. QALYs: 0.29 **ICER: £76,180**	Inc. Costs: £22,131 Inc. QALYs: 0.29 **ICER: £76,189**	Inc. Costs: £22,107 Inc. QALYs: 0.29 **ICER: £76,471**	Inc. Costs: £22,027 Inc. QALYs: 0.28 **ICER: £77,357**
9% continue treatment after 2 years	Inc. Costs: £21,907 Inc. QALYs: 0.29 **ICER: £75,405**	Inc. Costs: £21,906 Inc. QALYs: 0.29 **ICER: £75,413**	Inc. Costs: £21,882 Inc. QALYs: 0.29 **ICER: £75,693**	Inc. Costs: £21,805 Inc. QALYs: 0.28 **ICER: £76,577**
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £21,780 Inc. QALYs: 0.29 **ICER: £74,969**	Inc. Costs: £21,779 Inc. QALYs: 0.29 **ICER: £74,977**	Inc. Costs: £21,755 Inc. QALYs: 0.29 **ICER: £75,255**	Inc. Costs: £21,680 Inc. QALYs: 0.28 **ICER: £76,137**

Company did not apply the ERG method of projecting PFS and OS properly - The ERG was not able to update the model and recalculate the ICERs and it is difficult to estimate how much the ICERs would change if the calculations were corrected

ICER results: Company scenario

Whole population, including PAS credit, vs docetaxel

Exponential OS curve

Table 9 of company new 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: £20,805 Inc. QALYs: 0.29 **ICER: £71,473**	Inc. Costs: £20,805 Inc. QALYs: 0.29 **ICER: £71,891**	Inc. Costs: £20,780 Inc. QALYs: 0.29 **ICER: £72,255**	Inc. Costs: £20,688 Inc. QALYs: 0.28 **ICER: £72,758**
25% continue treatment after 2 years	Inc. Costs: £19,750 Inc. QALYs: 0.29 **ICER: £68,271**	Inc. Costs: £19,749 Inc. QALYs: 0.29 **ICER: £67,921**	Inc. Costs: £19,725 Inc. QALYs: 0.29 **ICER: £68,097**	Inc. Costs: £19,645 Inc. QALYs: 0.28 **ICER: £68,954**
9% continue treatment after 2 years	Inc. Costs: £19,525 Inc. QALYs: 0.29 **ICER: £67,355**	Inc. Costs: £19,524 Inc. QALYs: 0.29 **ICER: £67,133**	Inc. Costs: £19,500 Inc. QALYs: 0.29 **ICER: £67,503**	Inc. Costs: £19,423 Inc. QALYs: 0.28 **ICER: £68,263**
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £19,398 Inc. QALYs: 0.29 **ICER: £66,758**	Inc. Costs: £19,397 Inc. QALYs: 0.29 **ICER: £66,770**	Inc. Costs: £19,373 Inc. QALYs: 0.29 **ICER: £67,567**	Inc. Costs: £19,298 Inc. QALYs: 0.28 **ICER: £67,772**

Extrapolation of progression-free survival

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

PFS extrapolation curve	ICER results (all results include PAS credit)
Weibull	£48,643
Gamma	£50,235
Average ICER	**£49,439**

Nintedanib

Summary

- Nintedanib plus docetaxel is included as a comparator in the appraisal scope
- Nintedanib plus docetaxel was highlighted by clinical experts as a treatment option for NSCLC for people with adenocarcinoma
- Nintedanib has a simple discount patient access scheme
- Committee's most plausible ACD2 ICER >£150,000 per QALY gained
- Further discussion in part 2 due to confidentiality

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 vs docetaxel?
- What is the most plausible ICER with revised proposed PAS for nivolumab vs nintedanib?
- Does the committee consider nivolumab to be an innovative therapy?
- Is the committee satisfied that all the end-of-life criteria have been met?