Slides for PUBLIC – ACIC information redacted

NICE National Institute for Health and Care Excellence

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CDF review of TA558)

Lead team presentation

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Company: BMS

1st Appraisal Committee meeting: October 2020

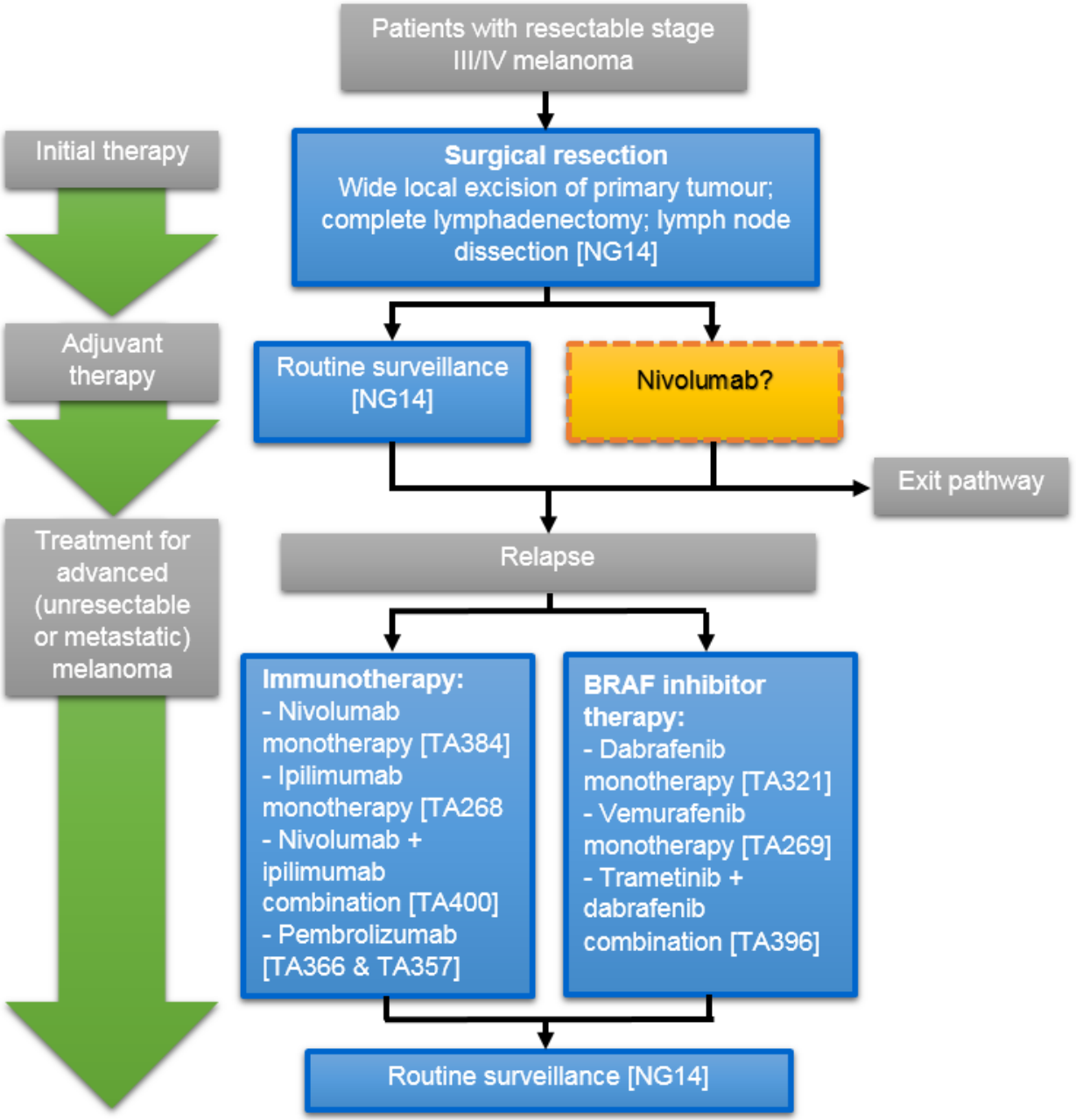
Key clinical issues

- **Staging of disease**:
  - Is the evidence from the trials generalisable to patients in the NHS with resected and metastatic melanoma?
- **Survival data**
  - OS data are still immature. What does committee make of the updated RFS and OS data?
- **Subsequent treatments:**
  - Which data, trial or SACT, should be used in the model?
  - At which point in the clinical pathway would patients most benefit from nivolumab?

