NICE National Institute for Health and Care Excellence

AIC and CIC redacted

Slides for public – redacted

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483)

CDF review TA483 committee meeting – 18 March 2020

Lead team: Paul Tappenden, Richard Nicholas & Stella O'Brien

ERG: Liverpool Reviews & Implementation Group (LRiG)

Technical team: Vicki Pollit, Alexandra Filby, Frances Sutcliffe

Company: BMS

TA483 appraisal background

Further data collection:

- Managed access agreement
- Additional data from CheckMate 017

[redacted]

Appraisal background

Marketing Authorisation: Nivolumab as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

NICE TA483: Nivolumab is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic squamous non-small-cell lung cancer in adults after chemotherapy, only if:
nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression

	TA483 appraisal
Population	People with previously treated locally advanced or metastatic (stage IIIB or IV) squamous NSCLC
Comparator	• Docetaxel (BSC and erlotinib considered)
Outcomes	• Overall survival, progression free survival, response rates, adverse events, health related quality of life

[redacted]

Treatment pathway for squamous NSCLC

First Line

Cisplatin or carboplatin + Gemcitabine, vinorelbine

New since nivolumab first scoped:

Pembrolizumab (PD-L1+) TA531, July 18

Second Line

Docetaxel

Erlotinib (for EGFR+ patients only, unlikely in squamous indication) TA374

Best supportive care

Nivolumab (CDF) TA483

New since nivolumab first scoped:

Pembrolizumab (if PDL1>1%) TA428, Jan 2017*

Atezolizumab (no PD-L1 expression) TA520, May 2018*

First line treatments are not included as part of TA483 or the current CDF review

*For CDF reviews, the scope doesn't change, so pembrolizumab and atezolizumab are not considered in the current CDF review

[redacted]

CDF review TA483 - Patient & Professional Perspectives

- Patients and professionals want treatments that are effective, minimally disruptive, and improve quality of life
- Nivolumab is life-changing
  - Living with metastatic lung cancer
  - Patients resent the 2 year stopping rule
  - Professionals and patient organisations say the stopping rule is arbitrary
- Inflexible treatment lines
  - Patients are increasingly protesting about restricted treatment lines
  - They want flexibility about treatments

#BusyLivingWithMets

The 2 year stopping rule is playing Russian roulette with our lives. It's because nobody cares about lung cancer patients.

The buzz words are "personalised care" but needless rationing like this will progress us towards death

[redacted]

Committee considerations in TA483

Topic	Committee consideration from TA483 appraisal
Comparators	Erlotinib is rarely used in clinical practice, docetaxel would be used in preference to best supportive care – docetaxel is the most appropriate comparator
PD-L1 subgroups	Potential that PD-L1 expression has an effect on overall survival with nivolumab. Deemed not to be a clinically significant difference
Generalisability	ECOG >1 excluded from the trial. However, CheckMate 017 generalisable to clinical practice in England
PFS extrapolation	Trial data + extrapolation with exponential distribution to avoid giving statistical weight to early progression data
OS extrapolation	Highly uncertain tail of overall survival extrapolations. Generalised gamma chosen by DSU to account for continued treatment effect
2-year stopping rule	Optimum treatment duration with immunotherapeutic treatments is uncertain, stopping treatment after 2 years improves cost-effectiveness and would be implemented by clinicians
Continued treatment effect	Mechanism of nivolumab means it continues to have an effect after stopping treatment, limited evidence to support this but it could last up to 3 years
End of life considerations	People with squamous NSCLC have a life expectancy of less than 24 months and nivolumab offers life extension greater than 3 months

CDF review TA483 - New clinical evidence – CheckMate 017

Population	Adults with squamous NSCLC that had progressed during or after treatment with 1 platinum combination chemotherapy
Intervention (n=135)	Nivolumab 3mg/kg every 2 weeks until disease progression or unacceptable toxicity
Comparator (n=137)	Docetaxel
Outcomes	Overall survival ,progression free survival, duration and time to response, health related quality of life, adverse events

	TA483 submission		**Updated submission**	
	Nivolumab	Docetaxel	Nivolumab	Docetaxel
Nominal follow-up period	**2-years**		**5-years**	
Median overall survival (months)	9.2	6.0	XXXX	XXXX
5-year overall survival (KM estimate)	N/A	N/A	XXXX	XXXX

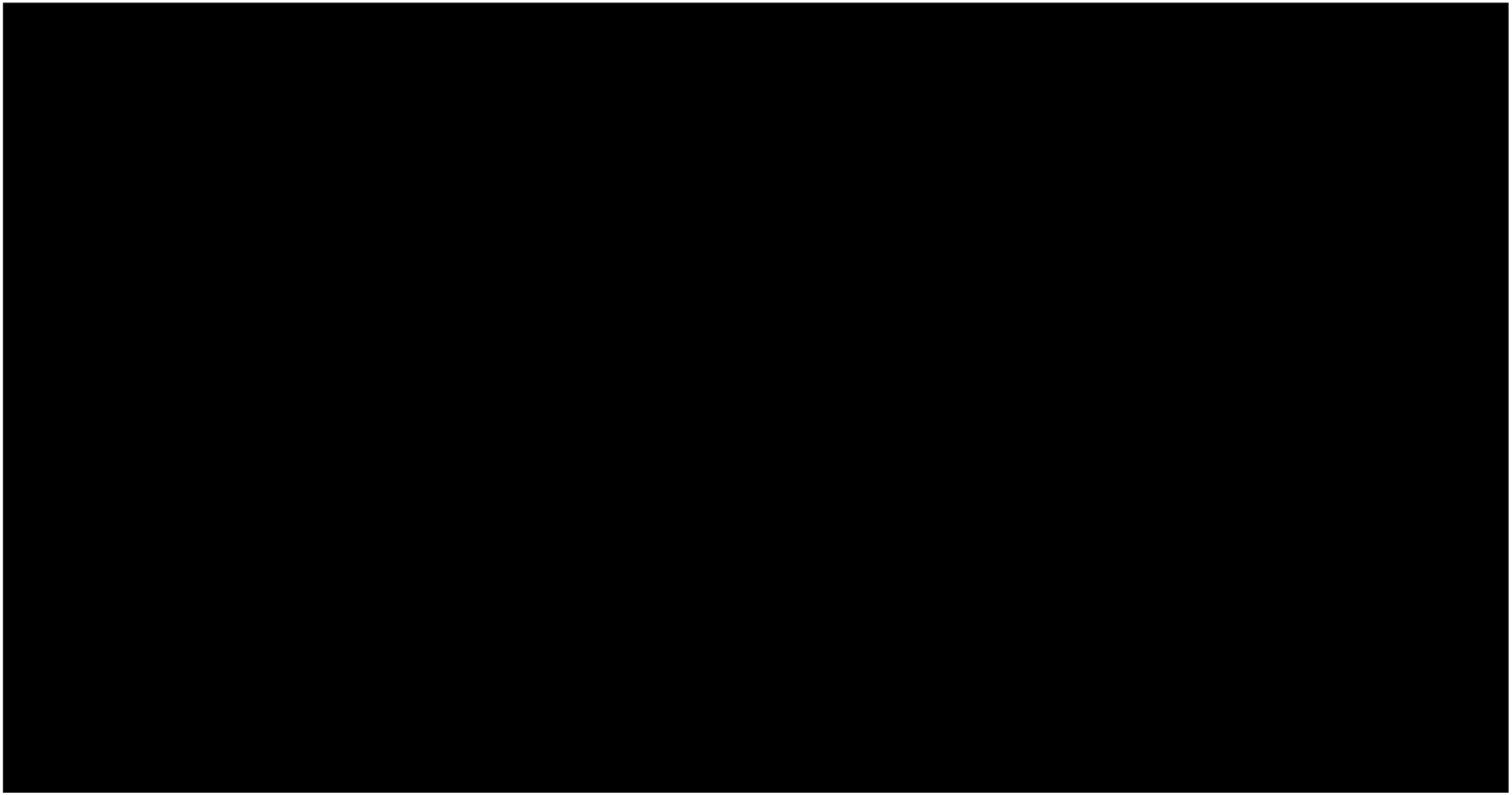
[redacted]

