Lead team presentation:

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

1st Appraisal Committee meeting

Background & Clinical Effectiveness

Iain Miller and Judith Wardle

13 April, 2016

Disease Background: Non-Squamous Non Small Cell Lung Cancer (NSCLC)

- In 2014, there were approximately 28,000 patients with a confirmed diagnosis of NSCLC in England
- Non-squamous disease is a sub-type of NSCLC comprising approximately 64% of total
  - Squamous sub-type under separate NICE review (ID811)
- Often diagnosed late in life: median age at diagnosis of lung cancer is 73 years
- Poor overall prognosis
  - The median survival for all lung cancer in England and Wales was 6 months in 2013
  - Lung cancer caused 28,000 deaths in England in 2012
- Common symptoms: cough, dyspnoea, weight loss, chest pain

Source: Cancer Research UK, National Lung Cancer Audit annual report 2015

Current Management of Non-Squamous NSCLC and Current NICE Guidance

Includes proposed position of nivolumab in pathway

Mutation status	First line	Second line	Third line
EGFR and ALK negative or unknown	• **Platinum-based chemotherapy** (CG121)	• **Docetaxel** (CG121) • **Erlotinib (EGFR unknown only;** TA374) • **Nintedanib + docetaxel (adenocarcinoma only;** TA347**)** **Nivolumab**	• **Erlotinib if not received previously (EGFR unknown only;** TA374**)** • **Docetaxel** • **BSC** **Nivolumab**
EGFR positive (10% of NSCLC patients)	• **Erlotinib** (TA258) • **Afatinib** (TA310) • **Gefitinib** (TA192)	• **Platinum-based chemotherapy** (CG121) • **Afatinib or erlotinib if no prior EGRF-TKI therapy** (TA310; TA374) • **Single agent gemcitabine and vinorelbine**	• **Docetaxel** • **BSC** • **Nintedanib + docetaxel (adenocarcinoma only;** TA347**)** **Nivolumab**
ALK positive (5% of NSCLC patients)	• **Platinum-based chemotherapy** (CG121)	• **Crizotinib (available via CDF;** TA296**)** **Nivolumab**	• **Ceritinib (currently being appraised by NICE;** ID729**)** **Nivolumab**

Nivolumab

- Marketing Authorisation – received in April, 2016
  - Indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults
- Mechanism of Action
  - Targets PD-1 receptor on the surface of lymphocytes, part of immune checkpoint pathway
- Dosage and Administration
  - 3 mg/kg every 2 weeks, by intravenous infusion over 60 minutes
- Cost
  - List price: £439.00 per 40-mg vial
  - Estimated total cost of course of treatment £31,960 (assumes 12.6 doses on average)

Impact on Patients and Carers (1)

- People with relapsed NSCLC have distressing symptoms, e.g. breathlessness
  - Symptoms can be difficult to manage
  - Options that reduce tumours have best effect on symptoms
- Chemotherapy is not well tolerated for many patients; even when it is, later treatment options limited
  - Important unmet need
- Patient group says outlook for these patients is poor
  - Improved QoL and even small extension of life is significant for patients & family
- Highlight the value of effective treatment options for people in the last 6 months of life

Impact on patients and carers (2)

- The patient group believes nivolumab offers important improvements
- Side effects of nivolumab appear to be well tolerated, especially in comparison with current 2nd line treatments

NICE Scope Decision Problem (1)

Population	People with previously treated locally advanced or metastatic non-squamous non-small cell lung cancer
Intervention	Nivolumab
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life

NICE Scope Decision Problem (2)

Comparators	**Non-squamous EGFR-TK mutation negative or unknown tumours:** *After one prior therapy*: - Docetaxel monotherapy - Erlotinib - Nintedanib in combination with docetaxel - Crizotinib (only for patients with ALK positive mutation status) - Ceritinib (only for patients with ALK positive mutation status; subject to ongoing NICE appraisal) - Best supportive care *After two prior therapies:* - Docetaxel monotherapy - Erlotinib (if not received previously; subject to ongoing NICE appraisal) - Best supportive care

Company decision problem:

Base case economic analysis is limited to nivolumab compared with:

- *Docetaxel monotherapy*
- *Nintedanib in combination with docetaxel*

NICE Scope Decision Problem (3)

Comparators	**Non-squamous EGFR-TK mutation positive tumours:** *After one prior therapy:* - Platinum therapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane) - Single agent gemcitabine and vinorelbine (for people for whom platinum therapy is not appropriate) - Afatinib, erlotinib or gefitinib (if no previous EGFR-TKI therapy received due to delayed confirmation of mutation status; erlotinib and gefitinib subject to ongoing NICE appraisal) *After two prior therapies* (an EGFR-TKI and one other therapy): - Docetaxel monotherapy - Erlotinib - Nintedanib in combination

Company decision problem:

Base case economic analysis is limited to nivolumab compared with:

- *Docetaxel monotherapy*
- *Nintedanib in combination with docetaxel*

Preview: Key issues for consideration

- Evidence not provided for EGFR positives/ALK positives. Should the committee's decision focus on the EGFR/ALK negative subgroups only?
- Do the comparators included in the submission (docetaxel, nintedanib plus docetaxel, best supportive care) reflect established clinical practice in the NHS?
- Are the results of CheckMate 057 generalisable to people with non-squamous NSCLC in clinical practice in England?
- Hazard ratios for death and progression were provided within the submission although the company states that the conditions for proportional hazards were violated. The ERG considers that HRs should therefore be interpreted with caution. Median statistics are provided as an alternative. What is the committee's view on the clinical effectiveness of nivolumab vs docetaxel based on CheckMate057?
- Is nivolumab clinically effective compared with nintedanib plus docetaxel?
- Is nivolumab clinically effective compared with best supportive care?
- No equality issues have been raised.

CheckMate-057

Population	Adult patients with non-squamous NSCLC whose disease has progressed during or after one prior platinum doublet-based chemotherapy regimen
Design	An international, open-label, phase III randomized controlled trial
Intervention	Nivolumab 3 mg/kg every 2 weeks until disease progression
Comparator	Docetaxel 75 mg/m^2 every 3 weeks until disease progression
Trial sites	106 sites in 22 countries worldwide (none from the UK)
Outcomes	Primary: overall survival Secondary: ORR, duration of response, time to response, PFS, level of PD-L1 expression, HRQoL, safety & tolerability, immunogenicity
Analysis	Enrolment Nov 2012-Dec 2013. Pre-planned interim analysis (March 2015, 12 month interim analysis) and additional 18 months analysis (July 2015) After interim analysis, trial stopped (primary endpoint met; patients in docetaxel arm could then switch to nivolumab; n=2)

CheckMate-057: Patient Characteristics

	Nivolumab (N=292)	Docetaxel (N=290)
Age: median (range), years	61 (37-84)	64 (21-85)
Sex: % male	52%	58%
Race: % white	91%	92%
PD-L1 expression level*: %		
<1%	46.8%	41.5%
<5%	58.9%	61.6%
<10%	62.8%	64.7%
Not quantifiable at baseline	20.9%	22.8%
Smoking: % current/former smokers	79%	78%
ECOG status: % ECOG 0	29%	33%
Disease stage: % stage IV	93%	92%

*Comment: Time point at which PD-L1 expression was measured was not stated (i.e. from archived sample or at pre-2nd line)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death 1 ligand
Source: company submission, page 70

CheckMate-057: Summary of Results (12 months Interim Analysis)

	Nivolumab	Docetaxel
Overall survival (OS)		
Median	**12.2** months (9.7–15.0)	**9.4** months (8.1–10.7)
Hazard ratio	HR: 0.73 (0.59–0.89), p = 0.002	
OS rate at 12 months	51% (45–56)	39% (33–45)
Progression-free survival (PFS)		
Median	**2.3** months (2.2–3.3)	**4.2** months (3.5–4.9)
Hazard ratio	0.92 (0.77-1.11), p=0.39	
PFS rate at 12 months	18.5% (14.1–23.4)	8% (5.1–12.0)
Response rates		
Overall response rate (ORR)	**19**% (15–24)	**12**% (9–17)
Odds ratio (95% CI)	1.7 (1.1 to 2.6) (p=0.02)	
Median time to response	2.1 months	2.6 months

Median OS and PFS and time to response shown in months. Brackets show 95% confidence intervals
Source: company submission, tables 16-18

