NICE National Institute for Health and Care Excellence

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

Second Appraisal Committee Meeting

10 February 2016

For public observers

Nivolumab

- Nivolumab is an inhibitor of *PD-1*, part of the immune checkpoint pathway
- Marketing authorisation for treating locally advanced or metastatic squamous NSCLC after prior chemotherapy – granted July 2015
  - 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
- CheckMate-017: nivolumab was associated with significant improvements in overall survival, progression-free survival and overall response rates vs docetaxel
- Economic model:
  - Company base-case ICER: £85,950 per QALY gained
  - ERG exploratory ICERs up to £132,989 per QALY gained
  - Committee had concerns regarding the extrapolation of survival, utility values and treatment costs

ICER, incremental cost-effectiveness ratio; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; NSCLC, non-small-cell lung cancer; QALY, quality-adjusted life year

Committee considerations and preliminary recommendations in the ACD

- 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 in the trial, and dramatic benefits seen in clinical practice
- Economic model:
  - ERG's approach to OS and PFS was more appropriate
  - Utility scores uncertain – limitations in company and ERG analyses
  - ERG's approaches to treatment costs were mostly appropriate
- Innovative treatment, and end-of-life criteria were met
- Most plausible ICER was £109,000–£129,000 per QALY gained

*Nivolumab was **not recommended***

ACD, appraisal consultation document; ICER, incremental cost-effectiveness ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

Committee's considerations in the ACD: Most plausible ICER

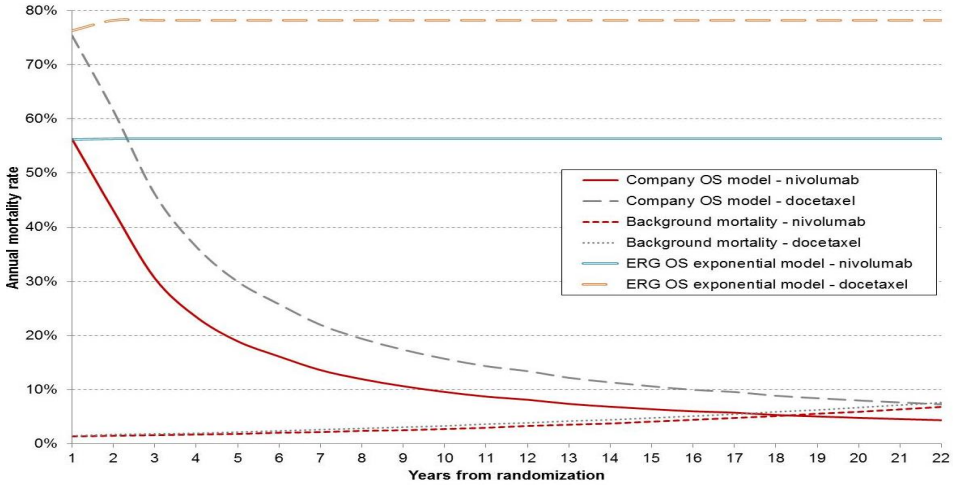
	ICER	Change vs original base case
Company's original base case	£85,950	–
ERG's revised analysis	£132,989	£47,039
Committee's preferred analysis	£109,000 – £129,000	£23,050 – £43,050
4.7 – ERG's PFS estimates	£68,912	*-£17,038*
4.8 – ERG's OS estimates	£131,979	£46,029
4.9 – Limitations in both company and ERG utilities	Base case to £105,915	£0 – £19,964
4.10 – Limitations in utility decrements	Not reported	Not reported*
4.11 – Duration based on time to discontinuation	£65,542	*-£20,409*
4.12 – Docetaxel not limited to 4 cycles	Per base case	£0
4.13 – Drug costs: • **Revised costs of 2nd line** • **Revised costs of 3rd line** • **Common admin cost** • **Drugs given at start of cycle**	 £91,867 £86,192 £82,970 £86,654	 £5,917 £241 *-£2,981* £704

*Committee considered that the adverse event disutilities were unlikely to have an important impact on the model results; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival

Committee's considerations in the ACD: Overall Survival

(1) Overall survival

- Company's modelling was not plausible, patients' risk of dying decreased as they got older



(2) Post-progression survival

- Most of the overall survival gain was accrued after progression

(months)	Nivolumab	Docetaxel	Survival gain
Progression-free survival	10.7	4.3	+6.5
Post-progression survival	16.4	7.2	+9.2
Overall survival	27.2	11.5	+15.7