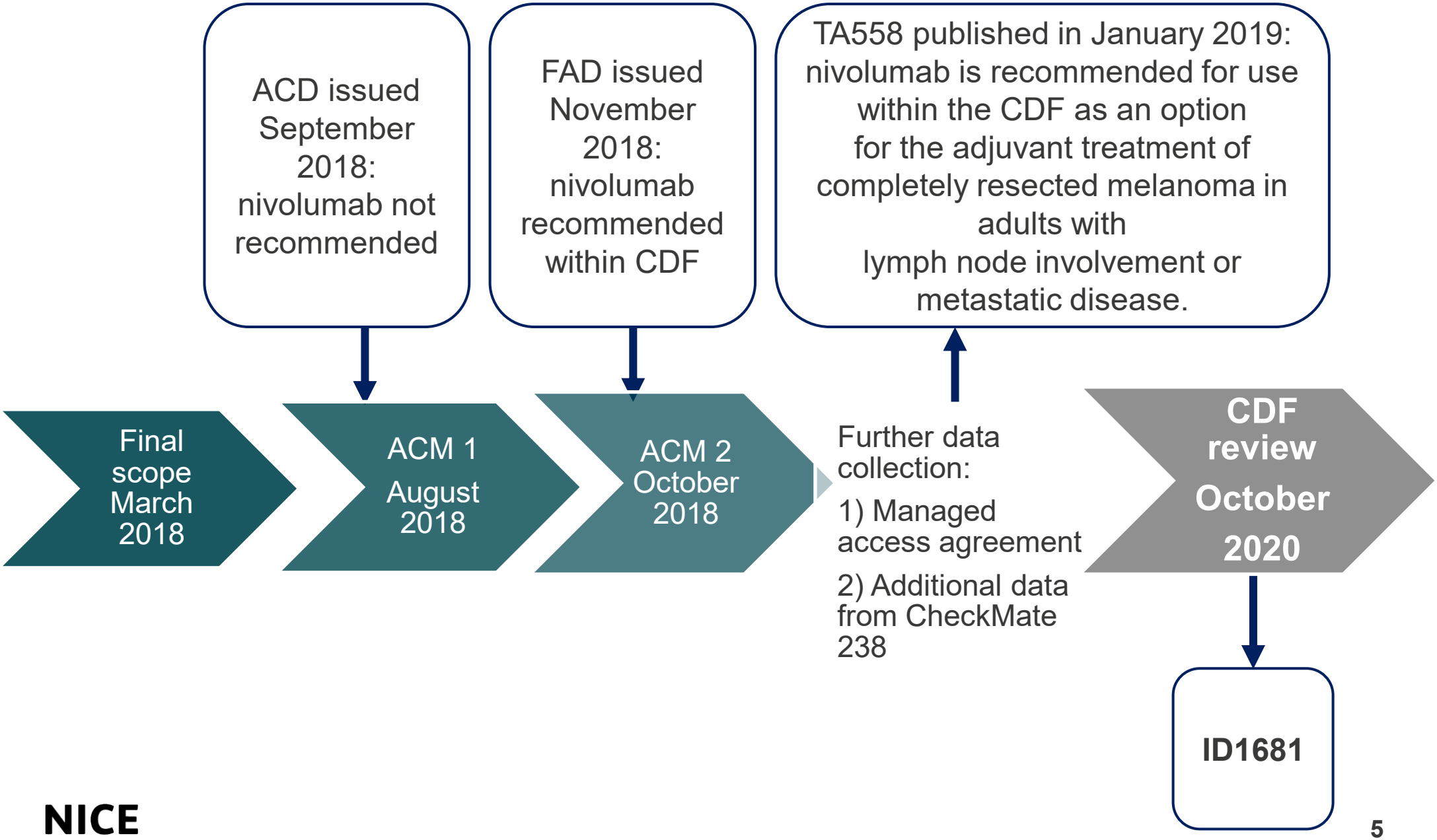
Nivolumab

Marketing authorisation	As monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
Administration	• Intravenous infusion • Maximum treatment duration 12 months **New flat dose of 240mg every 2 weeks or 480mg every 4 weeks** • TA588: 3mg/kg every 2 weeks as per CheckMate 238
Cost (list price)	£439.00 per 40mg/4ml, £1,097.00 per 100mg/10ml and £2,633.00 per 240mg/24ml concentrate for solution for infusion vial.
Patient access scheme	A commercial access agreement (CAA) has been approved which provides a simple discount to the list price

How is melanoma treated



Summary of original appraisal TA558



Patient and carer perspectives

- There are around 16,200 new melanoma cases in the UK every year

FAD TA558 (3.1 & 3.2)

- Melanoma is becoming more common and often affects people at a younger age than some other cancers. It has a substantial effect on patients, their carers and the wider society.
- Five year survival estimates are about 50% to 55% for stage III disease and 8% to 24% for stage IV disease. People with fully resected melanoma are still at high risk of disease recurrence; 5 year relapse-free survival is 28% to 44% for stage III melanoma and less for stage IV melanoma.
- The clinical and patient experts noted that significant developments in recent years, particularly the introduction of immunotherapies in the metastatic setting, having positive effect on the life expectancy and quality of life of people.
- The patient expert emphasised the importance of access to additional treatment options, particularly in the adjuvant setting, for people living with melanoma.

TA558 - Key committee assumptions 1

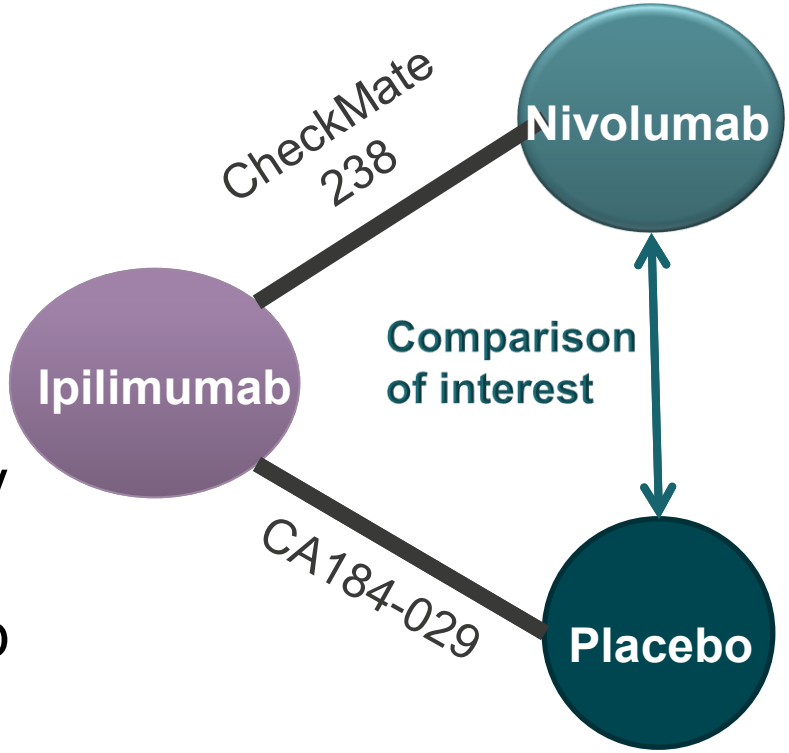
Area	Assumptions
Model	**The company should explore both model structures - a partitioned survival model and a Markov model**
Overall survival (OS)	**The CheckMate 238 OS data should be analysed & compared with routine surveillance in robust ITC.**
Indirect treatment comparison (ITC)	ITC of recurrence-free survival (period between 12 weeks & 10 years) was accepted. However, differences in inclusion criteria for CheckMate 238 and CA184-029 about disease stage were potentially not fully accounted for. **The company may consider accounting for these differences in updated ITC.**
Long-term recurrence-free survival	Methodologies used after 10 years for the comparison were complex and relied to some extent on data sources that were potentially inappropriate. **The company should explore the most appropriate methodology to estimate long-term recurrence-free survival based on updated CheckMate 238 data.**

