NICE National Institute for Health and Care Excellence

Slides for public observer – Redacted

Nivolumab for treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review of TA484)

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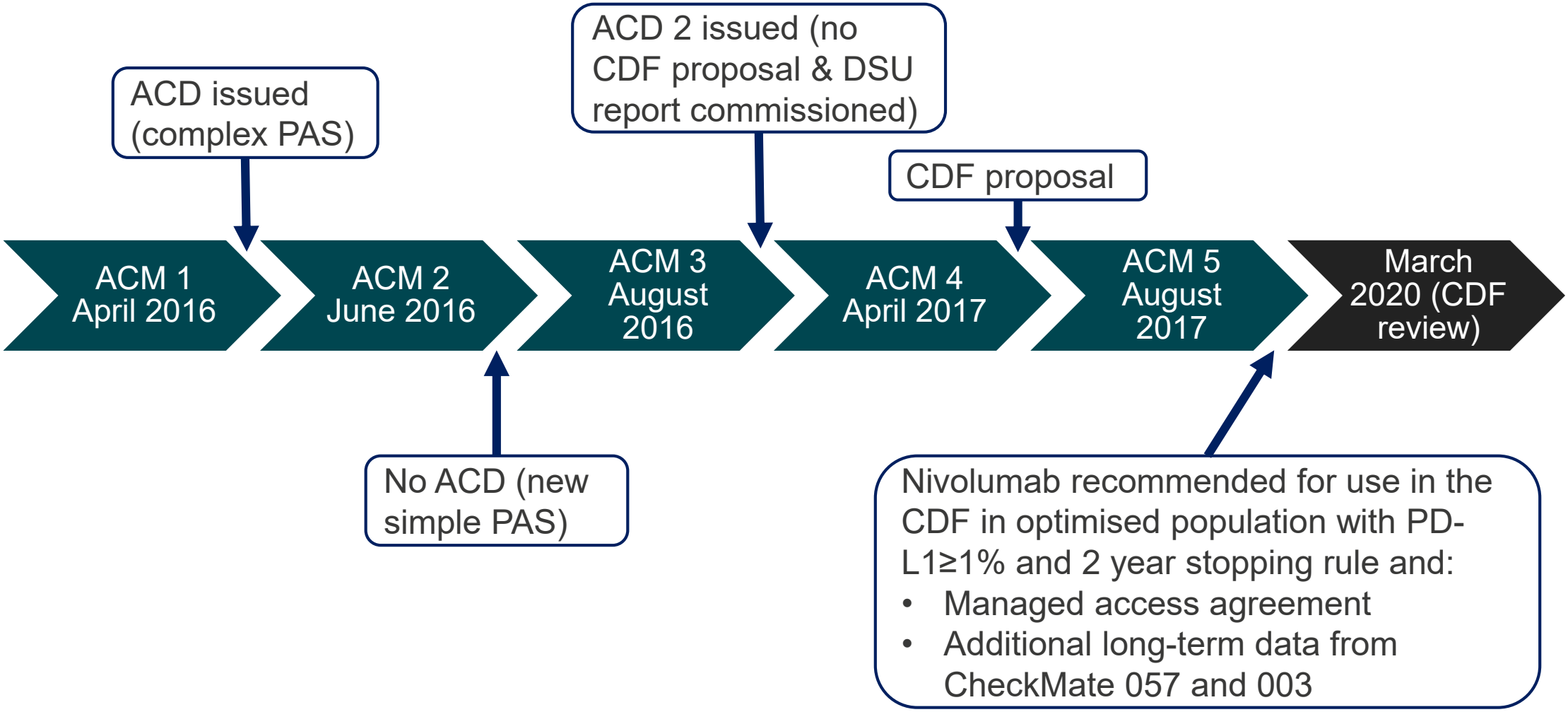
Company: BMS

CDF review committee meeting 18th March 2020

Summary of original appraisal TA484



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Appraisal background

Nivolumab marketing authorisation: treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