Committee's considerations in the ACD: Utility values

	Progression-free	Progressed-disease
Company's original base case	0.750	0.592
ERG's alternative utilities (Nafees et al)	0.65	0.43

- Considerations
- Quality of life evidence was collected in Checkmate-017, including EQ-5D
  - However, noted limitations in this evidence – selection bias, higher than previous NSCLC appraisals
  - ERG's values had better face validity, but also had limitations – standard gamble (not EQ-5D)
  - Most appropriate values between the company's and ERG's

Key issues for discussion

- Comments on ACD from company, patients, professional groups and public
- Assumptions and approaches in the economic analyses – company and ERG comments
  - Overall survival
  - Post-progression survival
  - Progression-free survival and time to discontinuation
  - Utility values
- Optimum duration of treatment and appropriateness of potential stopping rules
- Most plausible ICER
- Any equality, innovation, PPRS considerations?

Consultation comments

- Comments received from:
  - ***Company:*** Bristol-Myers Squibb
  - ***Professional groups:*** British Thoracic Society, endorsed by Royal College of Physicians
  - ***Patient group:*** Roy Castle Lung Cancer Foundation
  - ***Public***

Comments on the ACD: Patients, professional groups and public

- Emphasised that nivolumab would be a valuable treatment option for people with squamous NSCLC
  - Innovative and novel
  - Clinically effective
  - Important unmet need – few other options available and short life expectancy
- Noted potential cost savings through reducing hospital admissions associated with chemotherapy
- Rapid uptake of nivolumab and immunotherapies in the USA and other countries
- Urged NICE and company to address cost issues

Comments on the ACD: Company

- Emphasised innovative nature of nivolumab, unmet need and survival benefit
- Commented on the considerations on the economic model
  - Requested the Committee reconsider the OS extrapolation
  - Proposed alternative utility values
- Highlighted uncertainty in optimal duration of treatment
- Company was granted permission by NICE to submit new evidence and analyses at ACD stage
- Presented additional analyses:
  - Revised base case, based on company's preferred assumptions
  - Scenario analyses based on alternative utilities and maximum treatment durations

OS, overall survival; PFS, progression-free survival

Company comments on the ACD and new evidence:

Overall survival (1)

- Original submission was based on extrapolation of OS from 12-month follow-up data from CheckMate-017
- Extrapolation re-done with latest data – 18-month follow-up
  - Log-logistic model provides best fit
  - Validated against 4-year OS data from CheckMate-003 (dose escalation study, n=129 with NSCLC)
- Committee noted that the original model predicted that mortality would decrease below level of general population
  - Addressed by 'capping' the mortality rate so that it doesn't drop below general population
  - Clinical experts stated that nivolumab has the potential for long-term survival benefit – some patients may return to baseline mortality rate

NSCLC, non-small-cell lung cancer; OS, overall survival

Company comments on the ACD and new evidence:

Overall survival (2)

- New OS extrapolation (log-logistic based on 18-month data, mortality cap) is more conservative than original company model
  - Nivolumab: 25.4 months in new analysis vs 27.2 months in original

Company comments on the ACD and new evidence:

Progression-free survival

- PFS extrapolation should be based on ERG's approach but using 18-month (not 12 month) data
  - More accurately captures people who experience a durable response to nivolumab
  - Supports a greater OS gain
  - Reduces dependence of the model on post-progression survival gain and a higher est of PFS survival with nivolumab

OS, overall survival; PFS, progression-free survival

Company comments on the ACD and new evidence:

Post-progression survival

- Criticism of the clinical validity of the PPS gain with nivolumab was based on a flawed analysis
- ERG presented a comparison of PPS with nivolumab vs docetaxel and stated there was no difference. But this was affected by:
  - Selection bias – patients selected for PPS analysis were a non-representative subset of the trial population
  - Limited duration of follow-up and limited patient numbers for PPS analysis
- With longer follow-up, it is expected that PPS gain with nivolumab will be seen
  - Supported by biological rationale

Modelling treatment duration

- ERG was concerned about modelling of treatment duration based on PFS rather than time to discontinuation (TTD)
  - However, PFS and TTD are almost identical – PFS is a suitable proxy for treatment duration
  - ERG's analysis based on TTD only appeared to significantly affect the ICER because of different extrapolations for TTD and PFS

PFS, progression-free survival; TTD, time to discontinuation

Company comments on the ACD and new evidence:

