NICE National Institute for Health and Care Excellence

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

Third Appraisal Committee meeting

10 August 2016

For Public

Appraisal history

Committee meeting	Action
1st Committee meeting (13 April 2016)	• ACD issued • Complex patient access scheme (PAS) • Nivolumab not recommended
2nd Committee meeting (15 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3rd Committee meeting (10 August 2016)	• Complex PAS withdrawn: a simple discount PAS proposed by the company to DH

Key issues for consideration

- Most plausible ICER with revised proposed PAS for nivolumab?
- Should treatment duration be limited? Is it plausible patients continue to benefit from nivolumab after stopping treatment at 2 years?
- Unmet need of patients with non-sqNSCLC?
- Any equality, innovation, PPRS considerations?
- Could this be an appropriate candidate for the CDF?
  - i.e. could 2 years of data collection resolve the uncertainty?

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 Department of Health. The size of the discount is commercial in confidence

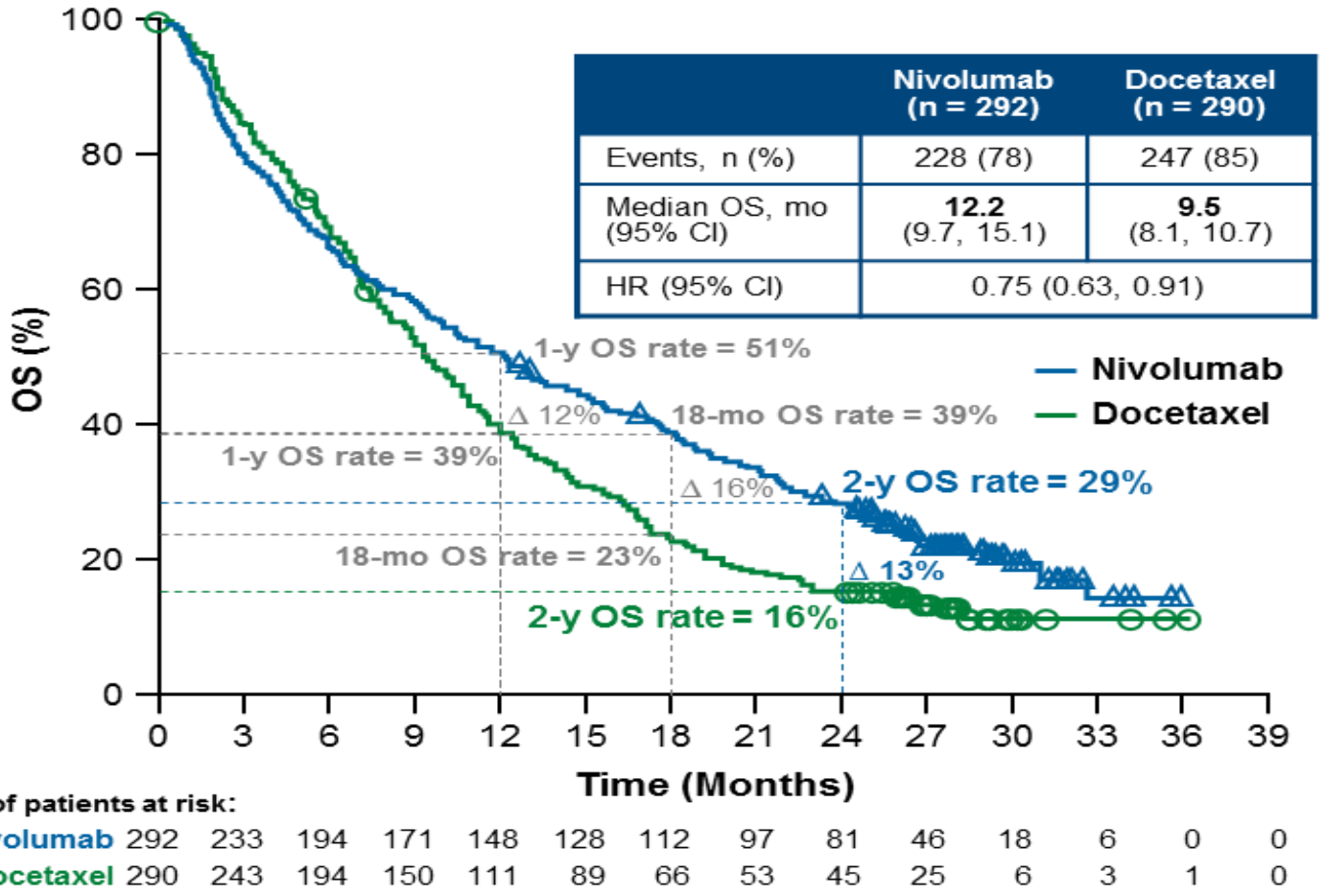
Committee considerations and preliminary recommendations in the ACD