TA558 - Key committee assumptions 2

Area	Assumptions
Subsequent treatments	At the time of the appraisal, there were no adjuvant treatments for stage III melanoma used in clinical practice. The committee anticipates that nivolumab will change the treatment pathway. Subsequent treatments used after adjuvant treatment in clinical practice, in particular re-use of nivolumab, could have an impact on the cost-effectiveness of nivolumab **More real-world data on subsequent treatment would help to validate the model assumptions.** Results of the Markov model were highly dependent on the subsequent treatments, and neither the company's nor the ERG's analyses fully captured the true complexity of the post-recurrence treatment pathway. **The company should explore adjusting CheckMate 238 results to reflect clinical costs & outcomes of subsequent treatments used in NHS practice.**
Most plausible ICER	It was not possible to specify a plausible ICER range at the time of the original appraisal because of the immaturity of the data.
Additional data	Ongoing trial, Keynote 054 (looking at the comparative efficacy of adjuvant pembrolizumab and placebo) may provide useful evidence at the NICE review.
End of life	Nivolumab does not meet the end-of-life criteria

Clinical evidence

- **CheckMate 238**:
  - N=906 patients with **stage IIIB, IIIC, or IV**
  - **Comparison: Nivolumab**: 3mg/kg 2 weekly IV up to 1 year vs. **ipilimumab**: 10 mg/kg 3 weekly IV x 4 doses then every 3 months up to a maximum of **1 year**



- **CA184-029**:
  - N=951 patients with **stage III** cutaneous melanoma
  - **Comparison: Ipilimumab**: 10mg/kg every 3 weeks IV X 4 doses then every 3 months up to a maximum of **3 years** vs. **placebo**

- **Key outcomes**: overall survival (OS) & recurrence free survival (RFS)

Issue: Staging of disease

Background

- No people with stage IV disease in CA184-029
- People with stage IIIA disease excluded from CheckMate 238. But the new American Joint Committee on Cancer (AJCC) v8 criteria mean that some people with stage IIIB disease in CheckMate could be now classed as having stage IIIA

Stakeholder comments

- Based on the new AJCC v8 criteria adjuvant treatment is offered to some patients who would not have been included in CheckMate 238.
- However, same treatment for resected stage IV as for stage III disease
- If data continues to be collected, we will have data on the benefits of adjuvant treatment using the new stage groupings.

Company:

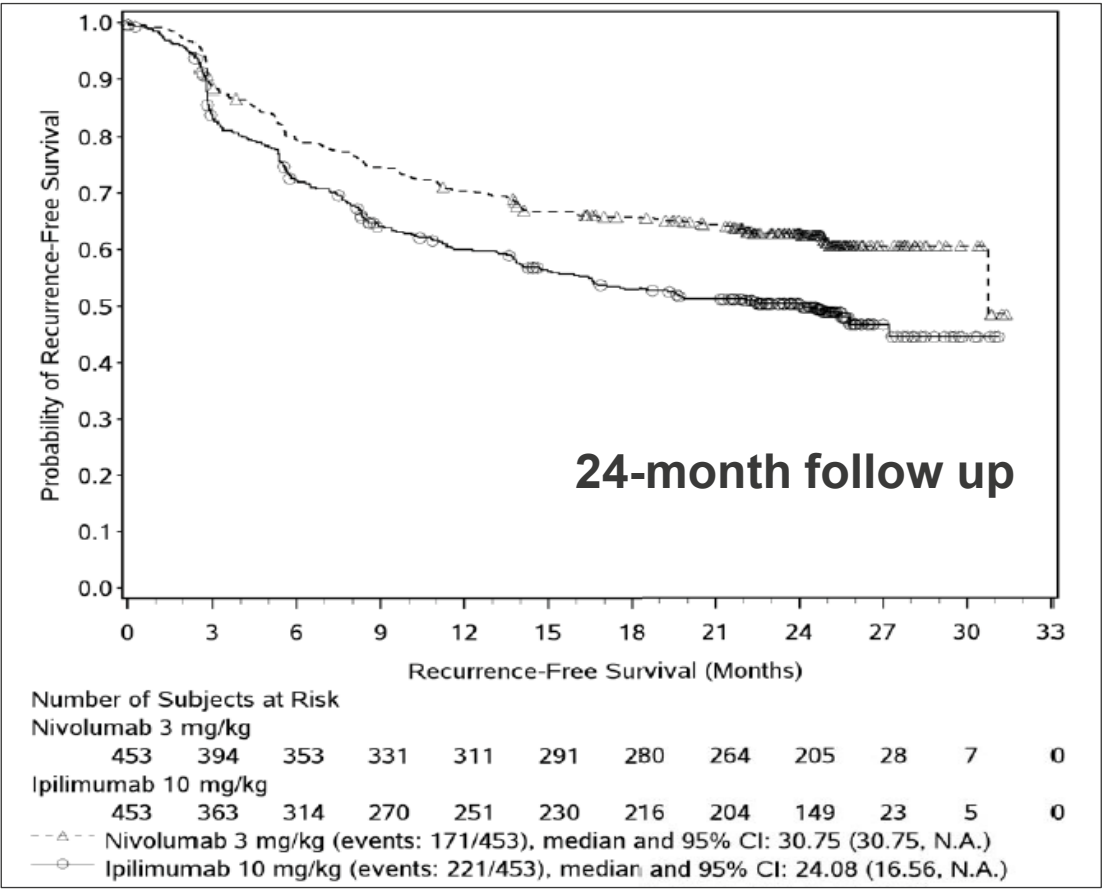
- The lack of overlap in disease stage is a limitation in the analysis
- But, CA184-029, CheckMate 238 & KEYNOTE 054 show similar results across all disease stages

ERG:

- No additional data from CheckMate 238 or CA184-029 to help resolve this issue

Is the evidence from the trials generalisable to patients in the NHS?