Optimum duration of therapy

- Optimum duration of nivolumab therapy is uncertain
  - May be appropriate to stop nivolumab before progression and maintain benefit – based on mechanism of action
- Evidence:
  - CheckMate-003 – 7 of 22 responders stopped treatment after 96 weeks, all continued to respond
  - CheckMate-153 – will examine effectiveness of stopping treatment at 1 year (**********)
- In practice, treatment is unlikely to exceed 1–2 years
  - 2 scenario analyses presented to reflect possible maximum treatment durations ("stopping rule")
- In the recent appraisal of nivolumab for melanoma, FAD recommends review of the guidance after 2 years in light of uncertainty in treatment duration

Company comments on the ACD and new evidence:

Utility values

- ERG noted that EQ-5D data from CheckMate-017 was limited – low completion rate and selection bias
  - ERG calculations were inappropriate – completion rates are higher than reported
  - Potential for selection bias is lower than stated by ERG
- Exploratory analyses to develop alternative utility values
  - "Average of averages": sum of each patients' mean EQ-5D score during each health state, divided by the number of patients
  - Reduces influence of later time-points when more drop-outs had occurred

	Progression-free	Progressed-disease
Company's original base case	0.750	0.592
ERG's alternative utilities (Nafees et al)	0.65	0.43
Company alternative: average of averages	*****	*****

Company's new economic analyses

- Company was granted permission by NICE to submit new evidence and analyses at ACD stage
- Revised base case:
  - New OS extrapolation: log-logistic based on 18-month data, mortality cap
  - PFS based on ERG's approach but using 18-month data
  - Treatment duration based on PFS
  - Other costs amended to be consistent with Committee's preferred assumptions
- Scenario analyses:
  - Alternative utility values – average of averages
  - 1- and 2-year stopping rules – as in the original company, these analyses were presented and revised

OS, overall survival; PFS, progression-free survival

Company's new economic analyses:

Results

	Total cost	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALYs	ICER (£/QALY gained)
Revised base case							
Nivolumab	£77,132	2.12	1.22	£62,014	1.16	0.68	£91,870
Docetaxel	£15,118	0.96	0.54				
Scenario 1: utilities based on average of averages							
Nivolumab	£77,132	2.12	1.17	£62,014	1.16	0.65	£94,933
Docetaxel	£15,118	0.96	0.52				
Scenario 2: stopping rule – maximum treatment duration 1 year							
Nivolumab	£56,669	2.12	1.12	£41,551	1.16	0.68	£61,555
Docetaxel	£15,118	0.96	0.54				
Scenario 3: stopping rule – maximum treatment duration 2 years							
Nivolumab	£69,326	2.12	1.22	£54,208	1.16	0.68	£80,306
Docetaxel	£15,118	0.96	0.54				

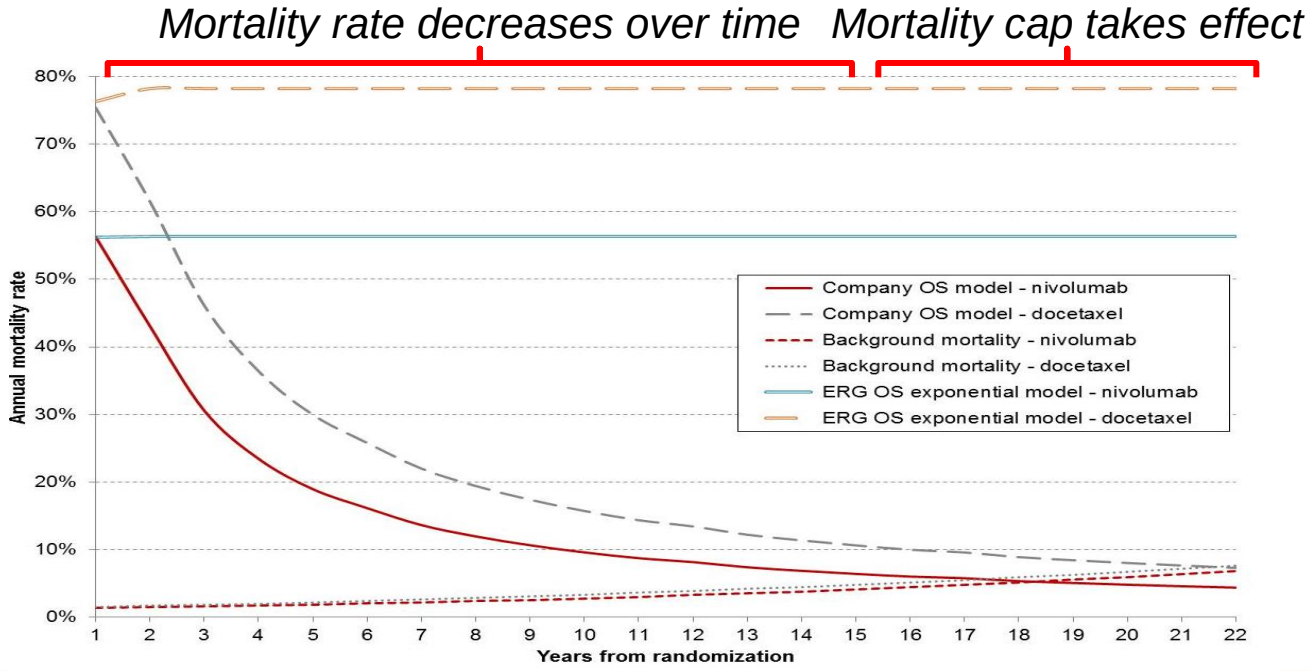
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life-year gained; QALY, quality-adjusted life year