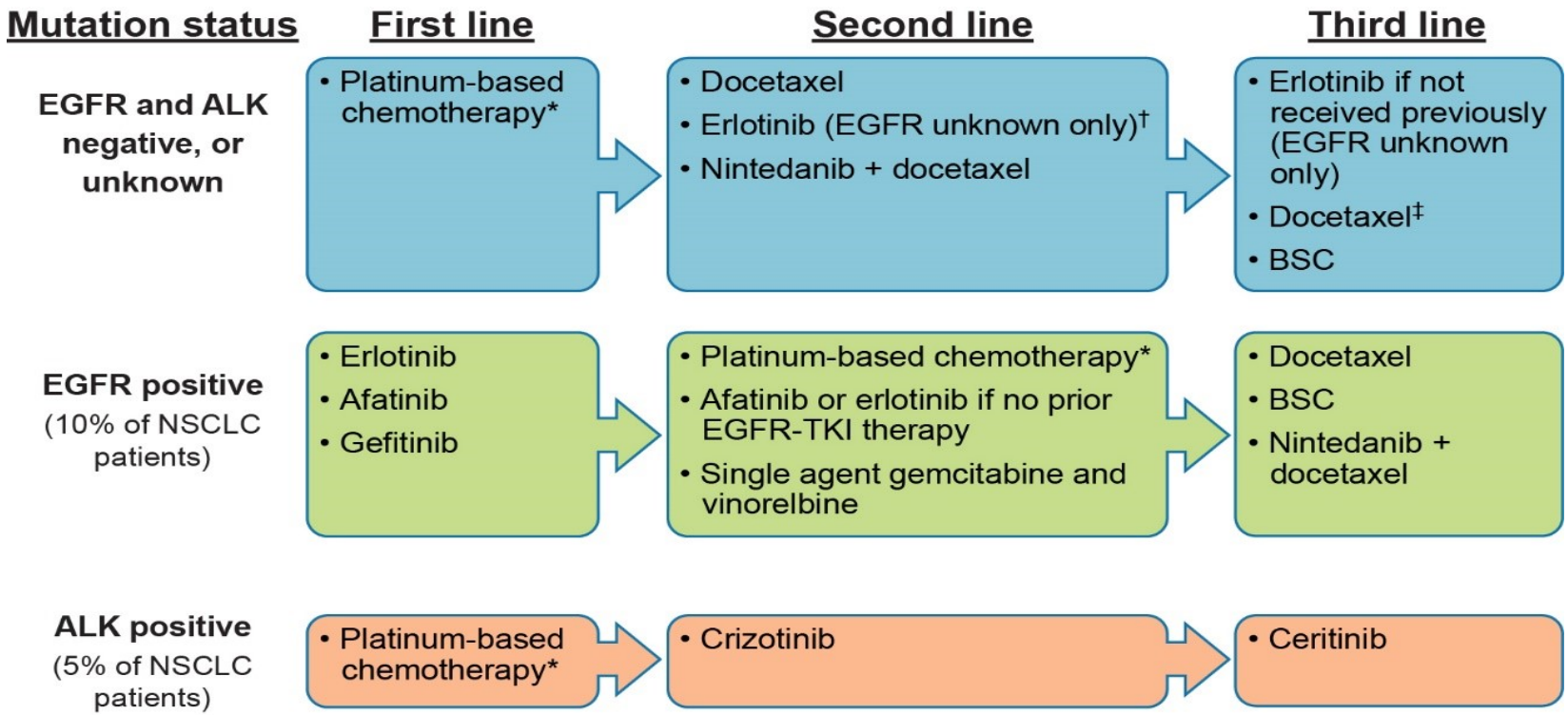
TA484 recommendation: Nivolumab is recommended in CDF for locally advanced or metastatic **non-squamous NSCLC** after chemotherapy only if:

- tumours are **PD-L1 positive**
- nivolumab is stopped at 2 years of uninterrupted treatment, or disease progression,
- the conditions in the managed access agreement are followed

	Original appraisal (TA484)	Current CDF review (ID1572)
Population	CDF recommendation restricted to PD-L1 positive disease	Company include analyses for ITT population, PD-L1 ≥1% & PD-L1 <1% **Only PD-L1≥1% is relevant**
Comparator	• nintedanib plus docetaxel (for adenocarcinoma) • docetaxel monotherapy • BSC (no ICERs presented)	Company only compare nivolumab with docetaxel monotherapy
Clinical data	3-year data from CheckMate 057	• 5-year data from CheckMate 057 • 6-year data from CheckMate 003 • SACT data (n=43, Sept 2017 to Dec 2018)

[redacted]

Treatment pathway from TA484 for non-squamous NSCLC



PD-L1≥1%

1st line: Pembrolizumab for PD-L1≥50% (TA557, Jan 2019; TA531, July 2018) Platinum-based chemo (TA181, Sept 2009)