Updated clinical evidence RFS - CheckMate 238



[redacted]

Treatment	Subjects	Events	Median (95% CI)	HR (95% CI)
24-month follow up				
Ipilimumab	453	171 (37.74%)	24.08 (16.56, NA)	**0.66 (0.54, 0.81)**
Nivolumab	453	221 (48.79%)	30.75 (30.75, NA)	
48-month follow up				
Ipilimumab	453	[redacted]	[redacted]	[redacted]
Nivolumab	453	[redacted]	[redacted]	

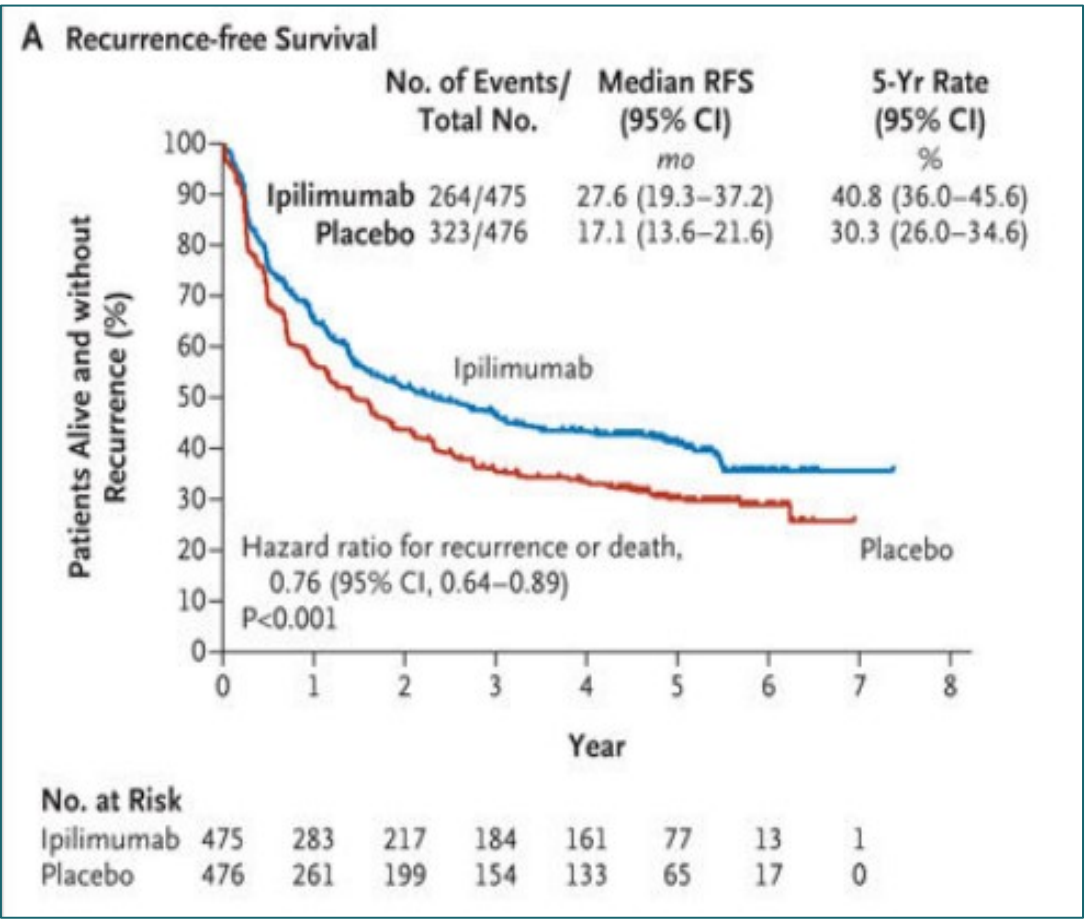
Updated clinical evidence OS - CheckMate 238

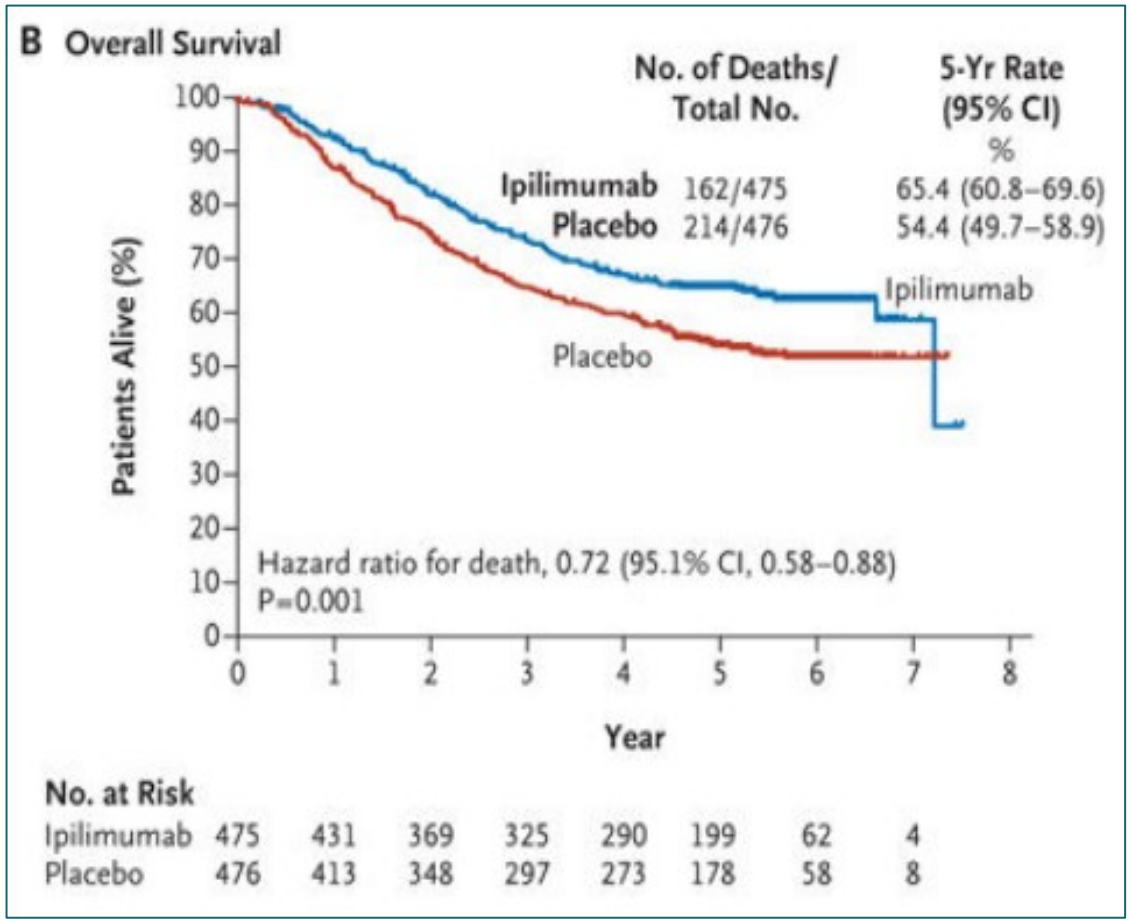
[redacted]