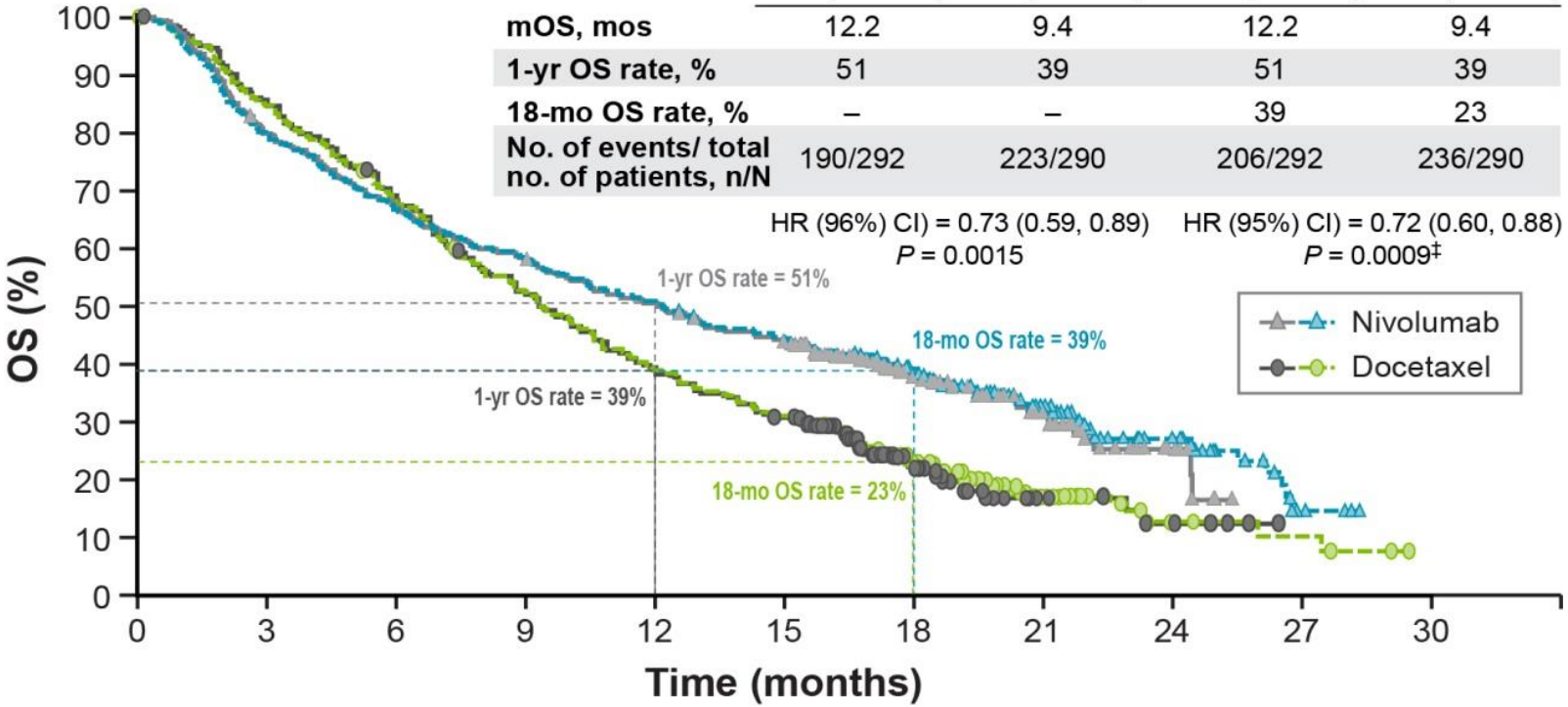
CheckMate-057: Summary of Results (18 months analysis)

	Nivolumab	Docetaxel
Overall survival (OS)		
OS rate at 12 months	**39%** (34 to 45)	**23%** (19 to 28)
Hazard ratio	0.72 (0.60 to 0.88), p=0.001	
Progression-free survival (PFS)		
PFS rate at 12 months	Not presented	Not presented
Hazard ratio	0.91 (0.76 to 1.09) p value was not presented	

Brackets show 95% confidence intervals
Source: company submission, tables 16-18

CheckMate-057: Overall survival (12 months and 18 months analyses)

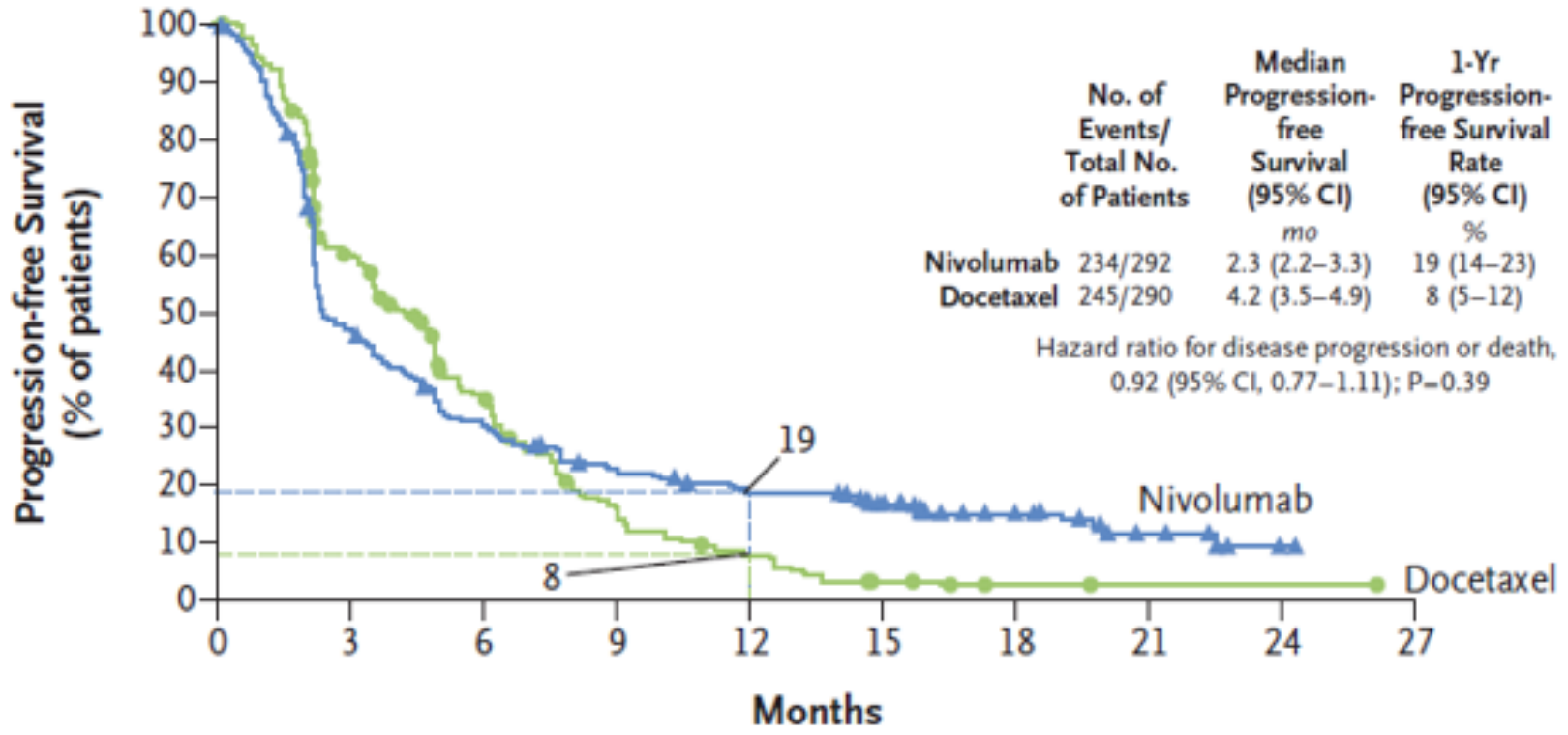
	12-mo OS*		18-mo OS†	
	Nivo (n = 292)	Doc (n = 290)	Nivo (n = 292)	Doc (n = 290)
mOS, mos	12.2	9.4	12.2	9.4
1-yr OS rate, %	51	39	51	39
18-mo OS rate, %	–	–	39	23
No. of events/ total no. of patients, n/N	190/292	223/290	206/292	236/290
	HR (96%) CI) = 0.73 (0.59, 0.89) *P* = 0.0015		HR (95%) CI) = 0.72 (0.60, 0.88) *P* = 0.0009‡	



No. of patients at risk (12-mo OS)*										
Nivolumab	292	232	194	169	146	123	62	32	9	0	0
Docetaxel	290	244	194	150	111	88	34	10	5	0	0
No. of patients at risk (18-mo OS)†											
Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

Source: company submission, figure 12

CheckMate-057: Progression-free survival (12 months Interim Analysis)



Source: company submission, figure 13

CheckMate-057: Quality of Life

- Lung Cancer Symptom Scale Average Symptom Burden Index (LCSS ASBI)
  - Results show improvements from baseline in lung cancer symptoms for patients with non-squamous NSCLC treated with nivolumab
  - For docetaxel, the scores worsened compared with baseline at every assessment through week 48, except at week 36
- EuroQol EQ-5D plus the EQ-5D Visual Analogue Scale (VAS)
  - The results of the EQ-5D VAS showed improvement for both patient groups while on treatment and returned to baseline values after discontinuation of treatment (baseline values range: 60.6-66.4)