Previously treated disease:
Nivolumab (TA484, Nov 2017)
Atezolizumab (TA520, May 2018)
Pembrolizumab (TA428, Jan 2017)
Docetaxel ± nintedanib (TA347, July 2015)

All technology appraisals published after TA484

CDF review scopes do not change, so these TAs are not considered in current CDF review

[redacted]

CDF review TA484 - Patient & Professional Perspectives

- Patients and professionals want treatments that are effective, minimally disruptive, and improve quality of life
- Nivolumab is life-changing
  - Patients want to move on with their lives and want to know is the treatment necessary or could they try a break
  - If I stop treatment, could I return to this and try again?
- Inflexible treatment lines
  - Patients are increasingly protesting about restricted treatment lines
  - They want flexibility about treatments.

Right now, nobody can confidently predict your potential for survival. The curve isn't known for people who are responding like you

I feel shackled to cancer. I wonder if a treatment break would help me to put the last 5 years behind me and move on with my life.

We may as well have a consultation with an algorithm.

[redacted]

CDF review TA484 PD-L1 ≥1% Key considerations

	Committee preferred in TA484	Company base case in current CDF review	Technical team
Comparator	Docetaxel monotherapy, nintedanib plus docetaxel (for adenocarcinoma) & BSC	Docetaxel monotherapy	Nintedanib + docetaxel may be relevant for people with adenocarcinoma (~70% of non-squamous NSCLC)
OS extrapolation	Hybrid exponential using 3 year KM data from CheckMate 057 then exponential curve	Lognormal curve fitted to 5-year KM data (scenario: spline with 3 knots)	The company's extrapolations based on updated 5-year OS and PFS data from CheckMate 057 are plausible, but so are some alternative curves (spline 3-knot for OS).
PFS extrapolation	Hybrid exponential using 2-year KM data then exponential curve	Spline normal 1 knot fitted to the 5-year KM data	
Utility values	• progressed disease **0.569** (midpoint of company & ERG) • prog-free **0.713**	• progressed disease **0.688** (updated from CheckMate 057) • prog-free **0.713**	Prefers utilities from TA484 because updated trial values are still likely to be influenced by selection bias

Note: Orange boxes issues not resolved at technical engagement and for discussion

[redacted]

CDF review TA484 PD-L1 ≥1% Key considerations

	Committee preferred in TA484	Company base case in current CDF review	Technical team
Stopping rule and continued treatment benefit	• Nivolumab's effectiveness is continued for **3 years** after treatment is stopped (at 2 years) • Docetaxel effectiveness applied thereafter	• 2-year stopping rule and **lifetime** treatment effect for nivolumab after it is stopped	2-year stopping rule is not evidence based and may be inappropriate

[redacted]

CDF review TA484 PD-L1 ≥1%
Key clinical data sources

Primary data source: CheckMate 057

582 adults with metastatic or recurrent non-squamous cell NSCLC after prior platinum-based chemotherapy

- Nivolumab (n =292, 3 mg/kg every 2 weeks) → PD-L1≥1% (n=122)
- Docetaxel (n=290, 75mg/m^2 every 3 weeks) → [redacted] crossed over to nivolumab during extension (5 year) & 7 had post-study nivolumab → PD-L1≥1% (n=123)

[redacted]

Secondary data sources (not used in model)

CheckMate 003

- single-arm, phase 1, dose-escalation study
- adults with advanced or recurrent malignancies (129 patients with squamous [n=54] & non-squamous [n=74] 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

SACT data

- 43 patients had nivolumab on CDF from Sept 2017 to Dec 2018
- used to validate survival extrapolations and assess duration of treatment in clinical practice

CDF review TA484 PD-L1 ≥1% Key clinical evidence

Outcome	Original TA484		CDF review			
	CheckMate 057 (3-year data)		CheckMate 057 (5-year data)		CheckMate 003	SACT
	Niv (n=122)	Doc (n=123)	Niv (n=122)	Doc (n=123)	Niv 3mg/kg (n=19)	Niv (n=43)
Median OS	17.7†	9.0†	[redacted]	[redacted]	18.2 (5.2 to 30.8)	9.2*
OS	HR 0.59 (0.43 to 0.82)**		[redacted]		N/A	N/A
1-year OS	NR		[redacted]	[redacted]	62% (37 to 80)	43% (28 to 58)
3-year OS	NR		[redacted]	[redacted]	24% (6 to 48)	NR
5-year OS	N/A		[redacted]	[redacted]	NR	NR
Median PFS	4.2	4.5	NR	NR	NR	NR
PFS	HR 0.70 (0.53 to 0.94)**		NR	NR	NR	NR