ERG review of company ACD comments and new evidence

- ERG reviewed the company's ACD comments and new evidence:
  - Overall survival
  - Post-progression survival
  - Progression-free survival and treatment duration
  - Utility values
- Clarified confusion regarding 12-month and 18-month data
- Presented an alternative exploratory analysis

Overall survival (1)

- Company's mortality cap does not address underlying issue with log-logistic extrapolation
  - Mortality rates still decrease throughout patients' lives



ERG review of company ACD comments and new evidence:

Overall survival (2)

- ERG considered the correspondence of its OS extrapolation with trial data
- Company presents comparison with CheckMate-003
  - This trial included several cancer types; 54 patients had squamous NSCLC, but company's comparison based on whole-trial data
  - After 3 years, only 12 patients remain (6 squamous NSCLC, 6 non-squamous NSCLC) – uncertainty
  - ERG's OS extrapolation falls within 95% confidence intervals for CheckMate-003 at 12, 24 and 36 months
- ERG presents a comparison with natural history of NSCLC, based on SEER database
  - Close match
  - ERG's exponential function is consistent with real-world data

NSCLC, non-small-cell lung cancer; OS, overall survival; SEER, 'Surveillance, Epidemiology, and End Results'

ERG review of company ACD comments and new evidence:

Progression-free survival and treatment duration

- Company Confirmed the ERG's view of the appropriate use of progression-free survival and time to discontinuation data
  - PFS should be used to determine movement between the progression-free and progressed-disease states
    - Health state costs and utilities
  - TTD data should be used for treatment costs
    - Acquisition, administration and monitoring costs
- TTD captures early discontinuation (e.g. due to adverse events) and treatment beyond progression

ERG review of company ACD comments and new evidence:

Post-progression survival

- ERG responded to company's comments on PPS analysis
- ***Selection bias:***
  - There will always be patients who progress at different times due to efficacy differences
  - Analysis aims to assess prognosis *at the time of progression* in each treatment arm
- ***Inadequate follow-up:***
  - Additional data would be ideal, but no sound reason to dismiss findings
- ***CheckMate-003:***
  - Does not provide comparative data to address relative outcomes after progression

ERG review of company ACD comments and new evidence:

Utility values

- Company's alternative utilities:
  - Effectively 'weights' individuals inversely by how many times they completed EQ-5D – reduces utility estimates
  - Novel, unconventional approach lacks obvious mathematical merit
- ERG presents new utility values:
  - Progression-free state: data from CheckMate-017, in period when mean utility is less than UK average (up to week 10; 50% of data)
  - Progressed-disease state: based on Dutch trial* (supportive care for NSCLC), adjusted for decline in utility near the end of life

	Progression-free	Progressed-disease
Company's original base case	0.750	0.592
ERG's alternative utilities (Nafees et al)	0.65	0.43
Company alternative: average of averages	*****	*****
ERG's new utilities (Dutch trial)	0.693	0.460