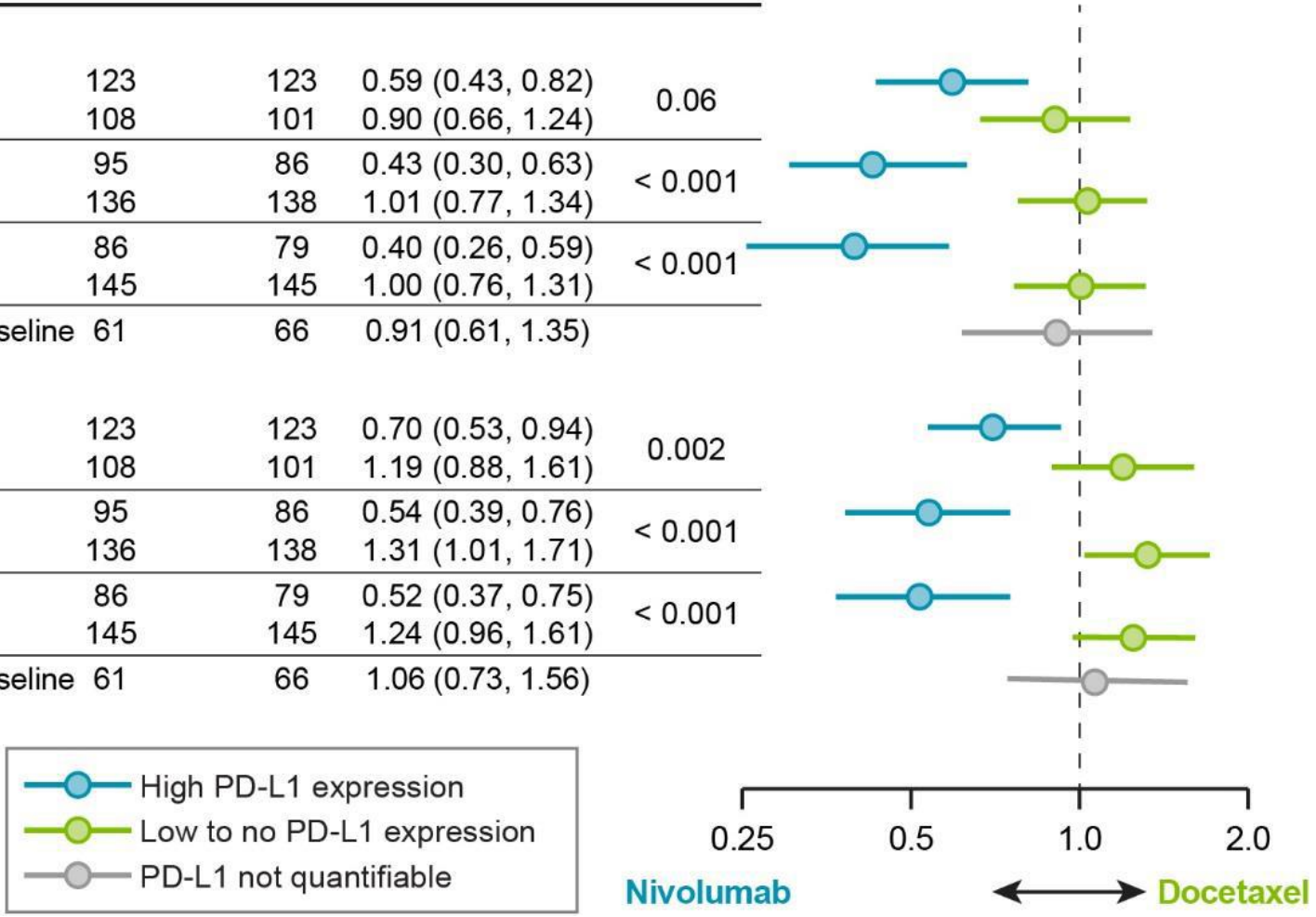
CheckMate-057: Subgroup Analysis

- Subgroup analyses of pre-specified demographic subgroups showed OS and PFS benefit for nivolumab compared with docetaxel for most of the subgroups
  - Confidence intervals were wide due to small subgroup sizes
  - Study was not powered to identify significant differences in these subgroups
- EGFR not detected/not reported subgroup
  - The results showed an overall survival benefit of 12.8 months (95% CI: 10.0-15.7) for nivolumab, compared with 9.30 months (95% CI: 8.0-10.6) for docetaxel (HR 0.69 [95% CI 0.56-0.85])
- PD-L1 subgroup
  - Nivolumab was associated with longer OS and PFS, and higher ORR than docetaxel at the pre-specified PD-L1 expression levels of ≥ 1%, ≥ 5% and ≥ 10% (Borghaei et al., 2015)
  - The magnitude of benefit across all the efficacy endpoints appeared to be greater at ≥ 1%, ≥ 5% and ≥ 10% PD-L1 expression levels (Borghaei et al., 2015)
  - Results should be interpreted with caution, the study was not powered to measure this. Note also that timing of PD-L1 measurement was not specified.

Source: company submission, section 4.8

CheckMate-017: PD-L1 Subgroup Analysis

PD-L1 expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥ 1%	123	123	0.59 (0.43, 0.82)	0.06
< 1%	108	101	0.90 (0.66, 1.24)	
≥ 5%	95	86	0.43 (0.30, 0.63)	< 0.001
< 5%	136	138	1.01 (0.77, 1.34)	
≥ 10%	86	79	0.40 (0.26, 0.59)	< 0.001
< 10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥ 1%	123	123	0.70 (0.53, 0.94)	0.002
< 1%	108	101	1.19 (0.88, 1.61)	
≥ 5%	95	86	0.54 (0.39, 0.76)	< 0.001
< 5%	136	138	1.31 (1.01, 1.71)	
≥ 10%	86	79	0.52 (0.37, 0.75)	< 0.001
< 10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	



Source: company submission, figure 19

Company Indirect Comparison (1)

- Company presented indirect comparisons for nivolumab vs. nintedanib plus docetaxel and BSC

  'all-comers' non-squamous NSCLC (all non-squamous patients included in the studies, regardless of mutation status)

  – XXXXXXXXXXXXXXXXX reduction in the risk of death for patients treated with nivolumab compared with nintedanib plus docetaxel (HR: XXX; 95% CI: XXXXXXX; p = XXX)

  – XXXXXXXXXXXXXXXXX benefit in OS with nivolumab was observed against BSC (HR: XXX; 95% CI: XXXXXX; p = XXX)

  'EGFR negative/unknown' NSCLC

  – XXXXXXXXXXXXXXXXX reduction in the risk of death for patients treated with nivolumab compared with nintedanib plus docetaxel (HR: XXX; 95% CI XXXXXXXX; p=XXX)

  – XXXXXXXXXXXXXXXXX benefit in OS with nivolumab was observed against BSC (HR: XXX, 95% CI XXXXXX; p=XXX)

- Company noted that there was a paucity of available evidence and heterogeneity among the studies, but it was not possible to control for this. Therefore, the foregoing results should be interpreted with caution.

Source: company submission, section 4.10

Company Indirect Comparison (2)

- The proportional hazard assumptions were violated, therefore the hazard ratio analysis results should be interpreted with caution. The company also presented results in terms of differences in restricted means survival time (RMST)

'All-comers' non-squamous NSCLC	Nivolumab vs. nintedanib plus docetaxel	Nivolumab vs. BSC
OS RMST difference (95% CI); p value	XXXXXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXXXXXX
PFS RMST difference (95% CI); p value	XXXXXXXXXXXXXXXXXXXXXX	

Base case economic analysis does not use the results of the company indirect comparison and is limited to nivolumab compared with:

- *Docetaxel monotherapy*
- *Nintedanib in combination with docetaxel*

CheckMate-057: Adverse Events

- Nivolumab demonstrated a more favourable safety profile than docetaxel (standard of care) (in both haematologic and non-haematologic AEs). Most first-onset AEs occurred within the first 3 to 6 months

	Nivolumab, n (%) (N = 287)	Docetaxel, n (%) (N = 268)
Patients with 1 or more AE	280 (98%)	265 (99%)
Grade 3–4 AE	132 (46%)	180 (67%)
Select AEs	27 (9.4%)	1 (0.4%)
SAEs	134 (46.7%)	111 (41.4%)
AEs leading to discontinuation	48 (16.7%)	58 (21.6%)
Deaths		
Deaths related to study drug toxicity	1 (0.35%)	1 (0.37%)
Treatment-related AEs		
Patients with 1 or more AE	199 (69%)	236 (88%)
Select AEs	132 (46%)	105 (39.3%)
SAEs	21 (7%)	53 (20%)
AEs leading to discontinuation	14 (5%)	40 (14.9%)

AE, adverse event; SAE, serious adverse event; 'select' AEs are a group of immune-related adverse events that are associated with the mode of action of nivolumab and that require additional monitoring.
Source: company submission, section 4.12