[redacted]

Treatment	Subjects	Events	Median (95% CI)	HR (95% CI)
24-month follow up				
Ipilimumab	453	[redacted]	[redacted]	[redacted]
Nivolumab	453	[redacted]	[redacted]	
48-month follow up				
Ipilimumab	453	[redacted]	[redacted]	[redacted]
Nivolumab	453	[redacted]	[redacted]	

RFS and OS results - CA184-029





Treatment	Subjects	Events	Median (95% CI)	HR (95% CI)
		OS		
Ipilimumab	475	162 (34.1%)	Not reported	0.72 (0.58, 0.88)
Placebo	476	214 (45.0%)	Not reported	
		RFS		
Ipilimumab	475	264 (55.6%)	27.6 (19.3, 37.2)	0.76 (0.64, 0.89)
Placebo	476	323 (67.9%)	17.1 (13.6, 21.6)	

Issue: Updated clinical data

Background:

- OS & RFS from CheckMate 238 remain immature. [redacted]

Stakeholder comments:

- Reasonable assumption that trend will continue on current lines with the benefit in RFS and assumption that this means OS.
- In this adjuvant setting patients who are going to recur tend to do so within the first few years, late recurrences are relatively rare, and effect is likely to be small.
- Other immunotherapy adjuvant studies continue to show an ongoing benefit. Reasonable assumption that another agent in the immuno-oncology class also continue to show benefit.

Company:

- [redacted]

ERG:

- [redacted]
- Despite updated data, OS remain immature and underpowered and RFS also remain immature.

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Survival data are still immature. What does committee make of the updated data?

Subsequent treatments – updated data

Nivolumab data n (n/N)	CheckMate 238		SACT data post TE
	Local/regional recurrence [redacted]	Distant recurrence - following a local recurrence. [redacted]	N=41/284 (14%)
Dacarbazine	[redacted]	[redacted]	1 (2.4%)
Temozolomide	[redacted]	[redacted]	-
Capecitabine	[redacted]	[redacted]	1 (2.4%)
Ipilimumab	[redacted]	[redacted]	**12 (29.3%)**
Ipilimumab + nivolumab	[redacted]	[redacted]	**14 (34.1%)**
Vemurafenib	[redacted]	[redacted]	-
Dabrafenib + trametinib	[redacted]	[redacted]	**9 (22.0%)**
Dabrafenib	[redacted]	[redacted]	1 (2.4%)
Binimetinib + encorafenib	[redacted]	[redacted]	**6 (14.6%)**
Pembrolizumab	[redacted]	[redacted]	1 (2.4%)
Nivolumab	[redacted]	[redacted]	-
Talimogene laherparepvec	[redacted]	[redacted]	1 (2.4%)
Bleomycin	[redacted]	[redacted]	1 (2.4%)
Cisplatin + dacarbazine + vinblastine	[redacted]	[redacted]	1 (2.4%)
Hydroxycarbamide	[redacted]	[redacted]	1 (2.4%)
Imatinib	[redacted]	[redacted]	1 (2.4%)
Trametinib	[redacted]	[redacted]	1 (2.4%)

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Note: % in CheckMate 238 calculated by NICE team (denominator is number of patients – [redacted] and [redacted] for local and distant recurrences respectively) to match % in SACT data

Issue: Subsequent treatments

Background:

- Subsequent treatment based on updated data from CheckMate 238
- Data from SACT cohort are immature - limited to 41/284 (14%) patients

Stakeholder comments:

- Clinicians noted that no significant changes in subsequent treatments for melanoma in the time period so this is reasonable.
- Issues remains as to whether re-challenge with an anti-PD1 is clinically the right thing to do, and most clinicians continue to do this only when there is a significant time period between completing adjuvant treatment and the recurrence as stated in the papers.

Company:

- Post technical engagement (TE) updated SACT data incorporated in sensitivity analyses for distant recurrences (before TE only 9% of patients provided data for the SACT sensitivity analyses)

ERG:

- The ERG's clinical experts reported that subsequent treatments from CheckMate 238 are consistent with expected clinical practice and SACT data remain immature

Which data, trial or SACT, should be used in the model?

Issue: Nivolumab dose - resolved during technical engagement

- The licenced dose of nivolumab has changed since the publication of TA558 to a flat dose of either 240 mg once every 2 weeks or 480 mg once every 4 weeks.
- The ERG's clinical experts agreed that the dose change would have no impact on clinical outcomes and expect most patients to receive the 4-weekly dose.
- Clinicians agreed that this is a reasonable approach and explained that patients are offered 2 or 4 weekly dosing, most choose 4 weekly for convenience
- Both the ERG and the company incorporated the new flat 4 weekly dose in its preferred base

Key clinical issues

- **Staging of disease**:
  - Is the evidence from the trials generalisable to patients in the NHS with resected and metastatic melanoma?
- **Survival data**
  - OS data are still immature. What does committee make of the updated RFS and OS data?
- **Subsequent treatments:**
  - Which data, trial or SACT, should be used in the model?
  - At which point in the clinical pathway would patients most benefit from nivolumab?