- Non-squamous NSCLC causes distressing symptoms and has few treatment options – important unmet need
- Nivolumab is clinically-effective compared with docetaxel (CheckMate-057)
- The most plausible ICERs were much higher than could be considered a cost-effective use of NHS resources using the Committee's preferred assumptions for the comparisons with docetaxel and nintedanib plus docetaxel
- Nivolumab is not recommended for treating locally advanced or metastatic non squamous non small cell lung cancer in adults whose disease has progressed after chemotherapy

*Nivolumab was **not recommended***

ACD, appraisal consultation document; ICER, incremental cost-effectiveness ratio; NSCLC, non-small-cell lung cancer

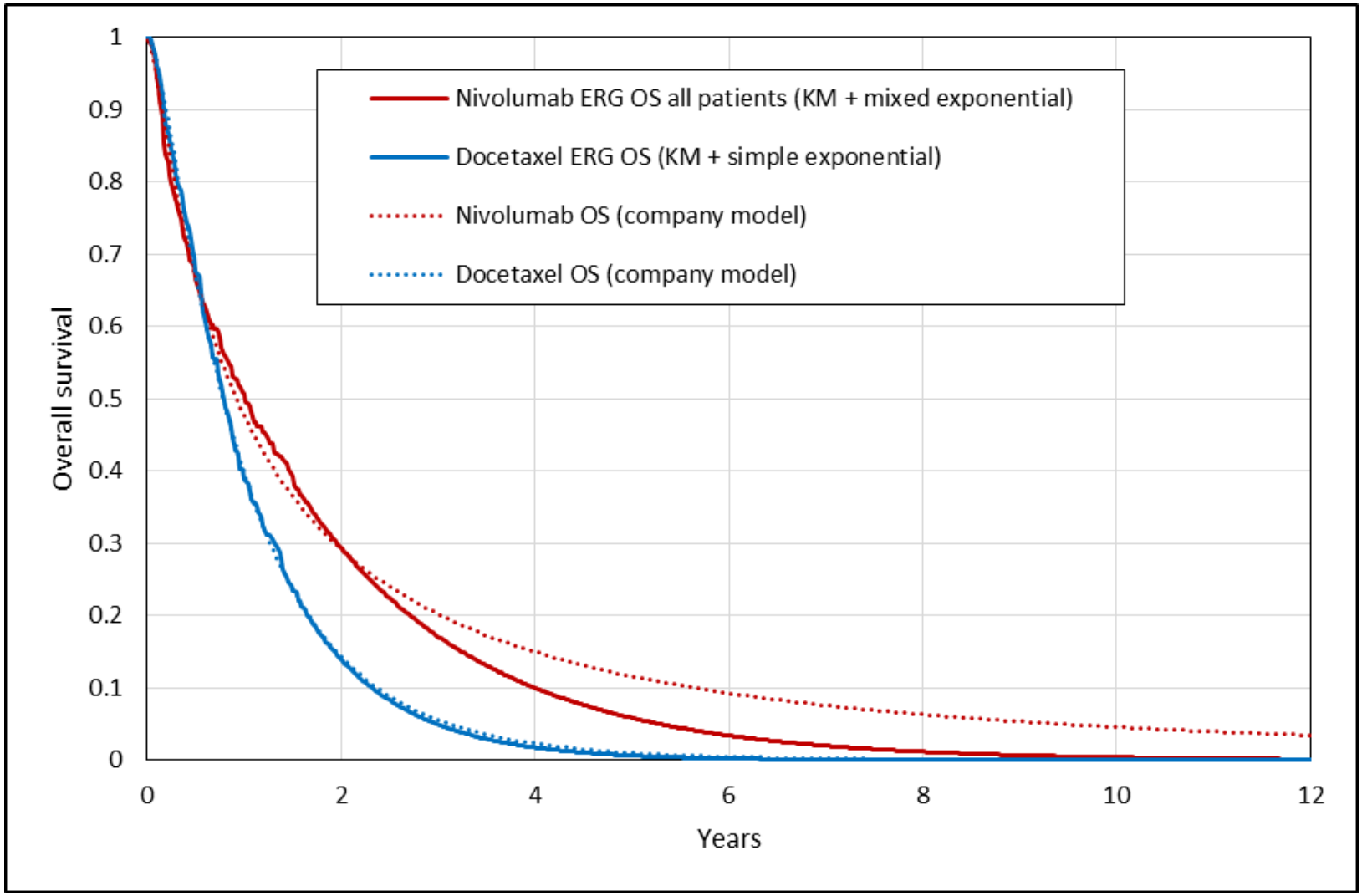
CheckMate-057: Overall survival (24 month analyses)