Clinical Evidence: Other Studies

- **CheckMate 153 –** a Phase IIIb/IV, open-label study in previously treated patients with locally advanced or metastatic non-squamous and squamous NSCLC and PS0-2 (n=147)
  - At the time of submission of this dossier to NICE, 147 patients had been treated for 1 year and randomised into cohorts A or B
  - BMS plan to analyse the results of CheckMate 153 in Q2-Q3 of 2016, and it is estimated that approximately 100 patients who have been randomised into cohorts A or B will have a minimum of 6 months of post-randomisation follow-up available for this analysis.
- **CheckMate 003 –** a dose-escalation, expansion cohort Phase Ib study in people with advanced or recurrent malignancies
  - People with NSCLC: 42.2%
  - 14.7% (n=19) received the licensed dose of nivolumab (3mg/kg every 2 weeks)
  - Long-term (4-year) data

Source: company submission, section 4.11

Evidence Review Group's Critique (1)

- CheckMate 057 provides evidence of median OS benefit of nivolumab over docetaxel at both 12 and 18 months (OS of 12.2 versus 9.4 months and OS rate of 39% versus 23%, respectively)
  - However, due to issues of pseudo progression (tumours that initially increase as a result of the treatment action before shrinking/stabilising) with nivolumab, the results for PFS are less clear
- The primary data provided comes from CheckMate 057 and an indirect treatment comparison that is limited by a lack of data to allow for comparison with all of relative comparators listed in the scope
  - The comparison of nivolumab is therefore limited to data related to docetaxel, nintedanib plus docetaxel and BSC
- CheckMate 057 was a well-conducted trial, but the use of HRs in the analysis cannot be considered a reliable estimate of treatment effectiveness because the proportional hazards assumption was violated for both OS and PFS

Evidence Review Group's Critique (2)

- The AE data presented indicate that nivolumab, although having a slightly different AE profile to standard cytotoxic chemotherapy, has fewer Grade 3-4 AEs than docetaxel. Data from additional non-randomised studies and studies of the use of nivolumab in patients with a variety of other cancers are provided to support this assertion
- The ERG noted the company's statement that the OS results, observed on the docetaxel arm are an overestimation, however this statement was not supported by other clinical trials results
- Crossover was allowed for a small number of patients (n=2) on the docetaxel arm after the trial was stopped in April 2015, after it had reached the primary endpoint in March 2015
- Subgroup analyses suggest that nivolumab is statistically significantly more effective in patients with higher PD-L1 expression levels than those with lower PD-L1 expression levels. The report is however somewhat inconsistent with regards to whether all patients should therefore be tested for PD-L1.

Potential equality issues

- No equality issues identified during the scoping process for this topic
- No equality issues raised by the company or consultees in submissions

Summary: Key issues for consideration

- Evidence not provided for EGFR positives/ALK positives. Should the committee's decision focus on the EGFR/ALK negative subgroups only?
- Do the comparators included in the submission (docetaxel, nintedanib plus docetaxel, best supportive care) reflect established clinical practice in the NHS?
- Are the results of CheckMate 057 generalisable to people with non-squamous NSCLC in clinical practice in England?
- Hazard ratios for death and progression were provided within the submission although the company states that the conditions for proportional hazards were violated. The ERG considers that HRs should therefore be interpreted with caution. Median statistics are provided as an alternative. What is the committee's view on the clinical effectiveness of nivolumab vs docetaxel based on CheckMate057?
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1st Appraisal Committee meeting

Cost Effectiveness

Peter Selby

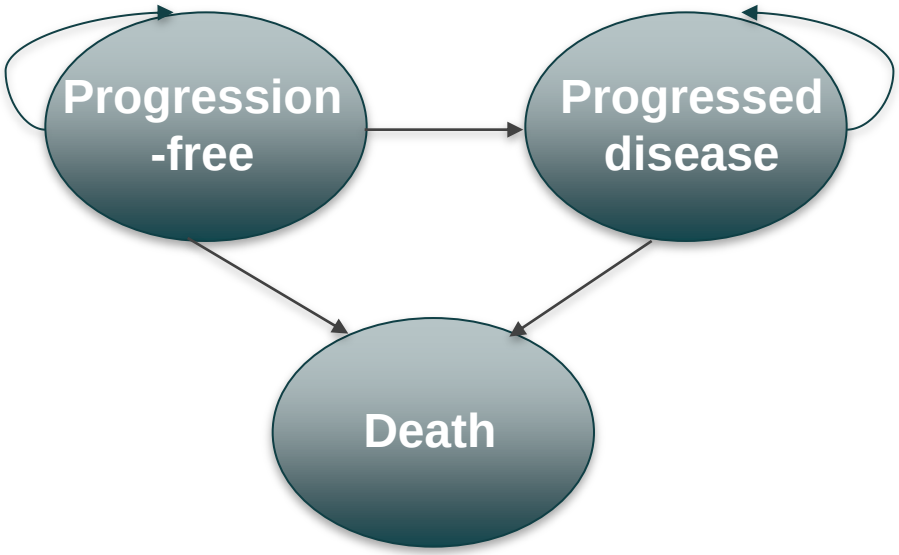
13 April 2016

For public

Preview:
Key issues for consideration

- Assumptions in the company's economic model – appropriate and plausible?
  - ***Survival projections:***
  - Are the ERG's concerns about the extrapolations valid? What are the most appropriate methods:
    - For modelling OS
    - For modelling PFS
  - Is the use of time to treatment discontinuation data for modelling PFS or only treatment related costs and AEs plausible?
  - ***Drug costs:***
    Most appropriate assumptions for acquisition costs, administration costs and duration of treatment?
  - ***Utility values:***
    Most plausible utility scores to use in model?
- What are the most plausible ICERs?
  - For those who can have docetaxel
  - For those who cannot have docetaxel (comparator is BSC)
- Are the end-of-life criteria met?
- Does the company want to make a case for inclusion in the CDF?

Model structure



- Cycle length 1 week
- Half cycle correction
- Time horizon 20 years (lifetime)
- Discount 3.5% for cost and utilities
- Perspective = NHS/PSS

Source: company submission, figure 26

Assumptions

- Proportion of people in each health state based on estimates of time to discontinuation data (instead of PFS) and OS using area under the curve
- **vs docetaxel**: estimated by extrapolation from 12 month data from CheckMate-057 extrapolated to time horizon of the model
  - Generalised gamma function used
- **vs docetaxel plus nintedanib**: HR for OS and time to discontinuation estimated from KM curves of LUME-Lung1 study and CheckMate 057 (indirect comparison not used)
  - OS: HR of 1 (up to 6 months); thereafter 0.75 (95% CI 0.60-0.93)
  - Time to treatment discontinuation: HR of 1 (up to 2 months); thereafter 0.98 (95% CI 0.73-1.33)
- **No comparison with BSC**

Resources and costs

- Drug costs derived from list prices
  - After progression 1 subsequent line of treatment lasting XXXXXX
- Costs of health states
  - Derived from previous NICE appraisals, NHS reference costs and expert opinion
- Costs of end of life care
- Costs of adverse events
  - severity grade of 3–4 and an incidence of at least 2% in either arm of CheckMate 057

Details in company's submission, section 5.5

Health states and utility values

- Derived from EQ-5D in Checkmate 057
  - Progression-free health state 0.739
  - Progressed disease health state 0.688
- Utility decrement for AEs:
  - From Checkmate 057
    - Incidence ≥ 2%; severity grade 3 or 4
  - For nintedanib plus docetaxel
    - Incidence ≥ 2% from LUME-Lung 1

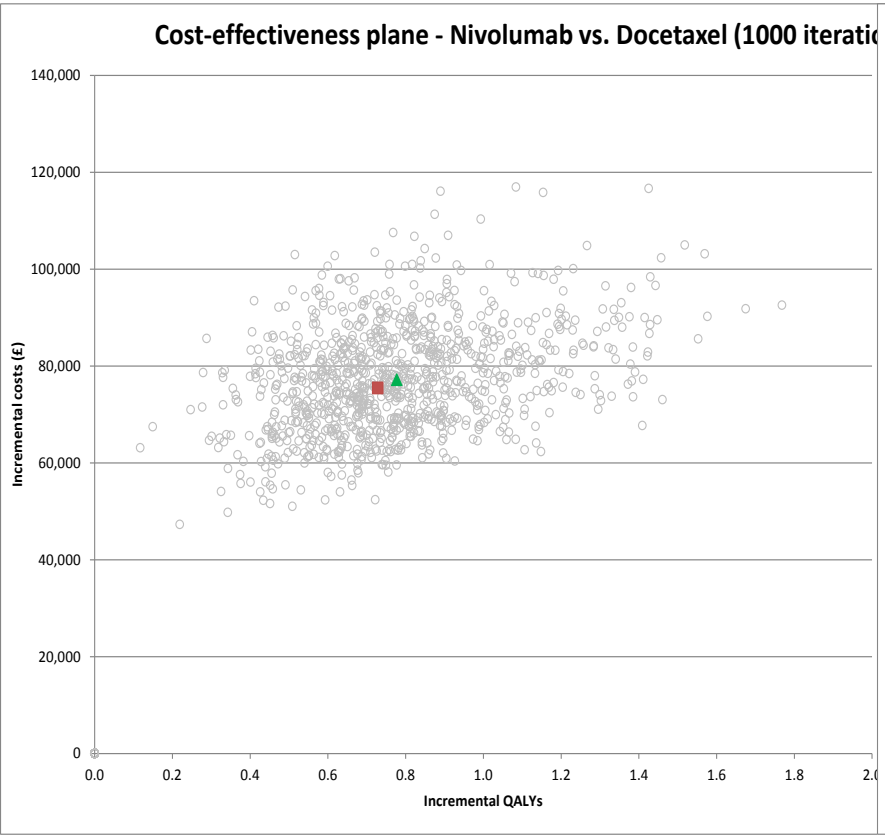
Company's base case results
(using list prices)