All data reported in months unless otherwise indicated. CheckMate 003 data is for non-squamous NSCLC only
*insufficient events for confidence interval; ** 1-year data; † based on 18-month data; ¥ estimated using 5-year KM plot

CDF review TA484 PD-L1 ≥1%
Outstanding issues after technical engagement

No issues were resolved during technical engagement

- **Issue 1:** Comparator
- **Issue 2:** Extrapolation of OS & PFS
- **Issue 3:** Utility values
- **Issue 4**: 2-year stopping rule & continued treatment benefit after nivolumab is stopped

[redacted]

Issue 1: Comparator

TA484 committee preferred

- Nintedanib + docetaxel is a relevant comparator for people with adenocarcinoma (70% of non-squamous NSCLC) despite high toxicity. Adenocarcinoma 90% of people in CheckMate 057
- Nintedanib + docetaxel has plausible potential to be cost effective for PD-L1 ≥ 1%
- BSC also relevant but no cost-effectiveness results presented so no recs made
- Based on uncertain clinical effectiveness data (unadjusted indirect comparison)

Nintedanib plus docetaxel is a relevant comparator

Company update (CDF review TA484)

- ICERs only presented for nivolumab vs docetaxel (not nivolumab vs. nintedanib + docetaxel)

Docetaxel is most appropriate comparator

ERG (CDF review TA484)

- Clinical advice to ERG is that nintedanib + docetaxel is not commonly used in NHS

Technical team (CDF review TA484)

- Nivolumab may not be a cost-effective treatment option for people with non-squamous NSCLC & adenocarcinoma with PD-L1 ≥1%

Nintedanib plus docetaxel may be a relevant comparator

CDF review technical engagement responses:

- **RCP**: With the introduction of immunotherapy, nintedanib + docetaxel is more likely to be used at **third line** than second line**,** and only in <5% of people with NSCLC
- **Company**: Nintedanib rarely used second line as immunotherapies recommended. Committee accepted in TA520 (atezolizumab second line) that it's only used for small number of people

[redacted]

Is nintedanib plus docetaxel also a relevant comparator?

Issue 2: Extrapolation of OS and PFS

TA484 committee preferred

- Prefer ERG's hybrid approach for full pop:
  - mixed hybrid model: KM data for first 18 months then exponential curve & assume 25% have post-progression nivolumab
- Uncertainty in company's hybrid extrapolations for PD-L1 ≥1% subgroup → approach differed to ERG preferred (ERG: split based on post-progression treatment & later timepoint to fit exponential curve)
- Accept DSU correction to cap PFS to OS when PFS and OS curves cross

OS & PFS: Hybrid exponential fitted to 3-year data

Company update (CDF review TA484)

- Committee's preferred hybrid exponential not a good fit to updated 5-year data
- Use appropriate extrapolations fitted to 5-year data

OS: Lognormal curve fitted to 5-year KM
PFS: Spline normal 1 knot to 5-year KM

Technical team (CDF review TA484)

- Uncertainties relate to reproducing committee's preferred hybrid model (TA484). Less important if company's approach is accepted

Company's updated extrapolations are plausible but so are some alternatives

CDF review technical engagement responses:

- **RCP**: Pooled analysis of 5 year data suggest survival of up to 15% for nivolumab, therefore we estimate 10+ year survival to be around 5%
- **Company**: Lognormal for OS selected based on statistical fit but poor fit to middle and tail of Niv arm may lead to underestimation of long-term survival. Scenario with 3-knot hazard ↓ ICERs

Issue 2: 5-year KM data, PD-L1 ≥1%

[redacted]

[redacted]