CDF review TA483 - Figure 1 - Kaplan-Meier of overall survival in CheckMate 017 (all randomised patients): 5-year update

Source: Company submission, figure 3

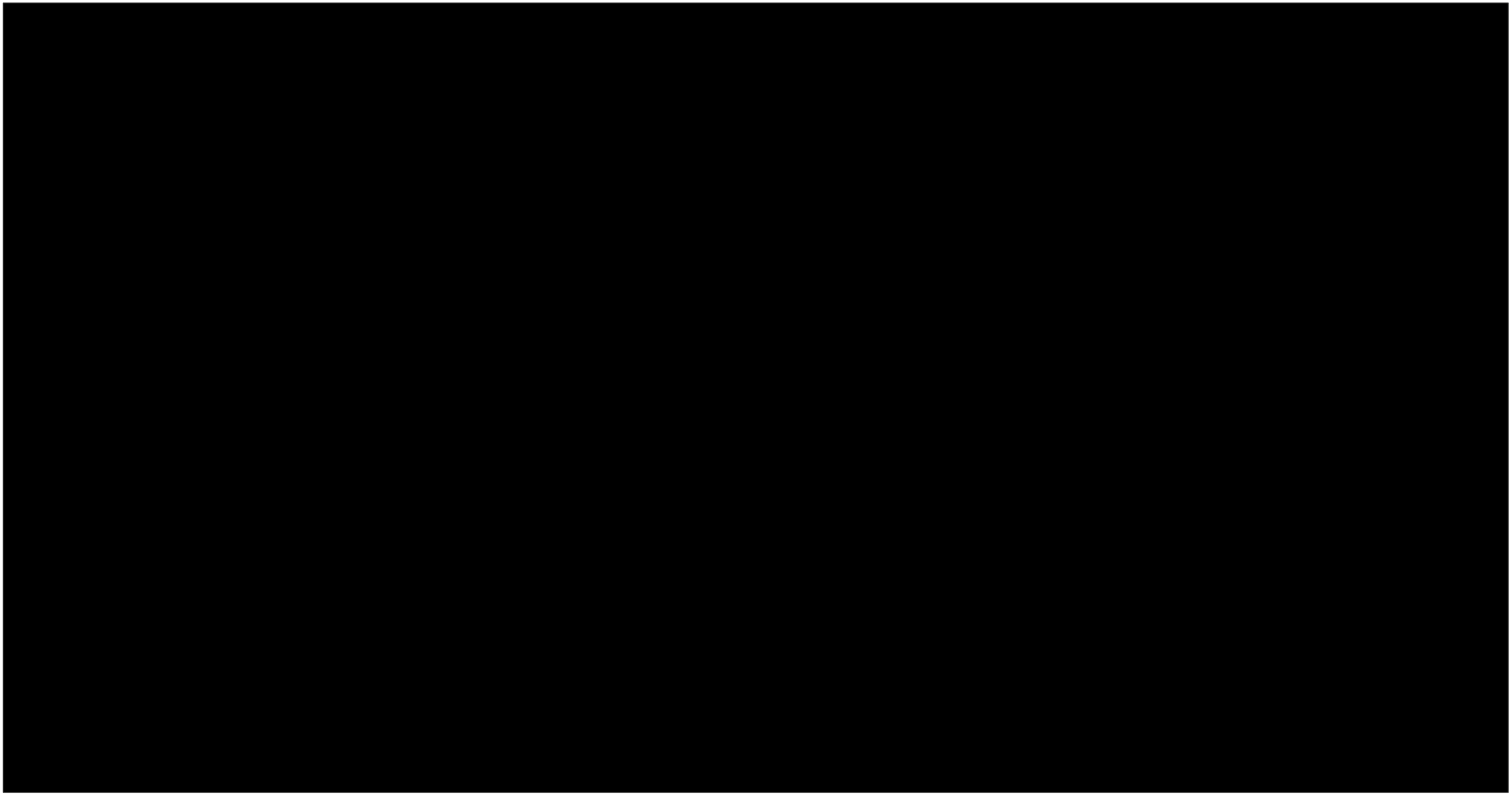
[redacted]

CDF review TA483 - Figure 2 – overall survival extrapolation distributions



[redacted] Source: Company submission, figure 20. All distributions were fitted to the updated data

CDF review TA483 - Figure 3 – progression-free survival extrapolation distributions



[redacted] Source: Company submission, figure 21. All distributions were fitted to the updated data