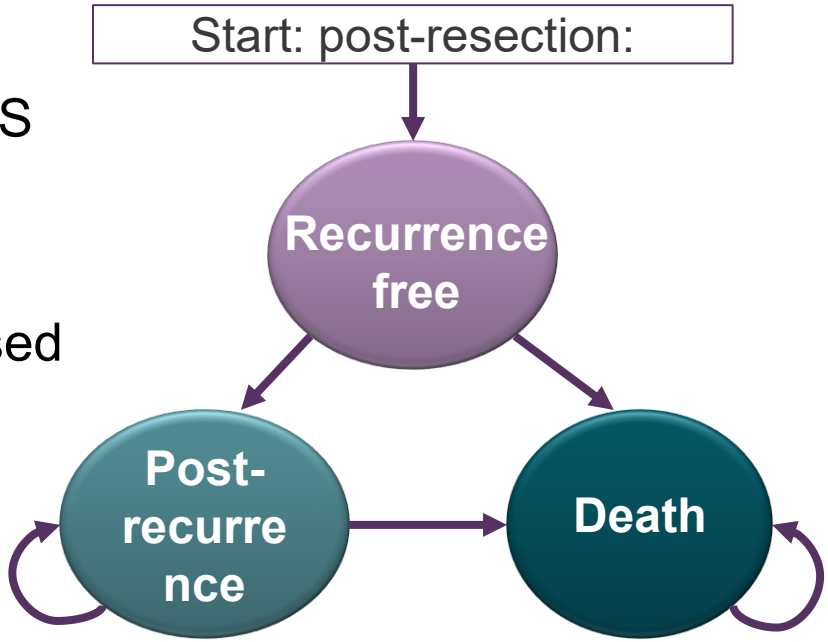
Key cost-effectiveness issues

- **Model structure:**
  - Does the committee have a preference for the partitioned survival model (PSM) or state transition model (STM)
- **Indirect treatment comparison (ITC):**
  - Is the observed or censored overall survival (OS) ITC analysis more appropriate?
- **Hazard of death:**
  - Given the remaining uncertainty with OS, which approach to OS modelling is preferred by committee?

Models

Partitioned survival model (PSM):

- **Recurrence-free state** is informed by individual participant data (IPD) meta-regression ITC of RFS
- **Post-recurrence** is informed by IPD ITC of OS & RFS
- **Death state** is informed by IPD ITC of OS
- **Note:** in TA558, OS ITC was not used in the model. Instead CA184-029 routine surveillance data were used and nivolumab was estimated through a surrogacy analysis using HR from an unpublished study



State transition model (STM)

- Same approach for **recurrence-free state** as PSM
- Different approach for estimating **Post-recurrence** & **Death states**:
  - Post-recurrent survival (PRS) is based on weighted subsequent treatment-specific survival data obtained from published sources
  - Nivolumab after recurrence re-treatment assumption: patients are not re-treated with anti-PD-1s for the first 2 years, instead, they are treated with ipilimumab.

Models: Company's post TE STM scenario analysis

Post-technical engagement (TE), the company made no changes to its preferred base-case for both models.

In response to ERG considering PSM to be more appropriate than the STM for decision making, the company provided a sensitivity analysis using STM exploring post-recurrence survival (PRS) from CheckMate 238 (instead of using published sources):

- CheckMate 238 PRS data were pooled and fitted with parametric curves using the same method as the for RFS and OS extrapolation.
- Because of immaturity of the data, PRS was pooled across treatment arms. This allows more data to be used to inform PRS, but it also assumes that once a patient has a recurrence, their hazard of death is assumed to be the same between both treatment arms
- To align subsequent treatment with PRS, subsequent treatment data were also pooled - assuming same treatments for both arms, and resulting in the same subsequent treatment cost for both arms. The company considers that SACT data shows that most patients are re-treated with anti-PD-L1s within 6 months of recurring.

Models: ERG - PSM & STM life years compared

Health state and treatment arm	State-transition model – company base case	State-transition model – company post TE scenario	Partitioned survival model – company base case
Recurrence-free			
Nivolumab	[redacted]	[redacted]	[redacted]
Routine surveillance	6.92	6.92	9.64
Incremental value	[redacted]	[redacted]	[redacted]
Post-recurrence			
Nivolumab	[redacted]	[redacted]	[redacted]
Routine surveillance	7.35	8.43	9.01
Incremental value	[redacted]	[redacted]	[redacted]
Total			
Nivolumab	[redacted]	[redacted]	[redacted]
Routine surveillance	14.27	15.35	18.65
Incremental value	[redacted]	[redacted]	[redacted]

ERG: both models utilise the same data from CheckMate 238 the two models should be producing similar estimates of life-years and should validate each other

Models: ERG - PSM & STM RFS extrapolation

ERG:

[redacted]

Issue: Model structure

Background:

- Both PSM and STM were considered appropriate in TA558
- IPD meta-regression ITC of OS now available - albeit immature
- Only PSM includes updated OS data from CheckMate 238.

Company:

- STM gives an alternative approach not relying on OS from CheckMate 238 by using subsequent treatment data directly. It separates RFS & PRS which allows scenarios regarding subsequent treatment usage linking both survival and cost outcomes
- Acknowledges the limitations of estimating PRS from literature.
- Post TE, CheckMate 238 has been used to inform PRS for both nivolumab and routine surveillance in a scenario. This analysis negates the use of CA184-029 to inform the OS.

ERG:

- PSM has fewer assumptions to model OS, it takes health states proportions directly from survival curves and provides a more robust estimate of survival compared to STM.
- STM requires more steps to estimate transition probabilities.
- STM doesn't pass face validity and further investigation is needed into why estimates of RFS life-years are markedly different compared to the PSM.
- Only presented PSM as their preferred base case

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Does the committee have a preference for the PSM or STM model?