Issue 2: Updated OS extrapolation, PD-L1 ≥1%

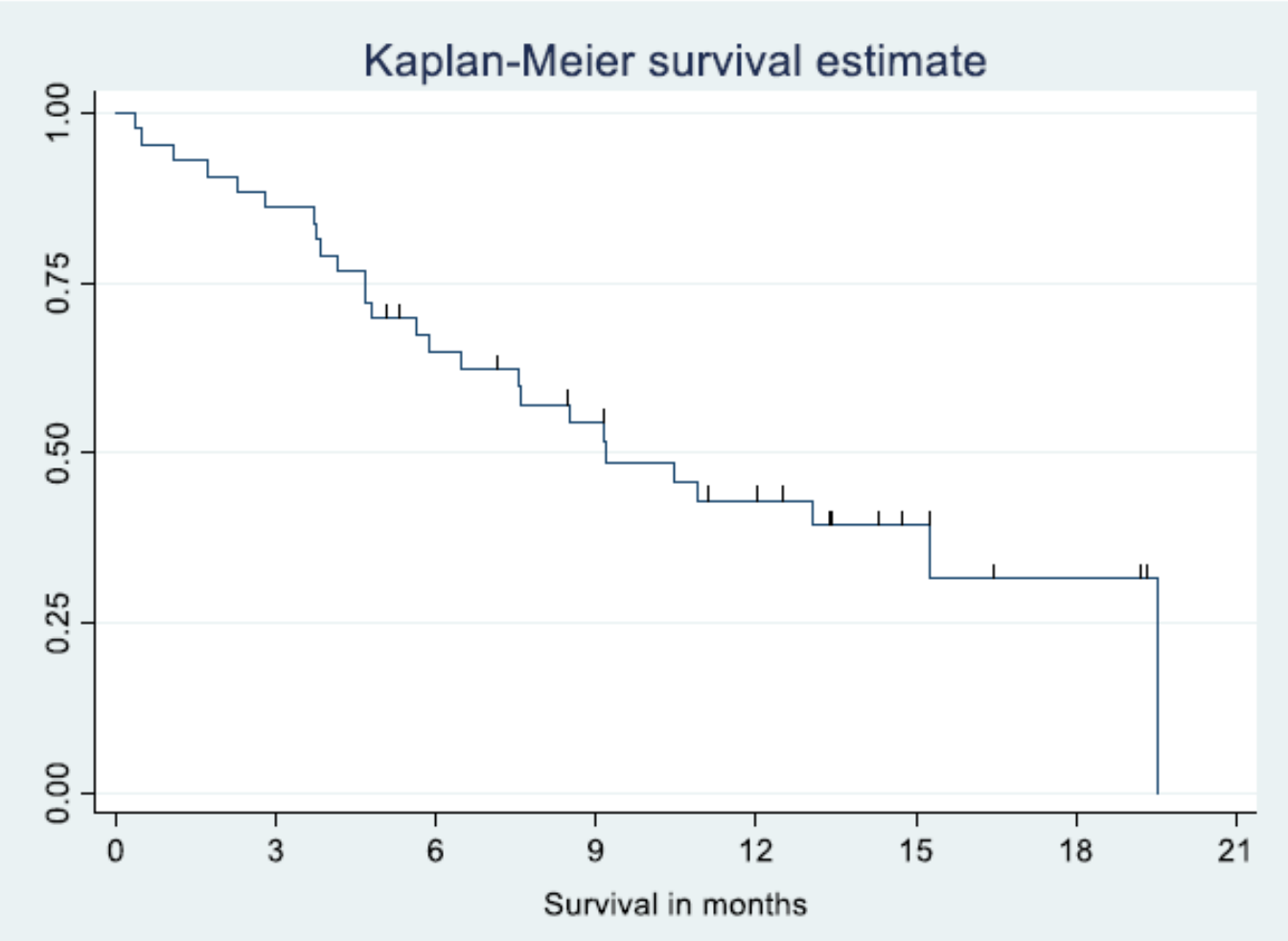
[redacted] Data source: figure 24 in CS

Issue 2: Company scenario OS extrapolation, PD-L1 ≥1%

[redacted]

[redacted] Data source: ERG chart following PMB

Issue 2: Updated OS from SACT, PD-L1 ≥1%



Time intervals (months)	0-20	3-20	6-20	9-20	12-20	15-20	18-20
Number at risk	43	37	26	20	13	6	3
Censored (alive)	17	17	15	13	10	4	2
Events (death)	26	20	11	7	3	2	1

- SACT N=43, median OS 9.2 months, no patient in SACT up to 2 year stopping rule
- Median treatment duration 4.1 months (95% CI 3.0 to 8.3)
- 47% (31 to 61%) having nivolumab at 6 months
- 21% (9 to 37%) having nivolumab at 12 months
- At data cut off 72% (n=31) no longer on treatment
  - 55% progression, 13% toxicity, 3% patient choice, 6% died on treatment
- Patient flagged as either:
  - Dead (event) at date of death recorded
  - Alive (censored) at date patients tracked for vital status