Committee's preferred assumptions agreed at ACM2

- **Modelling overall survival**
  - Use 24 month data and an exponential curve for extrapolation. For the comparison with nintedanib plus docetaxel, use more mature data of LUME-Lung 1, as introduced by the ERG
- **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
- **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
- **Dosing cost calculations**
  - ERG's amendments to calculating the cost per nivolumab dose and administration costs
- **End of life**
  - The committee concluded that nivolumab met the end-of-life criteria and that it can be considered a life-extending, end-of-life treatment

Overall survival projections for nivolumab vs. docetaxel



Source: ERG report figure 19

Introduction of revised proposed patient access scheme

- Simple discount confidential PAS (level of discount is commercial in confidence)
- will apply to all indications for nivolumab
  - Nivolumab as monotherapy for advanced unresectable or metastatic melanoma (TA384)
  - Nivolumab with ipilimumab for advanced unresectable or metastatic melanoma (TA400)
  - Nivolumab for advanced renal cell carcinoma after prior therapy (ID853)

Company's revised proposed PAS base case

- Company presented revised economic modelling using:
  - Pricing with the revised PAS
  - 2 base cases:
    - Company preferred assumptions
    - Committee preferred assumptions
  - 2 year stopping rule – **previously unseen**
  - Dose intensity adjustment – **previously unseen**

Company modelling revisions

2 year stopping rule

- Clinical opinion suggests that there should be a limit to the maximum treatment duration
- CheckMate-003 (phase 1 study): the majority (6/7) patients achieved a complete or partial response at 96 weeks (1.8 years)

Dose intensity adjustment

- Evidence shows patients rarely receive all planned doses
- Adjustments also applied in ongoing NICE TAs pembrolizumab (NSCLC) and nivolumab (renal cell carcinoma)
- Adjustments from CheckMate-057:
  - [redacted] nivolumab [redacted] docetaxel

Company's base case results

(including revised proposed PAS for nivolumab and list price for nintedanib)

Deterministic	With company assumptions			With committee assumptions		
	Inc. QALYs	Inc. Costs (£)	ICER (£)	Inc. QALYs	Inc. Costs (£)	ICER (£)
vs Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Committee assumptions met		
Overall survival	✘ Log normal	✓ KM data + exponential
PFS and TTD	✘ TDD to model all outcomes and costs	✓ TDD all related costs and AEs ✓ PFS modelled outcomes and costs
Cost calculations	✓ Correct costs	✓ Correct costs
Utilities	✘ PF= 0.739 ✘ PD = 0.657	✓ PF = 0.713 ✓/ ✘ PD between 0.480 - 0.657*
Stopping rule	New assumption applied	
Dose intensity reduction	New assumption applied	

Abbreviations: ICER, Incremental cost-effectiveness ratio; PAS, Patient Access Scheme; PF, progression free; PD, progressed disease; TTD, time-to-treatment discontinuation

* Exact value used is unknown

Company's base case results

(including revised proposed PAS for nivolumab and list price for nintedanib)

Probabilistic	With company assumptions			With committee assumptions		
	Inc. QALYs	Inc. Costs (£)	ICER (£)	Inc. QALYs	Inc. Costs (£)	ICER (£)
vs Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Committee assumptions met		
Overall survival	✗ Log normal	✓ KM data + exponential
PFS and TTD	✗ TDD to model all outcomes and costs	✓ TDD all related costs and AEs ✓ PFS modelled outcomes and costs
Cost calculations	✓ Correct costs	✓ Correct costs
Utilities	✗ PF= 0.739 ✗ PD = 0.657	✓ PF = 0.713 ✓/ ✗ PD between 0.480 - 0.657*
Stopping rule	New assumption applied	
Dose intensity reduction	New assumption applied	

Abbreviations: ICER, Incremental cost-effectiveness ratio; PAS, Patient Access Scheme; PF, progression free; PD, progressed disease; TTD, time-to-treatment discontinuation

* Exact value used is unknown

ERG's base case results

(including revised proposed PAS for nivolumab and list price for nintedanib)

Deterministic	Inc. QALYs	Inc. Costs	ICER
Vs Docetaxel	[redacted]	[redacted]	[redacted]
Vs Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]
Committee assumptions met			
Overall survival	✓ KM data + exponential		
PFS and TTD	✓ TDD all related costs and AEs ✓ PFS modelled outcomes and costs		
Cost calculations	✓ Correct costs		
Utilities	✓ PF= 0.713 ✓ PD between 0.480 - 0.657; mid point taken=0.5685		
Stopping rule	Not included		
Dose intensity reduction	Not included		