CDF review TA483 - Systemic Anti-Cancer Therapy (SACT) data

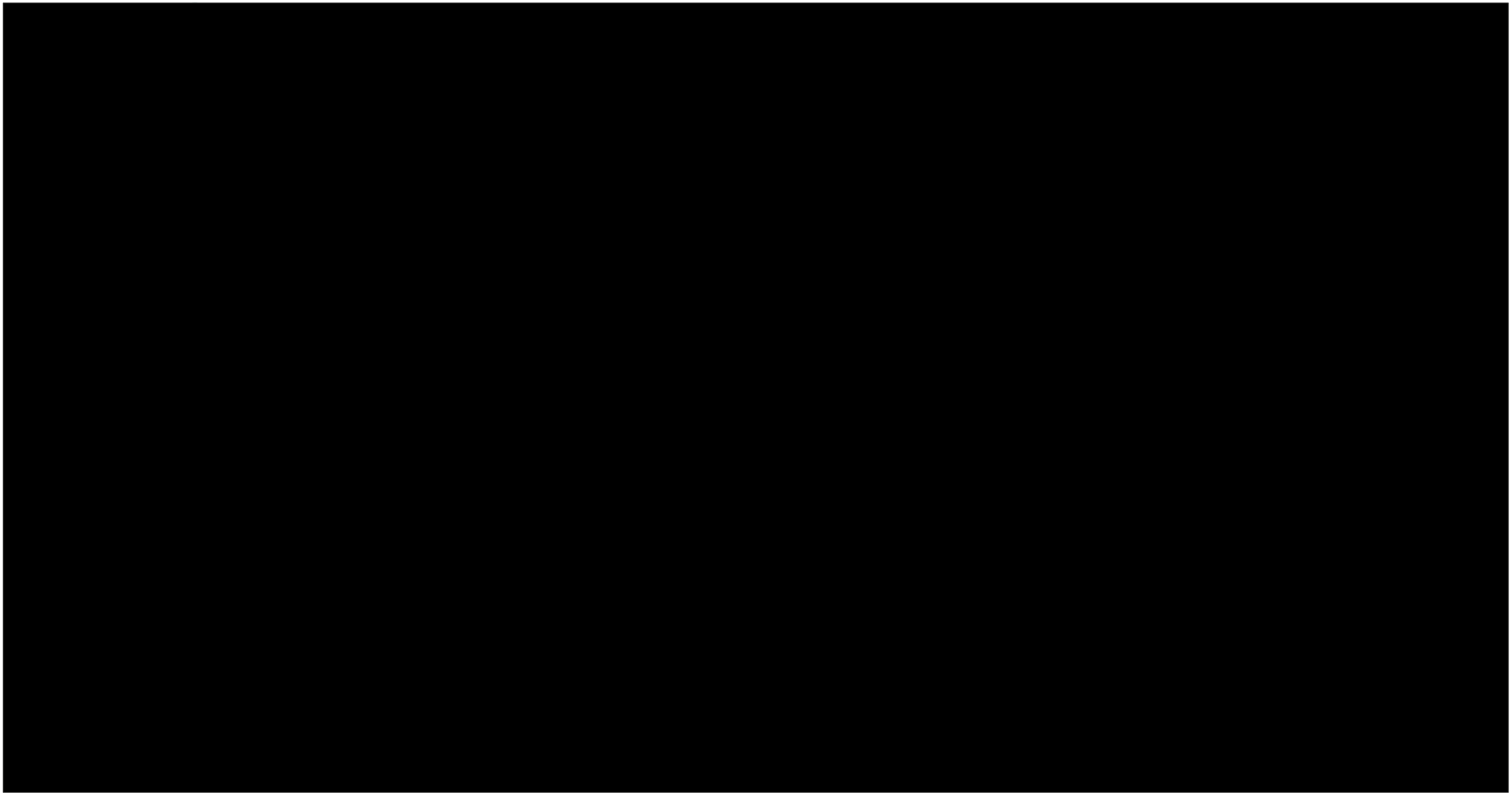
Characteristic	Patients with CDF application (n=348)
Male	230 (66%)
Age, median	70 years
PS 0 or 1	59 (17%) or 301 (71%)*
PD-L1<1%	241 (69%)
PD-L1≥1%	49 (14%)
PD-L1 not reported	58 (17%)
%completed tx by Jan 2019	278 (80%)
Median follow up time in SACT	487 days
(Range: minimum to maximum)	(5 months to 20 months)
Median treatment duration	3.5 months (95% CI: 3.0 to 4.1 months)

Survival	Estimate
Median OS	8.4 months (95% CI: 7.2 to 9.7 months)
Survival at 6 months	57% (95% CI: 51% to 62%)
Survival at 12 months	35% (95% CI: 30% to 41%)
Alive/dead at date of follow up	111/237

[redacted]