OS modelling – PSM

- The company produced OS indirect treatment comparison (ITC) to compare nivolumab with routine surveillance
- Unlike the ITC for RFS, ipilimumab data from CA184-029 were not censored for patients on treatment beyond 1 year.

  → **ITC censoring issue**
- CheckMate 238 data are still immature, and the company acknowledged that it is difficult to demonstrate a significant survival benefit with ipilimumab.
- As a result, the OS ITC and the resulting parametric survival curves are subject to a substantial amount of uncertainty.
- Post technical engagement both the ERG and company presented a scenario assuming same hazard of death based on CheckMate 238 median RFS for nivolumab (company) and routine surveillance (ERG)

  → **Hazard of death issue**

Issue: ITC ipilimumab censoring

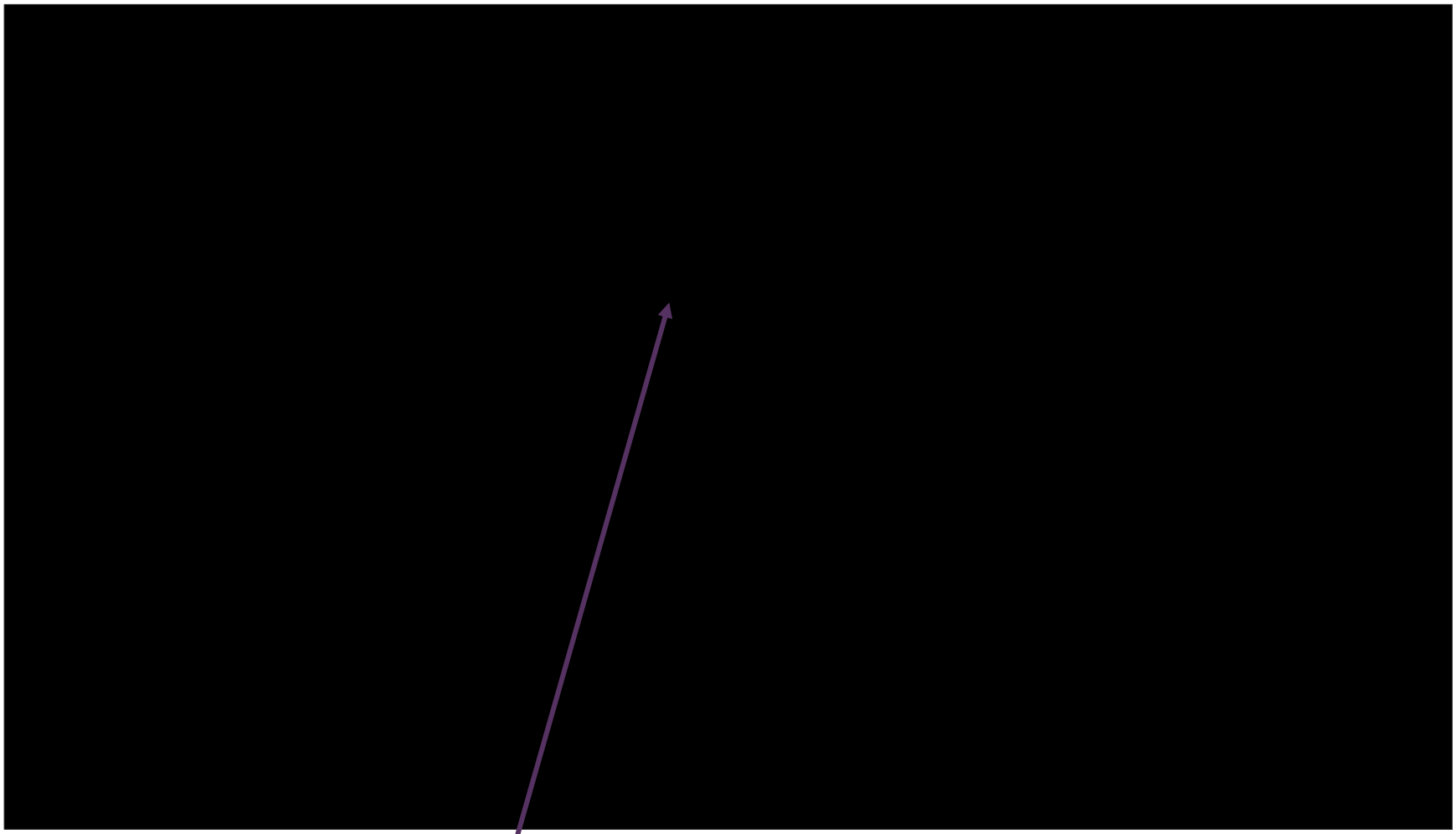
CheckMate 238	CA184-029
• Ipilimumab 10 mg/kg every 3 weeks for 4 doses & every 3 months up to **1 year** • 26.9% had ipilimumab for 1 year	• Ipilimumab 10 mg/kg every 3 weeks for 4 doses & every 3 months up to **3 years** • 25% had ipilimumab >1 year • 13.4% had ipilimumab for 3 years

Background:

- TA558 FAD: RFS ITC with censoring was accepted by the committee. OS ITC not used due to immature data, surrogacy analysis used to estimate nivolumab instead
- ID1681: company's ITC analysis of OS does not include censoring at 1-year for ipilimumab patients from CA184-029 who received treatment beyond 1-year
- The ERG does not consider 25% of patients receiving ipilimumab beyond 1 year to be an insignificant proportion.