Issue 2: Proportion alive in nivolumab arm, PD-L1 ≥1%

Year	1	2	3	4	5	6	10	20
% on nivolumab *								

Data source	Proportion alive at each year (95% confidence interval)							
CheckMate 057 (n=122)							-	-
SACT (n=43)	43 (28 to 58)	-	-	-	-	-	-	-
CheckMate 003 (n=129)							-	-
CheckMate 003 (n=19 non-squamous & 3mg/kg)	62 (37 to 80)	48 (22 to 69)	24 (6 to 48)	-	-	-	-	-
Company lognormal curve for PD-L1 ≥1% ¥								
Hybrid exponential (TA484) 21 month cut **								

* values determined by technical team using 5-year KM data in the ERG-corrected model for PD-L1≥1%

¥ values determined by technical team using the ERG-corrected model (company preferred extrapolation and lifetime continued treatment effect after stopping nivolumab [see issue 4])

** values determined by technical team using company's clarification model

Data source: Tables 8 and 9 clarification response and figure 9 in company submission

Tech team: Committee preferred hybrid extrapolation from TA484 does not represent the data well after 24 months. The continued treatment effect after nivolumab is stopped has a larger impact compared with parametric OS model (see issue 4).

Issue 2: Updated PFS extrapolation, PD-L1≥1%

[redacted]

What is the most appropriate model for OS and PFS?

[redacted]

Issue 3: Utility values

TA484 committee preferred

- EQ-5D-based values available from CheckMate 057 (on study assessment, follow up within 100 days of last dose, and survival assessments [every 3 months for 1st year then 6-monthly])
- Decline in EQ-5D completion rate (48% & 41% Niv and Doc at 12 weeks to 36% and 21% at 24 weeks) means post-progression values may influenced by selection bias
- Committee preferred mid-point between ERG (0.480) and company (0.657) for post-progression value

Prog-free: 0.713 **Progressed:** 0.569

Company update (CDF review TA484)

- Use updated 5-year post-progression utility value from CheckMate 057

Prog-free: 0.713 **Progressed:** 0.688

ERG (CDF review TA484)

- Company has not provided evidence for deviating from TA484 preferred values

Technical team (CDF review TA484)

- Updated utility values from CheckMate 057 would still be influenced by selection bias
- Prefers to use TA484 values

Prog-free: 0.713 **Progressed:** 0.569

CDF review technical engagement responses:

RCP: Prefers to use previously accepted utility values from TA484

Company: Previously accepted utilities somewhat arbitrary (ERG based values from Van den Hout 2006 Dutch study of alternative palliative radiotherapy for people with NSCLC). Preferable to use utilities based on recent EQ-5D from trial rather than assumptions

[redacted]

Which post-progression utility value should be used?

Issue 4: Stopping rule & continued treatment effect

TA484 committee preferred
• Company's proposed 2-year stopping rule accepted by committee after consultation comments from NHS England and other consultees suggested it was acceptable to patients and clinicians and would be implementable • Biologically plausible that benefit from nivolumab may continue after treatment is stopped, but there is a lack of evidence to support this, and the duration is uncertain • Based on available data, 3-year continued benefit after 2 year stopping rule is plausible • Accept DSU correction to apply docetaxel treatment effect to PFS as well as OS after nivolumab is stopped at 2 years
Duration: 2-year nivolumab stopping rule followed by 3-year continued benefit

Company update (CDF review TA484)
• 5-year data from CheckMate 057 confirms long-term OS benefit for on nivolumab arm, even though only [redacted] remain on treatment at 5 years • 6-year data from CheckMate 003 confirms long-term OS benefit for nivolumab (treatment stopped at 96 weeks), similar results to CheckMate 057
Duration: 2-year nivolumab stopping rule followed by lifetime (20-year) continued benefit

ERG (CDF review TA484)	• No robust evidence demonstrating the optimal duration of treatment with nivolumab

[redacted]

Issue 4: Stopping rule & continued treatment effect

Technical team

- No evidence to support a lifetime treatment effect after nivolumab is stopped at 2 years. OS data from CheckMate 057 are higher than SACT. Data from CheckMate 003 are limited due to:
  - mixed population (non-squamous n=74/129); only 19/74 had 3 mg/kg dose
  - data censoring obscured long-term survival
  - OS was lower compared with the PD-L1 ≥1% subgroup of CheckMate 057
- Company has not submitted data from CheckMate 153 (1-year stopping rule).
- Company's model does not apply docetaxel **PFS** after committee's preferred 3-year continued nivolumab effect, despite DSU correction being accepted in TA484
- Given lack of evidence it is uncertain if 2-year stopping rule remains appropriate (not in SPC)

Duration: Stopping rule may not be appropriate

Technical engagement responses:

RCP: 2-year stopping rule is not evidence based and we are awaiting results from trials addressing optimal duration. It is clinically plausible that the immune system could be 'reset' and treatment benefit be maintained for years after nivolumab is stopped.