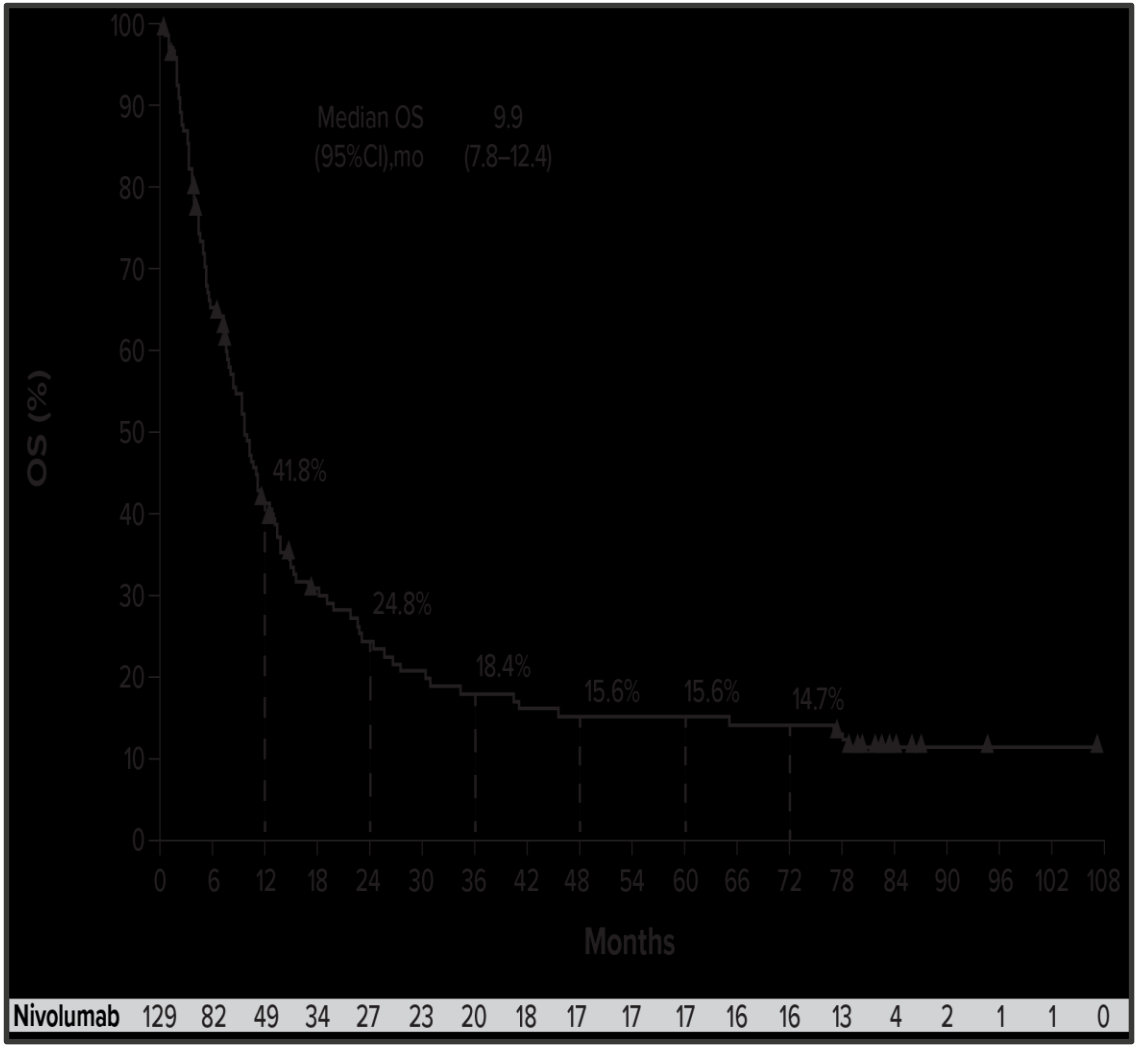
To note, no patient in SACT had been on therapy for sufficient time to reach the 2 year discontinuation rule

CDF review TA483 - Figure 4 – Kaplan-Meier for overall survival in the SACT database



[redacted] Source: Company submission, figure 11

CDF review TA483 - CheckMate-003 (not used in the model)



Source: CS figure 9

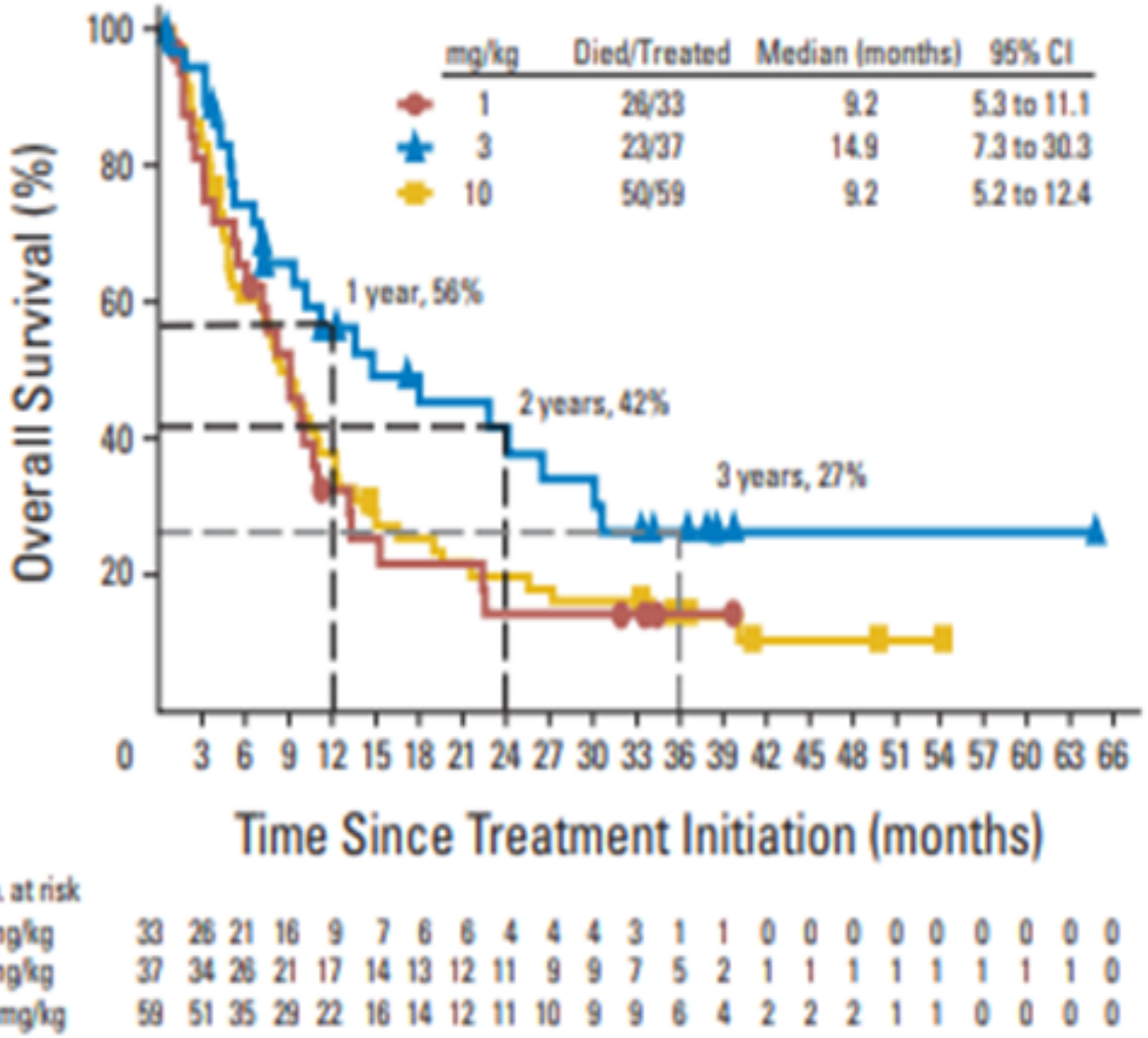
–**Background:**

- Single-arm, phase 1, dose-escalation study
- Adults with advanced or recurrent malignancies (129 patients with squamous & non-squamous NSCLC; 37 had 3 mg/kg), who had between 1 and 5 prior therapies and progression after at least 1 platinum/taxane-based chemo
- Treatment stopped after 96 weeks
- Used to validate survival extrapolations