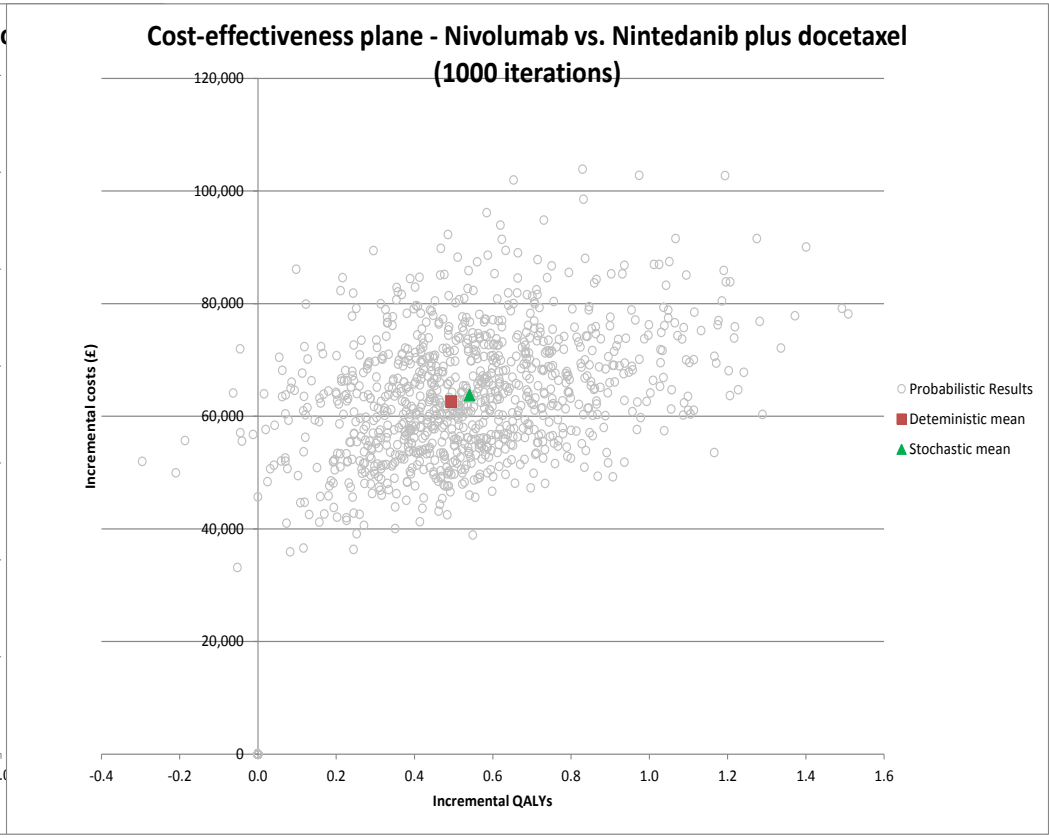
Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Deterministic analysis					
Nivolumab	93,306	1.42	-	-	-
Docetaxel	17,854	0.70	75,452	0.73	**103,589**
Nintedanib + doce	30,708	0.93	62,598	0.49	**126,861**
Probabilistic analysis					
Nivolumab	94,832	1.50	-	-	-
Docetaxel	17,666	0.72	77,166	0.78	**99,291**
Nintedanib + doce	31,070	0.96	63,761	0.54	**117,934**

Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio

Source: Table 76 and 102 of company submission

Company's probabilistic analysis

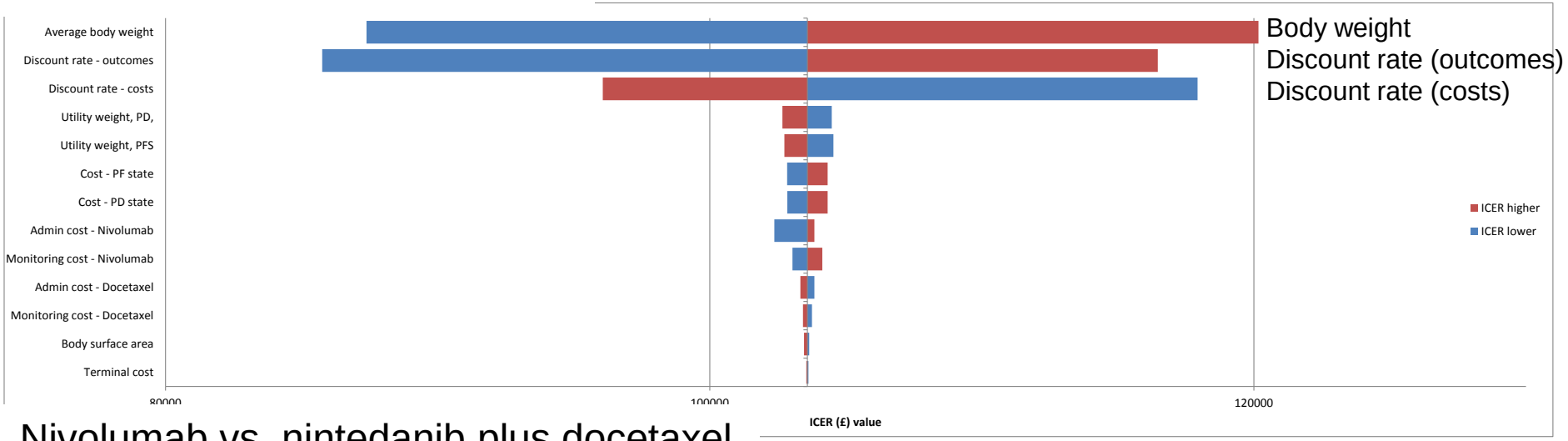




Source: company's submission figures 43 and 44

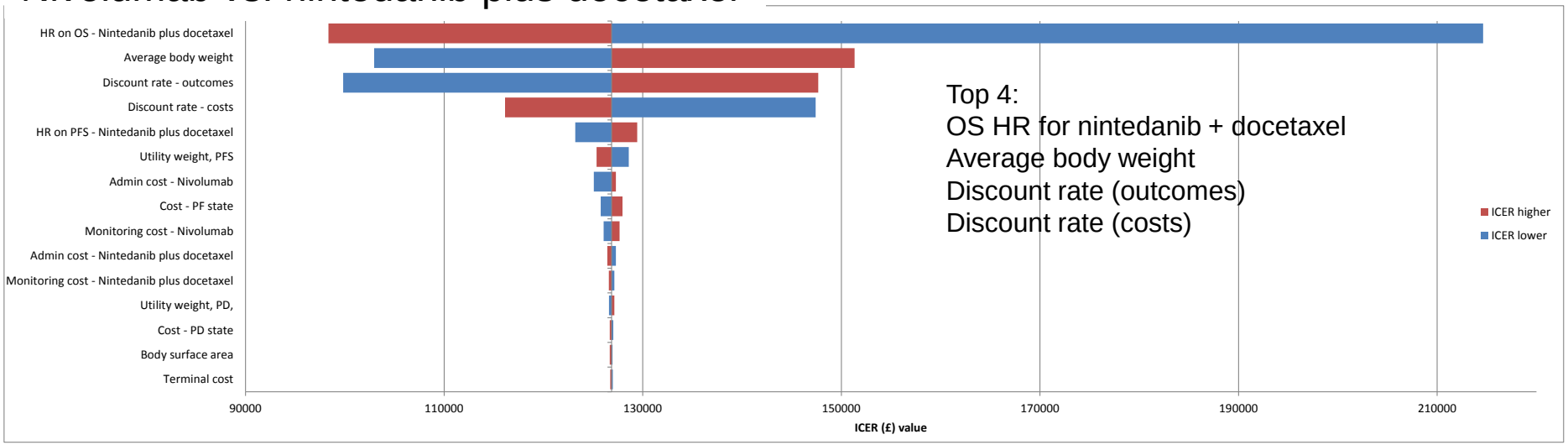
Deterministic sensitivity analyses

Nivolumab vs. docetaxel



Body weight
Discount rate (outcomes)
Discount rate (costs)

Nivolumab vs. nintedanib plus docetaxel



Top 4:
OS HR for nintedanib + docetaxel
Average body weight
Discount rate (outcomes)
Discount rate (costs)

Abbreviations: ICER, Incremental Cost-Effectiveness Ratio; PD, Progressed Disease; PF, Progression-Free; PFS, Progression-Free Survival