Abbreviations: ICER, Incremental cost-effectiveness ratio; PAS, Patient Access Scheme; PF, progression free; PD, progressed disease; TTD, time-to-treatment discontinuation

Company’s scenario analyses

- Presented for company's and committee preferred assumptions:
  - **Scenario 1**: Company assumptions (no stopping rule and full dosing)
  - **Scenario 2**: Committee assumptions (no stopping rule and full dosing)
  - **Scenario 3**: Utilities from ID811 nivolumab (squamous NSCLC) STA for both PFS and PD

Company's scenario 1: Company assumptions (no stopping rule and full dosing)

(including revised proposed PAS for nivolumab and list price for nintedanib)

Deterministic	Inc. QALYs	Inc. Costs	ICERs
vs Docetaxel	[redacted]	[redacted]	[redacted]
vs Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]
Committee assumptions met			
Overall survival	✗ Log normal		
PFS and TTD	✗ TTD to model all outcomes and costs		
Cost calculations	✓ Correct costs		
Utilities	✓ PF= 0.713 ✗ PD = 0.657 (upper limit of committee's preferred range)		
Stopping rule	Not included in this scenario		
Dose intensity reduction	Not included in this scenario		

Abbreviations: ICER, Incremental cost-effectiveness ratio; PAS, Patient Access Scheme; PF, progression free; PD, progressed disease; TTD, time-to-treatment discontinuation

Company's scenario 2: Committee assumptions (no stopping rule and full dosing)

(including revised proposed PAS for nivolumab and list price for nintedanib)

Deterministic	Inc. QALYs	Inc. Costs	ICERs
vs Docetaxel	[redacted]	[redacted]	[redacted]
vs Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]
Committee assumptions met			
Overall survival	✓ KM data + exponential		
PFS and TTD	✓ TDD all related costs and AEs ✓ PFS modelled outcomes and costs		
Cost calculations	✓ Correct costs		
Utilities	✓ PF= 0.713 ✓/✗ PD between 0.480 - 0.657, but not specified		
Stopping rule	Not included in this scenario		
Dose intensity reduction	Not included in this scenario		

Abbreviations: ICER, Incremental cost-effectiveness ratio; PAS, Patient Access Scheme; PF, progression free; PD, progressed disease; TTD, time-to-treatment discontinuation

Company's Scenario 3

(including revised proposed PAS for nivolumab and list price for nintedanib)

- Utilities from ID811 nivolumab (squamous NSCLC) STA for both PFS and PD

Utility values	Progression-free	Progressed-disease
Company original values	0.739	0.688
ERG values	0.713	0.476
Company new values	0.739	0.657
Committee preferred (ID900)	0.713	Between 0.480 and 0.657
Committee preferred (ID811)	0.693	0.50

Company's scenario 3: ID811 utilities

(including revised proposed PAS for nivolumab and list price for nintedanib)

Deterministic	Inc. QALYs	Inc. Costs	ICERs
vs Docetaxel	[redacted]	[redacted]	[redacted]
vs Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]
Committee assumptions met			
Overall survival	✓ KM data + exponential		
PFS and TTD	✓ TDD all related costs and AEs ✓ PFS modelled outcomes and costs		
Cost calculations	✓ Correct costs		
Utilities	✗ PF= 0.693 ✗ PD = 0.509		
Stopping rule	Not included in this scenario		
Dose intensity reduction	Not included in this scenario		

Abbreviations: ICER, Incremental cost-effectiveness ratio; PAS, Patient Access Scheme; PF, progression free; PD, progressed disease; TTD, time-to-treatment discontinuation

Summary of ICERs

(including revised proposed PAS for nivolumab and list price for nintedanib)

	vs Docetaxel	vs Nintedanib + docetaxel	Stopping rule
Company base case (dosing intensity)	[redacted]	[redacted]	stopping rule
Company base case using committee assumption (dosing intensity)	[redacted]	[redacted]	stopping rule
Sc1 (company assumptions plus full dose)	[redacted]	[redacted]	None
Sc2 (committee assumptions plus full dose)	[redacted]	[redacted]	None
Sc3 (committee assumptions plus new utilities and full dose)	[redacted]	[redacted]	None
ERG base case (full dose)	[redacted]	[redacted]	None

Brackets indicates list price for nintedanib

Key issues for consideration

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- Unmet need of patients with non-sqNSCLC
- Any equality, innovation, PPRS considerations?
- Could this be an appropriate candidate for the CDF?
  - i.e. could 2 years of data collection resolve the uncertainty?