–**Limitations:**

- Mixed population (squamous n=54/129); only 18/54 had 3 mg/kg dose
- Data censoring obscured long-term survival

CDF review TA483 - Checkmate 003



Note: 3mg/kg dose used in CheckMate 017

[redacted]

Source: Figure 1: Gettinger et al, 2015. Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-93 55, ONO-4538) in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology: 33(18)

CDF review TA483 - Checkmate 003

Response and overall survival for Squamous NSCLC

Dose mg/kg	Objective response rate		Duration of Response (months)	OS (months)	Overall Survival Rate: 1 year		Overall Survival Rate: 2 years		Overall Survival Rate: 3 years	
	n	% (95% CI)	Median (range)	Median (95% CI)	% (95% CI)	No. at Risk	% (95% CI)	No. at Risk	% (95% CI)	No. at Risk
All doses	9 of 54	16.7 (7.9 to 29.3)	NR (3.7 to 36.8)	9.2 (7.3 to 12.5)	41 (27 to 54)	20	24 (14 to 37)	12	19 (9 to 32)	6
1	0 of 15	0 (0)	0 (0)	8 (2.4 to 13.3)	29 (9 to 52)	4	14 (2 to 37)	2	0 (0)	0
3	4 of 18	22.2 (6.4 to 47.6)	NR (3.7 to 32.6)	9.5 (5.3 to NE)	49 (23 to 71)	7	35 (13 to 58)	5	28 (9 to 51)	3
10	5 of 21	23.8 (8.2 to 47.2)	19.1 (3.7 to 36.8)	10.5 (4.9 to 16.7)	43 (22 to 62)	9	24 (9 to 43)	5	18 (5 to 37)	3

Abbreviations: NR = not reported; NE = Not estimable; CI = Confidence interval

Note: 3mg/kg dose used in CheckMate 017

[redacted]

Source: Table 2: Gettinger et al, 2015. Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-93 55, ONO-4538) in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology: 33(18)

CDF review TA483 – Outstanding issues

Outstanding issues after technical engagement	Status	Tech team considerations
1. Choice of extrapolation What is the most appropriate extrapolation for overall survival? What is the most appropriate extrapolation for progression-free survival?	OS: For discussion PFS: Resolved at engagement	OS: For discussion. Company updated extrapolation is plausible. The Gompertz and spline 1 knot hazard also have a good visual fit. PFS: Company updated extrapolation is plausible. Choice of plausible extrapolation does not have a large impact on results
2. 2-year stopping rule & continued treatment benefit after nivolumab is stopped Is a 2-year stopping rule appropriate? What is the continued effect of nivolumab after treatment is stopped?	For discussion	For discussion
3. PD-L1 expression subgroups Is it appropriate to consider the full population irrespective of PD-L1 expression, and not subgroups by PD-L1 expression?	Resolved at engagement	It is appropriate to consider the full population. No clinically significant difference in OS according to PD-L1

Outstanding issues after technical engagement

Issue 1: Choice of extrapolation

- What is the most appropriate extrapolation for overall survival?

Issue 2: Continued treatment effect after nivolumab is stopped & 2-year stopping rule

- Is a 2-year stopping rule appropriate?
- What is the continued effect of nivolumab after treatment is stopped?

[redacted]

Issue 1: Choice of extrapolation (OS)

TA483 (2017) considerations

- OS extrapolated from CheckMate 017 survival data (3-year data-cut).
- DSU: the generalised gamma curve is the most appropriate extrapolation because it featured slowly decreasing hazards.
- Uncertainty due to the small number of people still alive at 36 months.
- The committee agreed that the generalised gamma curve was appropriate because the tail of the curve more closely reflected the likely continued treatment effect.

CDF review TA483: Company update

- Generalised gamma underestimates long-term OS for nivolumab.
- The spline hazard 2 knot distribution is a good fit for the survival data in both the nivolumab and docetaxel treatment arms

CDF review TA483: Technical team

- The updated survival data show that a long-term survival benefit is plausible
- It's reasonable to apply alternative functions to the new data, inclusive of the spline hazard 2 knot distribution

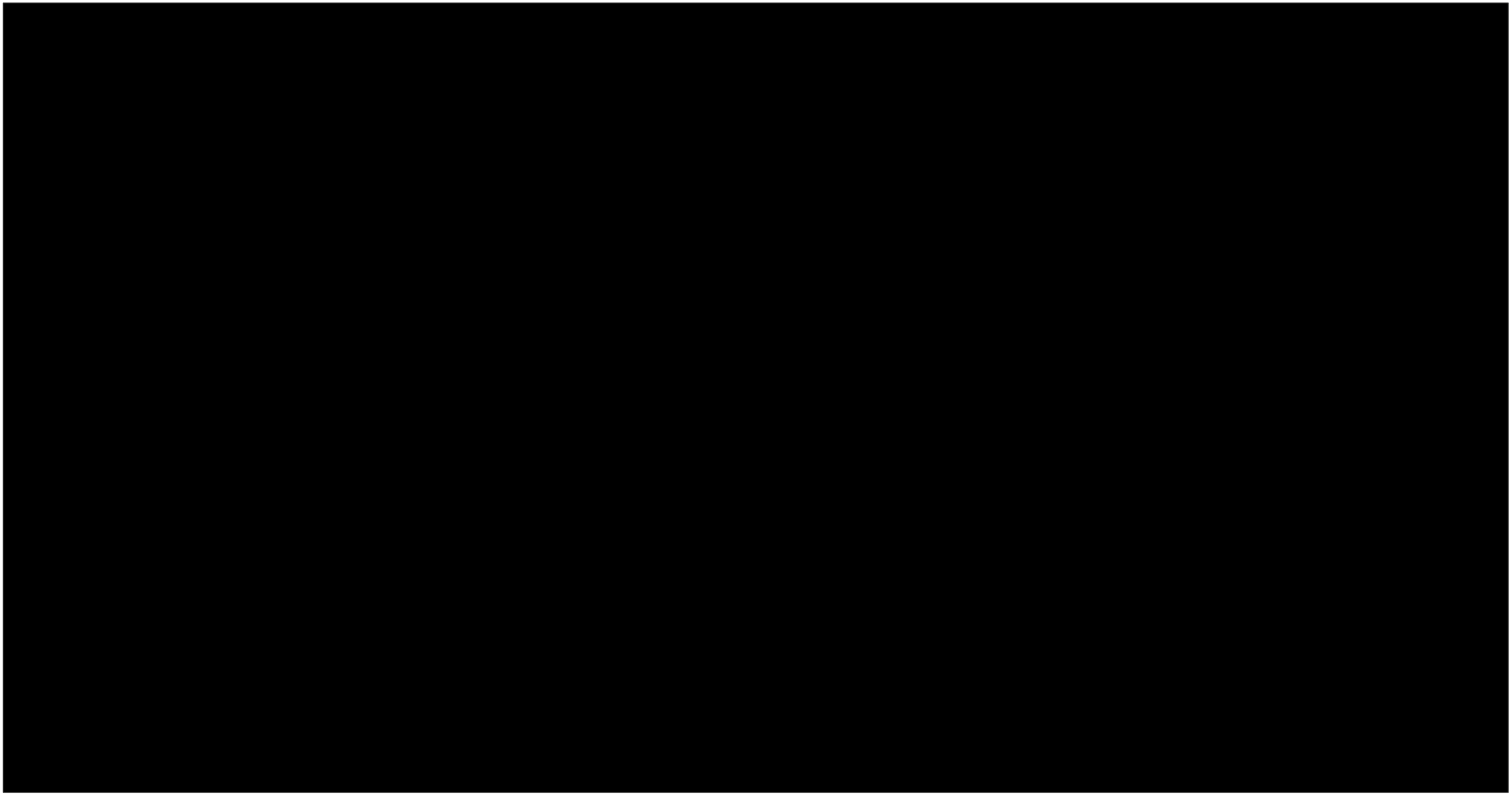
CDF review TA483: Technical engagement responses:

- **ERG:** The maturity of the OS data means that the distribution choice (amongst the models the ERG considered to be potentially appropriate) makes little difference to the cost effectiveness results.
- **Company:** SACT data shows that real world use of nivolumab follows trial data
- **ERG, technical team and company** in agreement the updated extrapolation is adequate

[redacted]

1. What is the most appropriate extrapolation for overall survival?

ERG analysis on overall survival



[redacted]

Issue 1: Proportion alive for nivolumab

Year		1	2	3	4	5	6	10	20
% on nivolumab*		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Data source		**Proportion alive at each year (95% conf. interval)**							
Kaplan-Meier	CheckMate 017 (n=135)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	SACT (n=348)	35 (30 to 41)	-	-	-	-	-	-	-
	CheckMate 003 (n=129)	42	25	18	16	16	15	-	-
	CheckMate 003 3mg/kg (n=37)	56 (38 to 71)	42 (24 to 58)	27 (12 to 43)					
Company preferred 5-yr Spline 2 knot hazard, lifetime benefit *		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-yr Spline 2 knot hazard, 3 year benefit ¥		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: all data relates to the nivolumab arm of the studies and model

* values determined by technical team using 5-year KM data in the ERG-corrected model, company base case

¥ values determined by technical team using the ERG-corrected model, company base case but with 3 years of continued treatment effect

Data sources:

Checkmate 017 data: Table 7 CS [note that KM graph ,CS figure 3, reports no.at risk: [redacted];

SACT data: page 23 CS [note that KM graph, CS figure 11, reports no. at risk: 1yr = 106/348 (30%)]

Checkmate 003: page 22 CS

[redacted]

2. Is a 2-year stopping rule appropriate?
3. What is the continued effect of nivolumab after treatment is stopped?

Issue 2: Stopping rule & continued treatment effect

TA483 committee preferred assumptions

- Recommendations for inclusion in the CDF the committee agreed that a 2-year stopping rule should be applied in the economic model.
- CheckMate 017 study protocol did not include a maximum duration of treatment, therefore the clinical evidence in the economic model was based on patients that could continue to receive nivolumab after 2 years.
- The company had an ongoing study (CheckMate 153) investigating the effect of a 1-year maximum treatment duration which could substantiate whether a stopping rule is appropriate.
- Biologically plausible that benefit from nivolumab may continue after treatment is stopped, but there was a lack of evidence to support this, and the duration was uncertain
- Based on available data, 3-year continued benefit after 2 year stopping rule was plausible

Duration: 2-year nivolumab stopping rule followed by 3-year continued benefit

[redacted]

2. Is a 2-year stopping rule appropriate?
3. What is the continued effect of nivolumab after treatment is stopped?

Issue 2: Stopping rule & continued treatment effect

CDF review TA483: Company update

- CDF review base case analysis includes a 2-year stopping rule.
- The protocol for CheckMate 017 does not include a stopping rule, so [redacted]% of patients continue to remain on nivolumab treatment at 5 years.
- The company considers that "continued follow-up of patients throughout data collection period shows no evidence of a waning of the treatment effect associated with nivolumab" and therefore model lifetime benefit of nivolumab.

CDF review TA483: Clinical/professional response

2 year stopping rule:

> "It is not an evidence based recommendation, we await the evidence from clinical trials addressing the optimal duration of these treatments."

Continued effect of nivolumab after treatment is stopped:

> "It is clinically plausible that the immune system could be 'reset' and hence benefit from treatment be maintained for years after the nivolumab is stopped at 2 years."

[redacted]

2. Is a 2-year stopping rule appropriate?
3. What is the continued effect of nivolumab after treatment is stopped?

Issue 2: 2-year stopping rule

CDF review TA483: Technical team team provisional judgement

- It is uncertain if the 2-year stopping rule remains appropriate in the absence of evidence of a continued treatment effect after discontinuation.
- Applying a 2-year stopping rule and continued treatment benefit (company base case) includes all the benefits of treatment but not all the costs of treatment
- The technical team note that CheckMate-017 did not include a stopping rule.
- Company has not submitted data from CheckMate 153 (1-year stopping rule).
- The trial evidence presented by the company does not fully rule out the possibility of a treatment waning effect occurring:
    - the length of time of any treatment effect is not known
    - The magnitude of effect over time is not known
    - some patients randomised to receive docetaxel crossed over to receive nivolumab in CheckMate 017, therefore it may not possible to determine the mortality and progression rates after treatment with nivolumab has ended.