Source: company's submission figures 46 and 47

Company's scenario analyses

(using list prices)

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Scenario 1 (Different OS distributions: 2-knot spline hazards model for nivolumab and gamma distribution for docetaxel)					
Nivolumab	89,553	1.16	-	-	**-**
Docetaxel	17,375	0.66	72,178	0.50	**144,594**
Nintedanib plus docetaxel	29,612	0.85	59,941	0.31	**195,348**
Scenario 2 (Different TTD distributions: 1-knot spline hazards model for nivolumab and gamma distribution for docetaxel)					
Nivolumab	112,380	1.48	-	-	**-**
Docetaxel	17,858	0.70	94,522	0.78	**120,773**
Nintedanib plus docetaxel	30,709	0.93	81,671	0.55	**149,112**
Scenario 3 (1 year stopping rule for nivolumab)					
Nivolumab	51,986	1.42	-	-	**-**
Docetaxel	17,854	0.70	34,132	0.73	**46,860**
Nintedanib plus docetaxel	30,708	0.93	21,278	0.49	**43,122**
Scenario 4 (2 year stopping rule for nivolumab)					
Nivolumab	62,252	1.42	-	-	**-**
Docetaxel	17,854	0.70	44,398	0.73	**60,955**
Nintedanib plus docetaxel	30,708	0.93	31,544	0.49	**63,928**

Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio

Source: company's submission Tables 108, 111, 114 and 117.

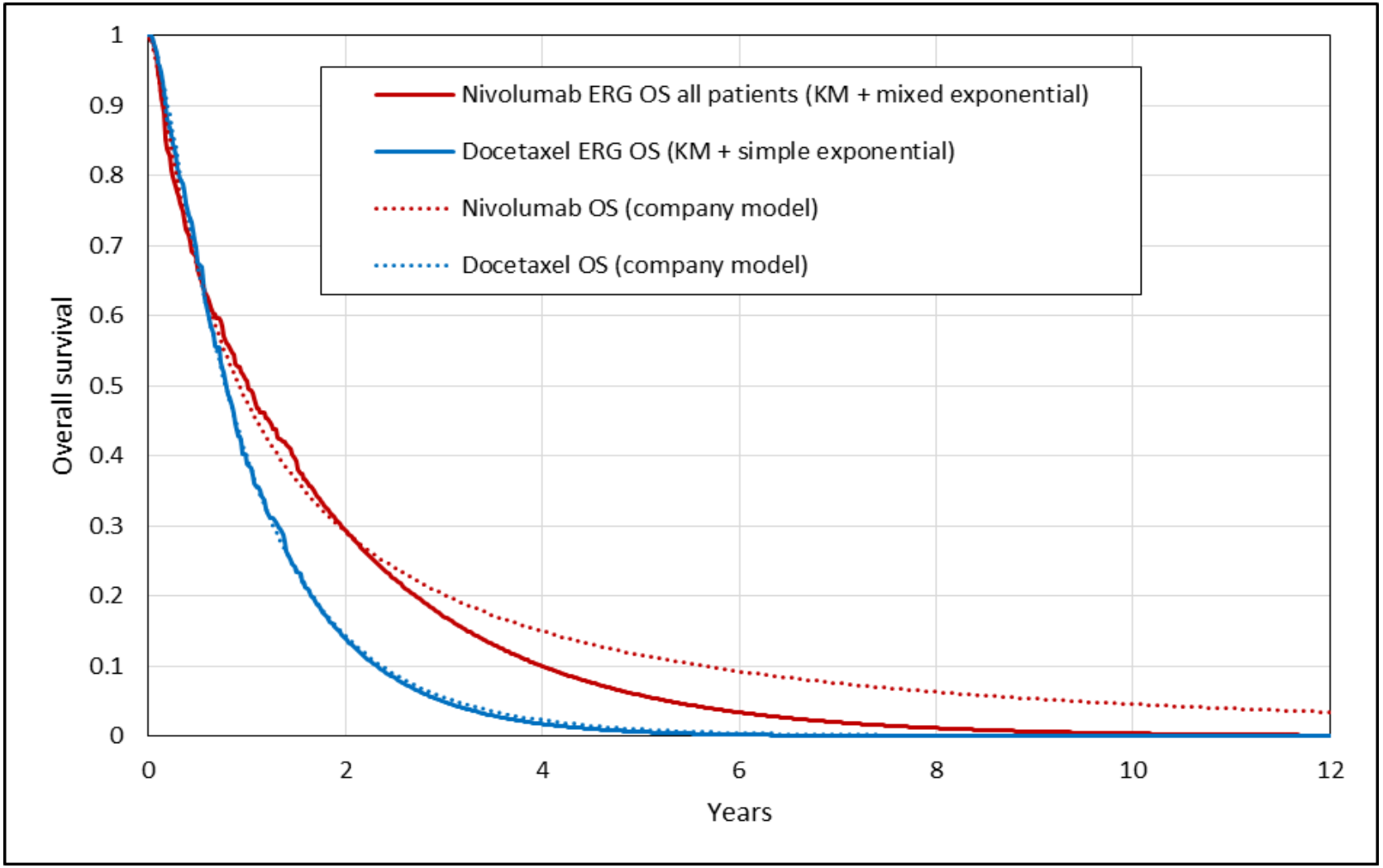
Evidence Review Group (ERG) comments: extrapolating clinical effectiveness data (1)

- ERG critique:
  - Treatment after progression was permitted in CheckMate 057
  - Generalised gamma model is not a good fit to the KM data
  - Use of 12 months rather than 18 months data from CheckMate057
  - Use of TTD to estimate PFS is implausible (85% of patients who were still alive at year 20, remained progression-free and were receiving nivolumab treatment).
  - TTD data should be used only for estimating costs and AEs associated with treatment (This approach in line with ID811)
  - Handling of PFS being greater than OS and OS being greater than all-cause mortality led to implausible results

ERG comments: extrapolating clinical effectiveness data (2)

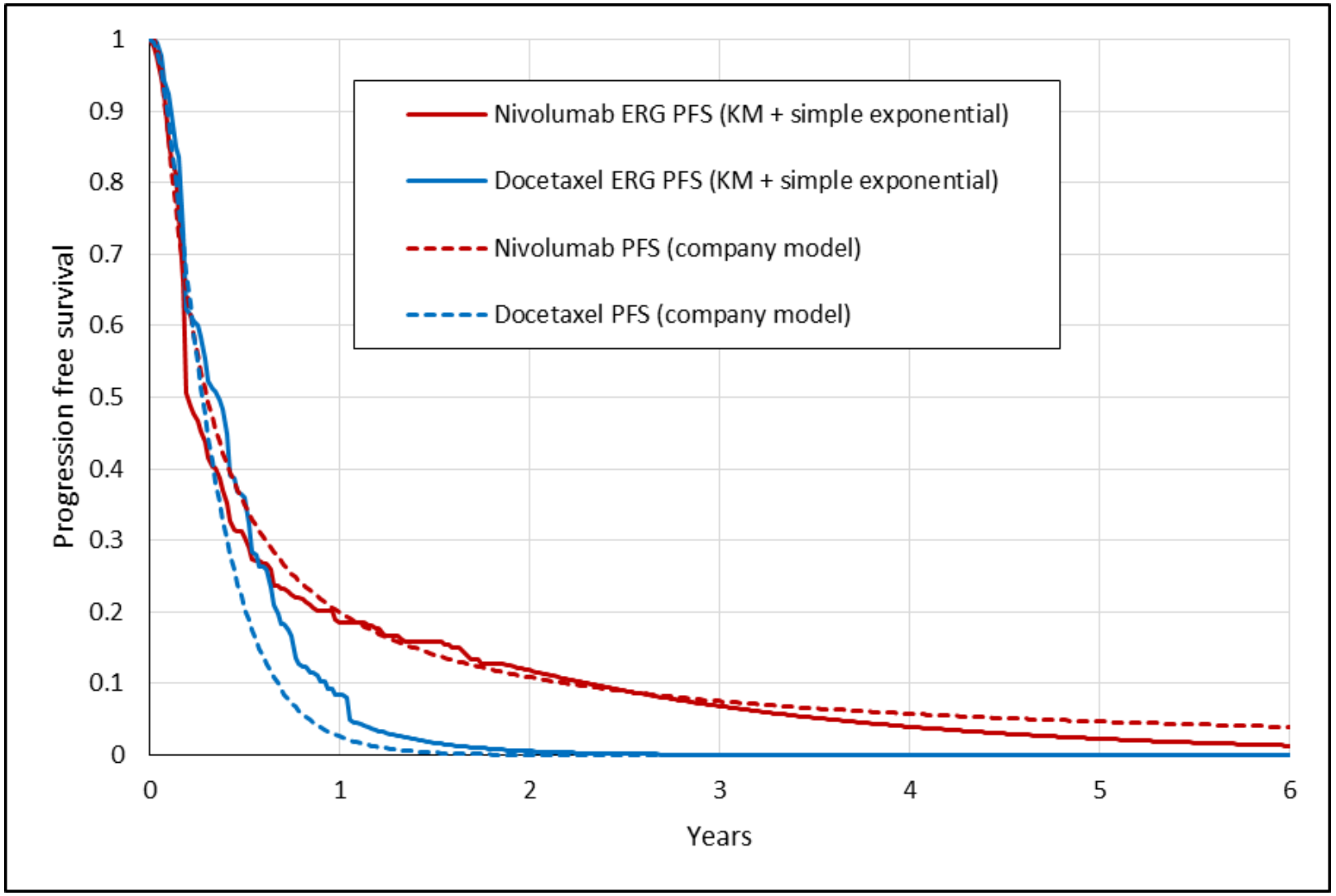
- ERG's suggestions:
  - Use 18 months PFS KM data from CheckMate 057
  - Use exponential model for extrapolation
  - For the comparison with docetaxel developed a mixed exponential model for PFS, based on 25% of patients receiving nivolumab after progression in CheckMate 075
  - For the comparison with nintedanib plus docetaxel the ERG used more mature KM data from LUME-Lung 1 study