*van den Hout et al. (2006) *JNCI* 98:1786–94; NSCLC, non-small-cell lung cancer

ERG's alternative exploratory analysis

Model scenario		Total cost	Total QALYs	Incr cost	Incr QALY	ICER (£/QALY gained)	*Change vs 'A'*
A. Company original base case	Nivo	£86,599	1.299	£65,355	0.76	**£85,950**	-
	Doce	£21,243	0.539				
R1) ERG PFS ests	Nivo	£71,219	1.265	£49,967	0.726	**£68,819**	*-£17,131*
	Doce	£21,252	0.539				
R2) ERG OS ests	Nivo	£79,958	0.897	£60,339	0.456	**£132,353**	*£46,402*
	Doce	£19,619	0.441				
R3) Revised costs of 2nd line drugs	Nivo	£85,597	1.299	£69,854	0.76	**£91,867**	*£5,916*
	Doce	£15,742	0.539				
R4) Revised costs of 3rd line drugs	Nivo	£86,089	1.299	£65,539	0.76	**£86,192**	*£241*
	Doce	£20,550	0.539				
R5) Common administration cost	Nivo	£84,332	1.299	£63,089	0.76	**£82,970**	*-£2,981*
	Doce	£21,243	0.539				
R7) Drugs given at the start of cycles	Nivo	£87,311	1.299	£65,891	0.76	**£86,654**	*£704*
	Doce	£21,420	0.539				
R8) Duration based on time to discontinuation	Nivo	£79,153	1.299	£59,968	0.76	**£78,865**	*-£7,086*
	Doce	£19,185	0.539				
R9) New utility scores	Nivo	£86,599	1.101	£65,355	0.656	**£99,669**	*£13,719*
	Doce	£21,243	0.445				
ERG's alternative analysis	Nivo	£69,880	0.738	£56,880	0.369	**£154,352**	*£68,401*
	Doce	£13,000	0.369				

New analyses vs Committee considerations in the ACD: Company

	ICER	Change vs original base case	Company's new analysis
Company's original base case	**£85,950**	–	ICER: **£91,870**
ERG's revised analysis	**£132,989**	£47,039	*Change vs company original base case: £5,920*
Committee's preferred analysis	**£109,000 – £129,000**	£23,050 – 43,050	
4.7 – ERG's PFS estimates	£68,912	*-£17,038*	✓ Follows Committee's preferred assumption, but updated to 18-month data
4.8 – ERG's OS estimates	£131,979	£46,029	✘ Uses new extrapolation – log-logistic (18-month data), mortality cap
4.9 – Limitations in both company and ERG utilities	Base case to £105,915	£0 – £19,964	✘ Uses company's original utilities in new base case, alternative utilities in scenario
4.10 – Limitations in utility decrements	Not reported	Not reported*	– Not reported
4.11 – Duration based on time to discontinuation	£65,542	*-£20,409*	✘ Treatment duration based on PFS
4.12 – Docetaxel not limited to 4 cycles	Per base case	£0	✓ Follows Committee's preferred assumption
4.13 – Drug costs: **• Revised costs of 2nd line** **• Revised costs of 3rd line** **• Common admin cost** **• Drugs given at start of cycle**	£91,867 £86,192 £82,970 £86,654	£5,917 £241 *-£2,981* £704	✓ Follows Committee's preferred assumptions

*Committee considered that the adverse event disutilities were unlikely to have an important impact on the model results; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival

New analyses vs Committee considerations in the ACD: ERG

	ICER	Change vs original base case	ERG's new analysis
Company's original base case	**£85,950**	–	ICER: **£154,352** *Change vs company original base case: £68,401*
ERG's revised analysis	**£132,989**	£47,039	
Committee's preferred analysis	**£109,000 – £129,000**	£23,050 – 43,050	
4.7 – ERG's PFS estimates	£68,912	*-£17,038*	✓ Follows Committee's preferred assumption, with updated data
4.8 – ERG's OS estimates	£131,979	£46,029	✓ Follows Committee's preferred assumption, with updated data
4.9 – Limitations in both company and ERG utilities	Base case to £105,915	£0 – £19,964	– New utilities based on CheckMate-017 and Dutch trial
4.10 – Limitations in utility decrements	Not reported	Not reported*	– Not reported
4.11 – Duration based on time to discontinuation	£65,542	*-£20,409*	✓ Follows Committee's preferred assumption, with updated data
4.12 – Docetaxel not limited to 4 cycles	Per base case	£0	✓ Follows Committee's preferred assumption
4.13 – Drug costs: **• Revised costs of 2nd line** **• Revised costs of 3rd line** **• Common admin cost** **• Drugs given at start of cycle**	£91,867 £86,192 £82,970 £86,654	£5,917 £241 *-£2,981* £704	✓ Follows Committee's preferred assumptions

*Committee considered that the adverse event disutilities were unlikely to have an important impact on the model results; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival

Key issues for discussion

- Comments on ACD from company, patients, professional groups and public
- Assumptions and approaches in the economic analyses – company and ERG comments
  - Overall survival
  - Post-progression survival
  - Progression-free survival and time to discontinuation
  - Utility values
- Optimum duration of treatment and appropriateness of potential stopping rules
- Most plausible ICER
- Any equality, innovation, PPRS considerations?