[redacted]

2. Is a 2-year stopping rule appropriate?
3. What is the continued effect of nivolumab after treatment is stopped?

Issue 2: Response to technical engagement

CDF review TA483: Company response to Q2	CDF review TA483: ERG comments
• A two-year stopping rule has been consistently accepted in other Technology Appraisals for IO therapies, and was supported as implementable by NHSE (citing TA520 [atezolizumab in 2L NSCLC]) • A sustained treatment effect of nivolumab is a plausible assumption based on the data now available and the known mechanism of action of IO therapies, • 5-year follow-up confirms a long-term OS benefit for patients treated with nivolumab, even though patients in the docetaxel arm had switched over to nivolumab as subsequent treatment. • By 60 months, two-thirds of patients continue to show long-term benefit from the earlier treatment with nivolumab. • In CheckMate 003, nivolumab treatment was stopped after 96 weeks, and six-year survival was comparable to that in CheckMate 017 (14.7% vs. XXXX 5-year survival). In CheckMate 017, X.X% on nivolumab treatment at 2-years. • Long-term survival of nivolumab in CheckMate 017 and CheckMate 003 is very similar despite differences in duration of therapy.	There is no robust evidence to support any conclusions about the effect of nivolumab after treatment is stopped

[redacted]

3. Is a 2-year stopping rule appropriate?
4 What is the continued effect of nivolumab after treatment is stopped?

Cost-effectiveness results, company

	Total			Incremental			ICER
	costs (£)	LYG	QALYs	costs (£)	LYGs	QALYs	(£/QALY)
1a) Replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry with CDF PAS							
Nivolumab	XXXX	XXXX	XXXX				
Docetaxel	XXXX	XXXX	XXXX	£23,153	0.80	0.46	£49,992
1b) With new operational PAS							
Nivolumab	XXXX	XXXX	XXXX				
Docetaxel	XXXX	XXXX	XXXX	£31,881	0.80	0.46	£68,838
2) Incorporating updated OS (generalised gamma) and PFS (hybrid exponential) fitted to 5-year CheckMate-017 K-M data							
Nivolumab	XXXX	XXXX	XXXX				
Docetaxel	XXXX	XXXX	XXXX	£29,683	0.66	0.43	£69,647
3) Company base case: OS (2-knot spline hazards model), PFS (1-knot spline hazards model) with 2-year stopping rule and continued treatment effect.							
Nivolumab	XXXX	XXXX	XXXX				
Docetaxel	XXXX	XXXX	XXXX	£31,281	1.49	0.88	**£35,657**

Notes:

- Nivolumab flat dose used in all scenarios.
- ICERs reported from original company submission (uncorrected model)

[redacted]

Issue 2: additional analysis by company

- Company: When using 2-year stopping rule, current model assumes all nivolumab patients switch to docetaxel hazards after additional 3 years of benefit. Considers this an abrupt & implausible shift in the modelled survival curve
- Scenario analyses show impact of adjusting the proportion of patients switching to docetaxel OS hazard, and assuming longer continued benefit in non-switchers
  - 49% considered most relevant based on proportion in CheckMate 017 with complete/partial response or stable disease

Proportion	Duration of additional benefit after 3 years (X)*			
	3 years (total: 6 yrs)	5 years (total: 8 yrs)	10 yrs (total: 13 yrs)	Lifetime (total: 20 yrs)
0%	£40,168	£40,168	£40,168	£40,168
25%	£39,554	£39,317	£39,058	£39,004
49%	£38,988	£38,527	£37,997	£37,883
75%	£38,400	£37,734	£36,894	£36,705
100%	£37,857	£37,024	£35,976	£35,710

* New analysis not checked by ERG due to late submission

[redacted]

Cost-effectiveness results

- The ERG did not consider that any amendments could be made to the company model or company parameter choices that would result in a more accurate estimate of cost effectiveness.

- The technical team present 6 scenarios; all of which use the ERG corrected model and the updated 5 year data to fit extrapolations.

- ERG provided further analyses which evaluated the ICER under different plausible OS extrapolations and without the stopping rule.

[redacted]

CONFIDENTIAL

Cost-effectiveness results, technical team

Deterministic analysis	Total costs (£)	LYG	QALYs	Incremental costs (£)	LYGs	QALYs	ICER (£/QALY)
1. Corrected company base case (overall survival extrapolated using a 2 spline knot hazard)							
Nivolumab	XXXX	XXXX	XXXX	£31,275	1.48	0.88	£35,710
Docetaxel	XXXX	XXXX	XXXX				
2. Committee preferred assumptions from TA483 with updated 5-year survival curves							
Nivolumab	XXXX	XXXX	XXXX	£30,096	0.66	0.43	£70,617
Docetaxel	XXXX	XXXX	XXXX				
3. Corrected company base case with overall survival extrapolated using generalised gamma							
Nivolumab	XXXX	XXXX	XXXX	£27,920	0.70	0.52	£53,881
Docetaxel	XXXX	XXXX	XXXX				
4. Corrected company base case with 3-year continued effect after stopping nivolumab at 2-years (no nivolumab costs after 2 years)							
Nivolumab	XXXX	XXXX	XXXX	£30,206	1.18	0.75	£40,168
Docetaxel	XXXX	XXXX	XXXX				
5. Corrected company base case with 3-year continued effect and 5 year stopping rule							
Nivolumab	XXXX	XXXX	XXXX	£39,330	1.18	0.75	£52,300
Docetaxel	XXXX	XXXX	XXXX				
6. Tech team preferred: Corrected company base case with removal of stopping rule (nivolumab costs and treatment effect from trial)							
Nivolumab	XXXX	XXXX	XXXX	£43,163	1.48	0.88	£49,284
Docetaxel	XXXX	XXXX	XXXX				

ICER run by the technical team using the ERG's corrected model. Please note this table has been updated since that presented in the technical report sent for technical engagement.