ERG comments: Overall survival projections for nivolumab vs. docetaxel



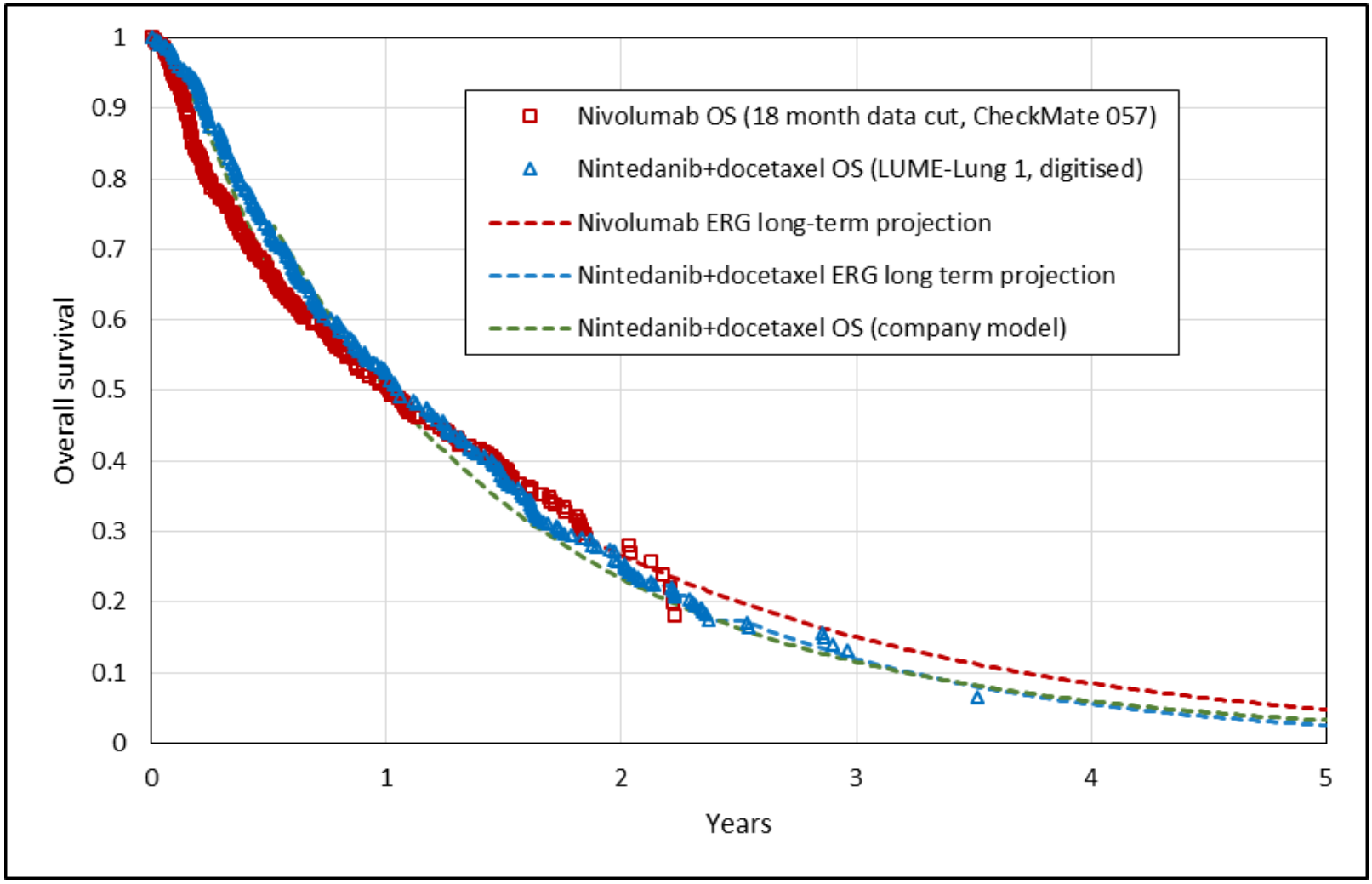
Source: ERG report figure 19

ERG comments: progression-free survival projections for nivolumab vs. docetaxel



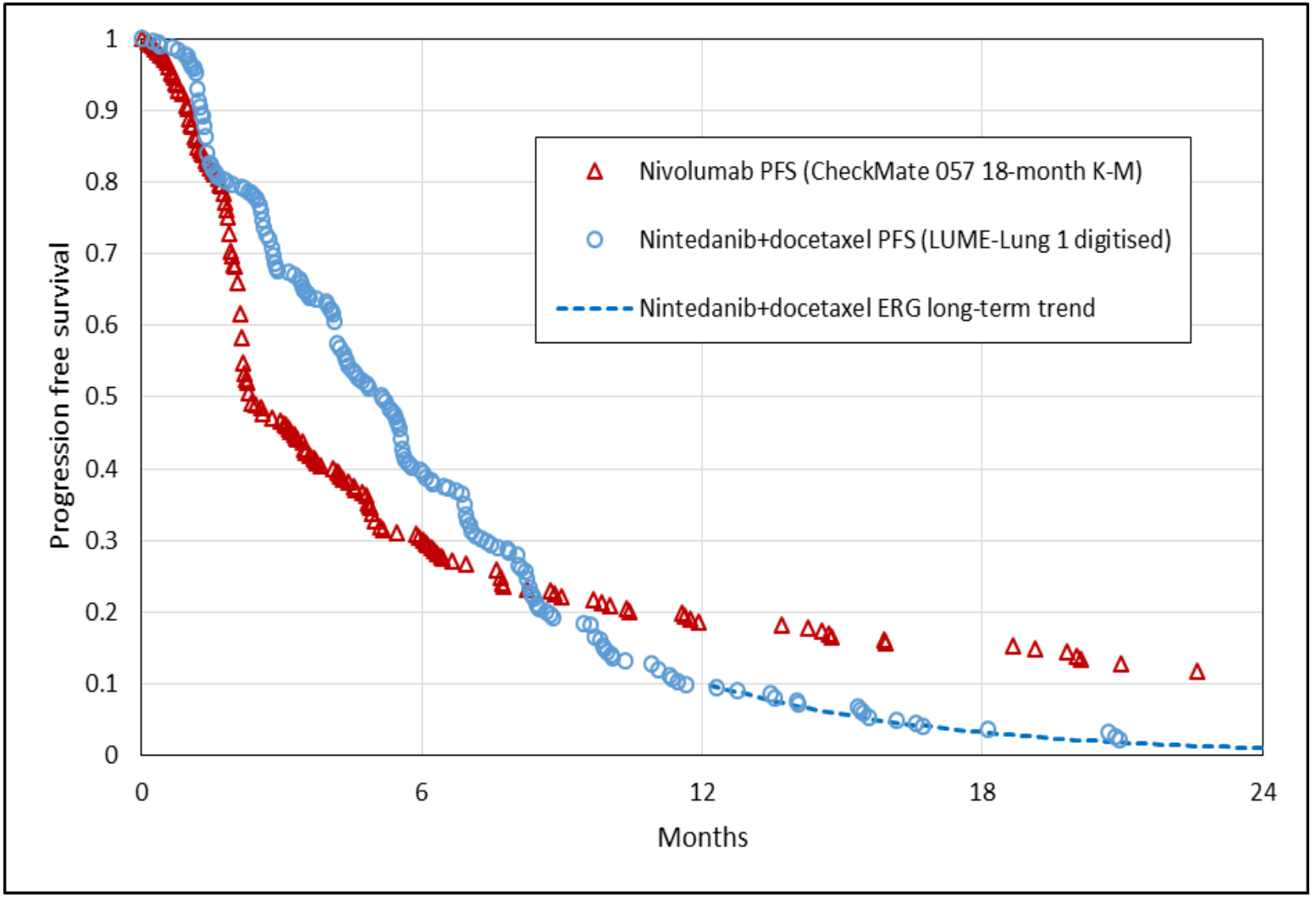
Source: ERG report figure 25

ERG comments: Overall survival projections for nivolumab vs. nintedanib plus docetaxel