Company: 2-year stopping rule is appropriate and accepted in other appraisals. Survival rate of [redacted] at 5-years when only [redacted] remain on nivolumab suggests continued benefit. Switching to docetaxel hazard at 3 years causes a clinically implausible 'kinked' OS curve → not appropriate.

Issue 4: Proportion alive in nivolumab arm, PD-L1 ≥1%

Year		1	2	3	4	5	6	10	20
% on nivolumab *		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Data source		**Proportion alive at each year (95% conf. interval)**							
Kaplan-Meier	CheckMate 057 (n=122)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
	SACT (n=43)	43 (28 to 58)	-	-	-	-	-	-	-
	CheckMate 003 (n=129)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
	CheckMate 003 (n=19 3mg/kg)	62 (37 to 80)	48 (22 to 69)	24 (6 to 48)	-	-	-	-	-
Niv lifetime benefit	Company preferred Lognormal ¥	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company scenario: Spline 3 knot ¥	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Hybrid exponential**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-year benefit	Lognormal ¥	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 3 knot ¥	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Hybrid exponential**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* values determined by technical team using 5-year KM data in the ERG-corrected model for PD-L1≥1%
¥ values determined by technical team using the ERG-corrected model (company preferred utility)
**values determined by technical team using company's clarification model

[redacted]

Is a 2-year stopping rule appropriate? If so, should the committee's preferred 3-year treatment effect duration from TA484 be used?

Cost-effectiveness results, PD-L1 ≥1%

	Total			Incremental			ICER
	costs (£)	LYG	QALYs	costs (£)	LYGs	QALYs	(£/QALY)
1) Company assumptions for PD-L1≥1% subgroup (ERG corrected model)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£43,128	2.24	1.30	£33,191
2) Committee's preferred utility from TA484							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£43,128	2.24	1.23	£34,940
3a) 3-year continued treatment effect after stopping nivolumab at 2-years (no nivolumab costs after 2 years)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£39,030	1.39	0.90	£43,270
3b) Remove 2-year stopping rule (nivolumab costs and treatment effect from trial)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£61,839	2.24	1.30	£47,591
Tech team preferred 2 + 3b above (nivolumab costs & treatment effect from trial)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£61,839	2.24	1.23	**£50,099***
All ICERs use updated 5-year data and ERG corrected model. *Please note this a correction to the ICER reported in the technical report							

Issue 4: PD-L1 ≥1% scenarios for continued treatment effect with 2-year stopping rule (company TE response)