Cost-effectiveness results, technical team

Overview of assumptions for technical team ICERs, all analyses undertaken using ERG corrected model and with extrapolations fitted to the updated 5 year data

Scenario	ICER	PFS	OS	Stop rule	Cont. effect
1. Company assumptions	£35,710	spline 1-knot hazard	spline 2-knot hazard	2 years	lifetime
2. TA483 committee preferred assumptions	£70,617	trial data + exponential	generalised gamma	2 years	3 years
3. Company assumptions using generalised gamma for OS	£53,881	spline 1-knot hazard	generalised gamma	2 years	lifetime
4. Company assumptions using 3-year effect	£40,168	spline 1-knot hazard	spline 2-knot hazard	2 years	3 years
5. Company assumptions using 3-year effect, costs stop after 5 years	£52,300	spline 1-knot hazard	spline 2-knot hazard	5 years	3 years
6. Company assumptions with removal of stopping rule (nivolumab costs and treatment effect from trial)	£49,284	spline 1-knot hazard	spline 2-knot hazard	lifetime	lifetime

Cost-effectiveness results

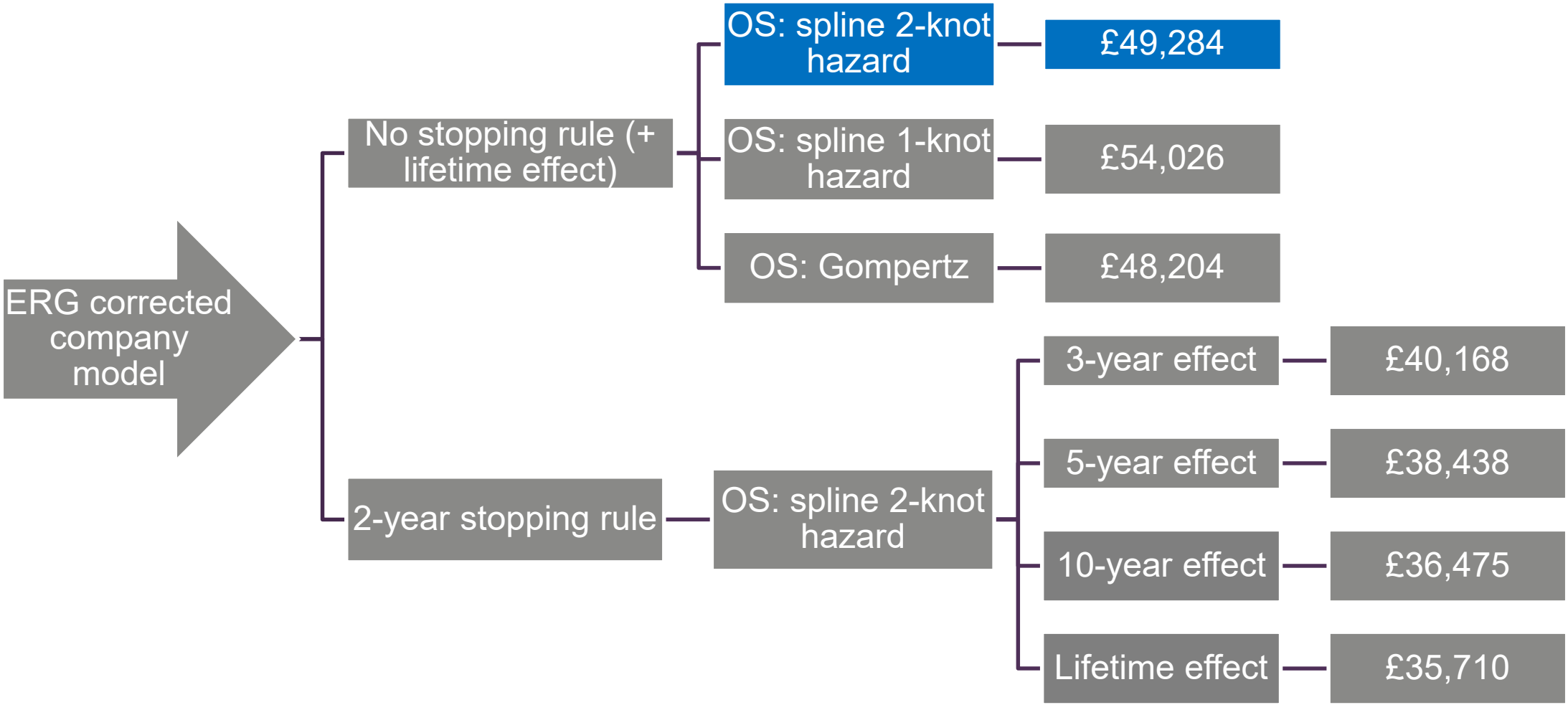
Deterministic analysis	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
OS extrapolated with 5-year spline 2-knot hazard (company preferred extrapolation)							
Nivolumab	XXXX	XXXX	XXXX				
Docetaxel	XXXX	XXXX	XXXX	£43,163	1.482	0.876	£49,284
OS extrapolated with 5-year spline 1-knot hazard (ERG scenario)							
Nivolumab	XXXX	XXXX	XXXX				
Docetaxel	XXXX	XXXX	XXXX	£42,381	1.271	0.784	£54,026
OS extrapolated with 5-year Gompertz (ERG scenario)							
Nivolumab	XXXX	XXXX	XXXX				
Docetaxel	XXXX	XXXX	XXXX	£43,756	1.587	0.908	£48,204

All analyses have been carried out using:

- CheckMate-057 trial 5-year data
- Progression free survival (PFS) modelled using the company preferred spline 1-knot hazard function
- Nivolumab flat dose
- No stopping rule
- Cost of nivolumab estimated using the Patient Access Scheme (PAS) price
- ERG corrected company model.

[redacted]

Scenario: with and without stopping rule



[redacted] Note: ICERs calculated by tech team in company model with ERG correction

Unresolvable uncertainty

From table 3 technical report → these are areas of uncertainty that cannot be resolved. Committee should be aware of these when making its recommendations.

Issue	Likely impact on ICER
Change of dosing schedule In the TA483 appraisal, dosing was weight based (3mg/kg every 2 weeks) but this has since changed in the summary of product characteristics to a flat dose of 240mg every 2 weeks. The company assume that this dose will have equivalent clinical effectiveness.	Reversing this change in dosing regimen decreases the company base case ICER to £35,570 per QALY gained.
[redacted]	[redacted]

[redacted] Note: *ICERs calculated by tech team in ERG corrected model.

Innovation, Equality and End-of-life

- Innovation
- End of Life
- Equality considerations

No changes identified in CDF review to date for these TA483 guidance decisions

Key issues

Issue 1: Choice of extrapolation

- What is the most appropriate extrapolation for overall survival?

Issue 2: Continued treatment effect after nivolumab is stopped & 2-year stopping rule

- Is a 2-year stopping rule appropriate?
- What is the continued effect of nivolumab after treatment is stopped?

[redacted]