Source: ERG report figure 31

ERG comments: progression-free survival projections for nivolumab vs. nintedanib plus docetaxel



Source: ERG report figure 34

ERG comments: Utility values and costs

- Decline in EQ-5D response rate over time
  - May have influenced utility values
  - Progressed disease health state: Used data from a study published by van den Hout et al., and applied disutility values associated with terminal care
  - Progression-free health state: used early (12 weeks) EQ-5D results from CheckMate057 for European patients alone

Utility values	Company	ERG	N.B. ID811 squamous
Progression-free health state	0.739	0.713	0.693
Progressed disease health state	0.688	0.476	0.509

- Calculation errors relating to costs rectified (administration costs from beginning, not middle, of cycle; body weight calculation error)
- Company's scenario analyses: No evidence of clinical effects of stopping nivolumab

ERG's exploratory analyses: nivolumab vs. docetaxel

- ERG's preferred method for modelling overall survival: (used 18 months data and a mixed exponential model based on 25% of patients receiving nivolumab after progression on the nivolumab arm; and simple exponential model for extrapolation on the docetaxel arm)
- Uses progression-free survival for modelling health state costs and QALYs (based on 18 months data and used exponential model for extrapolation). Used time to treatment discontinuation data for modelling costs and AEs associated with treatment and exponential model for extrapolation on the nivolumab arm.
- Corrected calculation errors
- Used the ERG's preferred utility values

ERG's exploratory analyses: nivolumab (list price) vs. docetaxel

Scenario	Inc. cost	Inc. QALY	ICER	ICER Change
A. Company's base case	+75,452	+0.728	**103,589**	-
R1) ERG OS	+72,207	+0.501	**143,984**	+40,395
R2) ERG PFS*	+57,328	+0.708	**80,940**	-22,649
R3) ERG TTD*	+58,577	+0.719	**81,513**	-22,077
R4) ERG PFS for disease costs and QALYs, ERG TTD for treatment costs and AEs	+59,208	+0.708	**83,594**	-19,996
R7) Nivolumab dosing calculations	+74,100	+0.728	**101,734**	-1,855
R8) Treatment administration costed at start of cycle	+74,587	+0.728	**102,403**	-1,187
R9) ERG utility values (Van den Hout + CheckMate 057)	+75,452	+0.654	**115,443**	+11,853
B. ERG revised base case A+R1, R4, R7:R9	+53,343	+0.323	**165,234**	+61,644

Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation

Source Table 46 of ERG report * Revisions R2 and R3 are superseded by R4

ERG's exploratory analyses: nivolumab vs. nintedanib plus docetaxel

- Used the ERG's preferred method for modelling overall survival (used 18 months data on the nivolumab arm, more mature data from the LUME-Lung 1 trial and exponential model for extrapolation)
- Used progression-free survival for modelling health state costs and QALYs for nivolumab and used time to treatment discontinuation data for modelling costs and AEs associated with nivolumab treatment. Used the ERG's preferred method for modelling progression free survival for nintedanib plus docetaxel (used more mature data from LUME-Lung 1 trial).
- Corrected calculation errors
- Used the ERG's preferred utility values

ERG's exploratory analyses (list prices): nivolumab vs. nintedanib plus docetaxel

Scenario	Inc. cost	Inc. QALY	ICER	ICER Change
A. Company's base case	+62,598	+0.493	**126,861**	-
R1) ERG OS	+59,164	+0.238	**248,838**	+121,977
R2) ERG PFS*	+41,069	+0.471	**87,202**	-39,660
R5) ERG TTD for nivolumab treatment costs and AEs, ERG PFS for nintedanib+docetaxel disease costs and QALYs*	+41,593	+0.472	**88,147**	-38,714
R6) ERG PFS for nivolumab disease costs and QALYs, ERG TTD for nivolumab treatment costs and AEs; ERG PFS for nintedanib+docetaxel disease costs and QALYs	+41,149	+0.471	**87,371**	-39,491
R7) Nivolumab dosing calculations	+61,247	+0.493	**124,123**	-2,738
R8) Treatment administration costed at start of cycle	+62,611	+0.493	**126,887**	+26
R9) ERG utility values (Van den Hout + CheckMate 057)	+62,598	+0.486	**128,916**	+2,055
B. ERG revised base case A+R1, R4, R7:R9	+35,116	+0.120	**293,232**	+166,370

Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation

Source Table 46 of ERG report * Revisions R2 and R5 are superseded by R6

Innovation

- Manufacturer considers nivolumab to be innovative:
  - Step change in management
  - Limited options for non-squamous NSCLC without ALK or EGFR mutations
  - First immunotherapy and first PD-1 inhibitor for NSCLC
  - Designated a “Promising Innovative Medicine” by MHRA and approved through Early Access to Medicines Scheme
  - Provides significant survival benefit compared to docetaxel
- Patient group also considers it innovative
  - Novel mechanism of action
  - Major milestone in treatment of NSCLC
- Company did not provide additional evidence of benefits that have not been captured in the QALY calculation

End of Life (1)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	In CheckMate 057 the median overall survival for patients on the docetaxel arm was 9.4 months Median survival for stage III NSCLC is 9.6 months. Median survival for stage IV NSCLC is 3.3 months.
The treatment is licensed or otherwise indicated for small patient populations	The company estimated that 1413 patients with non-squamous NSCLC would be eligible for nivolumab in England and Wales. The population size for the melanoma indication is estimated to be 2200 and for the squamous indication is 853. The total population size is therefore in the region of 4500.

End of Life (2)

- Evidence of an extension to life, normally of at least an additional 3 months, compared with current NHS treatment

	Median OS	Diff.
Nivolumab (CheckMate057)	12.2	-
Docetaxel (CheckMate057)	9.4	2.8
Nintedanib + docetaxel (LUME-Lung 1)	12.6	0.4

Company's model:	Mean OS	Diff.	Median OS	Diff.
Nivolumab	26.8	-	11.1	-
Docetaxel	13.1	13.7	9.2	1.8
Nintedanib + docetaxel	17.2	9.6	12.1	-1.0

ERG assumptions:	Mean OS	Diff.	Median OS	Diff.
Nivolumab	21.6	-	12.1	-
Docetaxel	12.8	8.8	9.2	2.9
Nintedanib + docetaxel	17.4	4.1	12.5	-0.4

Abbreviations: OS, overall survival; Diff., OS difference compared with nivolumab

Key issues for consideration

- Assumptions in the company's economic model – appropriate and plausible?
  - ***Survival projections:***
  - Are the ERG's concerns about the extrapolations valid? What are the most appropriate methods:
    - For modelling OS
    - For modelling PFS
  - Is the use of time to treatment discontinuation data for modelling PFS or only treatment related costs and AEs plausible?
  - ***Drug costs:***
    Most appropriate assumptions for acquisition costs, administration costs and duration of treatment?
  - ***Utility values:***
    Most plausible utility scores to use in model?
- What are the most plausible ICERs?
  - For those people who can have docetaxel
  - For those people who cannot have docetaxel (comparator BSC)
- Are the end-of-life criteria met?
- Does the company want to make a case for inclusion in the CDF?

Patient Access Scheme for nivolumab

- Economic dose cap – BMS will cover the cost of nivolumab after 26 administrations (1 year)
- The costs of *administering* nivolumab still need to be borne by the NHS beyond 1 year

	Company			ERG		
	Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	ICER
nivolumab PAS						
Nivolumab						
Docetaxel	37,733	0.73	**51,805**	29,407	0.323	**91,089**
Nintedanib + docetaxel	24,880	0.49	**50,421**	11,180	0.120	**93,355**

Abbreviations:
Inc., incremental; QALY, Quality adjusted life years; ICER, Incremental cost-effectiveness ratio

NB. Table does not include the PAS for nintedanib

ERG's exploratory analyses: nivolumab (with PAS) vs. docetaxel

Scenario	Inc. cost	Inc. QALY	ICER	ICER Change
A. Company's base case	+37,733	+0.728	**51,805**	-
R1) ERG OS	+34,488	+0.501	**68,772**	16,967
R2) ERG PFS*	+36,166	+0.708	**51,062**	-17,710
R3) ERG TTD*	+34,153	+0.719	**47,526**	-3,536
R4) ERG PFS for disease costs and QALYs, ERG TTD for treatment costs and AEs	+34,784	+0.708	**49,110**	1,584
R7) Nivolumab dosing calculations	+37,135	+0.728	**50,983**	1,873
R8) Treatment administration costed at start of cycle	+36,869	+0.728	**50,618**	-365
R9) ERG utility values (Van den Hout + CheckMate 057)	+37,733	+0.654	**57,733**	7,115
B. ERG revised base case A+R1, R4, R7:R9	+29,407	+0.323	**91,089**	33,356

Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation

Source Table 46 of ERG report * Revisions R2 and R3 are superseded by R4