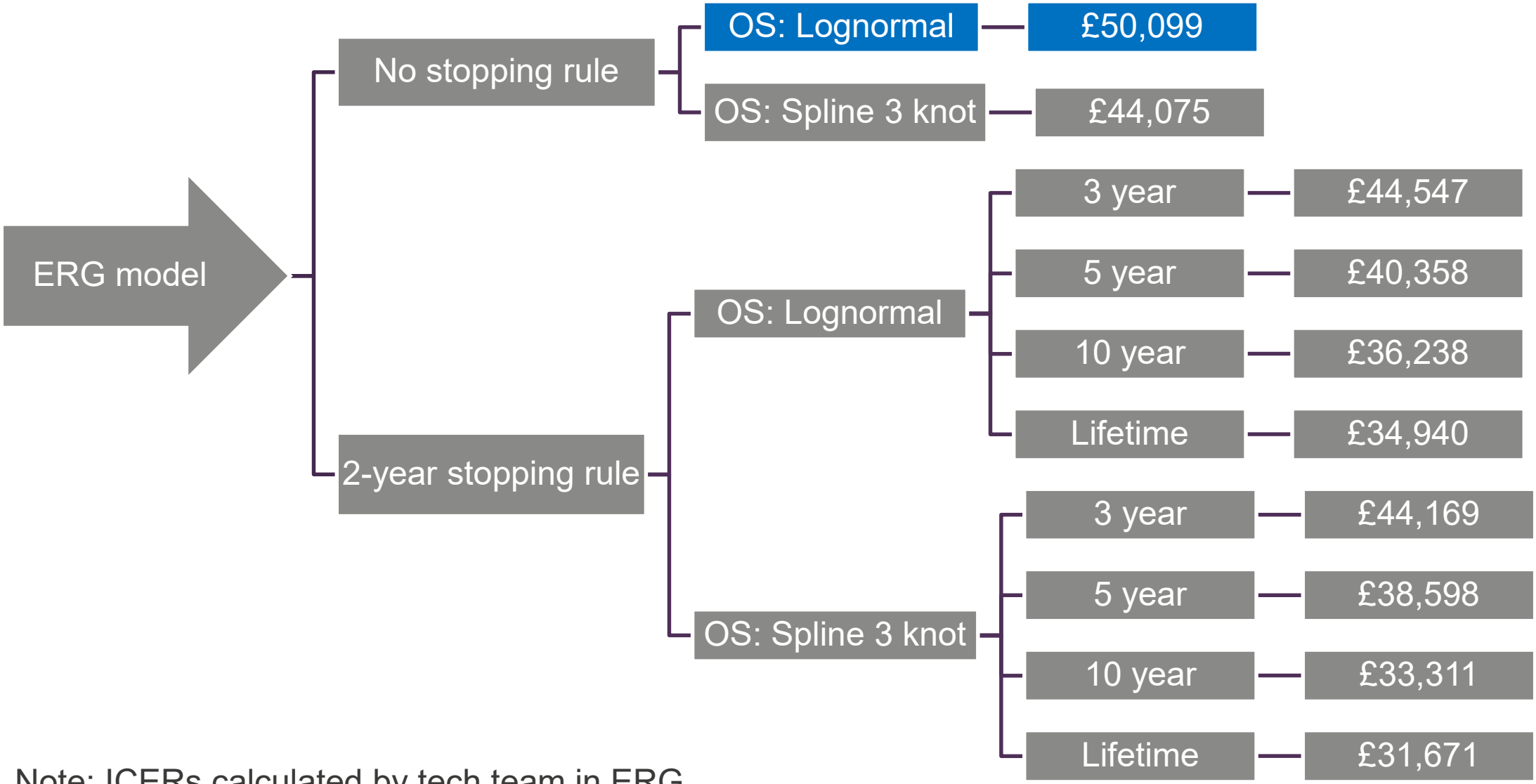
- Company: When using 2-year stopping rule, current model assumes all nivolumab patients switch to docetaxel hazards after additional 3 years of benefit. Considers this an abrupt & implausible shift in the modelled survival curve
- Scenario analyses show impact of adjusting the proportion of patients switching to docetaxel OS hazard, and assuming longer continued benefit in non-switchers
  - 44% considered most relevant based on proportion in CheckMate 057 with complete/partial response or stable disease
  - Note: ICERs in table below from company model with ERG correction and use TA484 committee preferred utility values

Proportion continuing with further Niv benefit	Duration of additional benefit after 3 years			
	3 years (total: 6 yrs)	5 years (total: 8 yrs)	10 yrs (total: 13 yrs)	Lifetime (total: 18 yrs)
0%	£44,547	£44,547	£44,547	£44,547
25%	£43,177	£42,751	£42,374	£42,312
44%	£42,138	£41,347	£40,566	£40,422
75%	£40,447	£39,112	£37,527	£37,156
100%	£39,090	£37,331	£35,347	£34,940

[redacted]

Scenario: with and without stopping rule

All ICERs below include previously accepted utility values from TA484 and are for the relevant PD-L1≥1% subgroup



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 TA484 guidance decisions

CDF review TA484 issues that cannot be resolved

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

Issue	Why issue is important	Impact on ICER
Change of dosing schedule	In the original 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 preferred ICER from £33,191 to £30,048 per QALY gained.
[redacted]	[redacted]	[redacted]

[redacted]

Key issues

Issue 1: Comparator

- Is nintedanib plus docetaxel a relevant comparator?

Issue 2: Extrapolation of OS and PFS

- What is the most appropriate model for OS and PFS?

Issue 3: Utility & duration of treatment effect

- Should the committee's preferred post-progression utility value (0.569) from TA484 be used?

Issue 4: Continued treatment effect after nivolumab is stopped & 2-year stopping rule

- Is a 2-year stopping rule appropriate?
- If treatment is stopped after 2 years, should the committee's preferred 3-year continued treatment benefit from TA484 be used?

[redacted]