CA184-029: censoring of OS data

KM data - observed ITT population & censored population after 1 year of treatment:



NICE **Note:** censored placebo KM data are not used in the model - only ipilimumab is censored at 1 year for ITC

ITC – meta-regression and Bucher method

- The company conducted two analyses:
  - primary ITC is individual participant data (IPD) meta-regression and is utilised in the model
  - Bucher method is used as a sensitivity analysis

Trials and Bucher ITC results (censored & uncensored) for OS:

	ITT 24 months follow-up HR (95% CI)	ITT 48 months follow-up HR (95% CI)	Ipilimumab censored analysis HR (95% CI)
Nivolumab vs ipilimumab	[redacted]	[redacted]	[redacted]
Placebo vs ipilimumab	[redacted]	[redacted]	[redacted]
ITC Nivolumab vs placebo	[redacted]	[redacted]	[redacted]

ITC - IPD meta-regression

Model OS no censoring (RFS censored)

Model OS with censoring (RFS censored)

Issue: ITC censoring

Stakeholder comments:

- Censoring sounds reasonable to be consistent.
- But patients who stopped treatment at 1 year in CA184-029 may have recurred or had toxicity issues. If censoring enriches the group who recur will this alter the model? However only 25% patients went beyond 1 year, so only minor concerns?

Company:

- Based on data and clinical opinion bias from ipilimumab duration in CA184-029 is small.
- But big informative censoring issue: patients with the best prognosis are censored. ERG in TA558 considered this analysis to be the 'worst case' scenario.
- The effect of censoring is more pronounced for OS than for RFS. Almost all censored patients are in recurrence-free health state, but ~ [redacted] of uncensored patients are in post-recurrence state. Patients in post-recurrence state are likely to have increased risk of mortality vs . pre-recurrence state. By definition, all uncensored patients in the corresponding RFS analysis are recurrence-free

ERG:

- Agrees with company that censoring is likely to bias ITC results against nivolumab. However, uncensored analyses are biased against routine surveillance.
- 25% of patients receiving ipilimumab beyond 1 year is significant proportion
- Uses censored ITC in it's preferred base-case

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Is the observed or censored OS ITC analysis more appropriate?

Issue: Hazard of death - PSM

OS extrapolation - uncertainty

Mean of covariates approach to provide graphical estimates of uncertainty around the extrapolations:

- [redacted]

Hazard of death - company's new post TE scenarios

To explore uncertainty around the OS estimate, the company provided 2 analyses:

- Company provided PSM analysis based on median RFS for nivolumab - a more plausible time point for an OS adjustment to all patients - assuming hazard of death for routine surveillance and nivolumab are the same after [redacted].
- It also tried to adjust OS in CA184-029 as if CheckMate 238 subsequent therapies were used. This estimated that there was an average increase of XXX in PRS for ipilimumab in CheckMate 238 vs. CA184-029. This factor was used to estimate hazard ration (HR) of [redacted] in ITC for nivolumab vs. placebo. This estimate was considered in line with the observed ITC HR of [redacted]. The new HR was not used in scenario analysis, but the average increase was varied by -10%, 10% and 20% for the placebo arm. The resulting HRs ranged from [redacted].

ITC – OS Bucher method	ITT observed HR (95% CI)	Ipilimumab censored HR (95% CI)	Company's new analysis HR (95% CI)
ITC Nivolumab vs placebo	[redacted]	[redacted]	[redacted]

Issue: Hazard of death

Background:

- TA558: placebo in CA184-029 does not reflect routine surveillance OS due to advances in subsequent treatment - OS ITC in PSM potentially overestimates nivolumab benefit

Stakeholders:

- Is it scanning frequency or clinical examination frequency which makes the placebo arm not up to date? Subsequent treatments have not significantly changed therefore the placebo arm does reflect current treatments.

Company:

- ERG's pre TE scenarios are chosen as surrogates for re-challenge by immunotherapies - assuming that patient outcomes are the same between treatment arms. But CheckMate 238 PFS2 shows nivolumab vs. ipilimumab HR of [redacted])
- Further treatment is only given once a patient has a recurrence, while but ERG's scenarios assume all patients have 1 year of treatment and can be re-challenged after 1 year. However, nivolumab median RFS in CheckMate 238 is [redacted]).
- Provided new analysis based on nivolumab median RFS in response to TE, but made no changes to its PSM preferred base case (OS ITC data are extrapolated for the first 10 years and AJCC data were used for long-term estimation of survival).

ERG: Hazard of death

- The aim of the hazard of death scenarios is to explore improvements in OS for routine surveillance in line with expectations of survival due to advancements in treatments for patients who have a recurrence in their disease.
- All routine surveillance OS assumptions have a high degree of uncertainty.
- The company's base case analysis is biased towards nivolumab and can be considered optimistic and representative of the lower bound of cost-effectiveness.
- Company's scenario with median RFS for nivolumab is plausible. However, median for routine surveillances is substantially shorter - [redacted]. Therefore there is a delay in improved OS for routine surveillance patients.
- Therefore ERG considers the median RFS for routine surveillance (rounded up to two years for simplicity) to be a plausible upper bound of cost-effectiveness:
  - Patients on routine surveillance with recurrence after the threshold of 2 years are likely to be given an immunotherapy. Therefore nivolumab (for simplicity) is assumed for routine surveillance patients with recurrence after 2 years.

Given the remaining uncertainty with OS, which approach to OS modelling is preferred by committee?

Company's results (nivolumab & ipilimumab PAS)

	Incremental			ICER £/QALY
Deterministic results	Costs, £	LYs	QALYs	
Partitioned survival model (PSM)				
Company's new base case • Updated clinical evidence & new dose 480mg Q4	[redacted]	[redacted]	[redacted]	£14,301
• Probabilistic results	[redacted]	[redacted]	[redacted]	14,566
State-transition model (STM)				
Company's new base case • Updated clinical evidence & new dose 480mg Q4	[redacted]	[redacted]	[redacted]	£16,171
• Probabilistic results	[redacted]	[redacted]	[redacted]	15,954

Note: results with PAS prices for subsequent treatments are presented in part 2

Company: key sensitivity analyses

Parameter	Base case	Scenario	Incremental			ICER £/QALY
			Costs, £	LYs	QALYs	
Partitioned survival model (PSM)						
Base case			[redacted]	[redacted]	[redacted]	**14,301**
Nivolumab dosing	480mg Q4W	3 mg/kg Q2W	[redacted]	[redacted]	[redacted]	14,935
		240 Q2W	[redacted]	[redacted]	[redacted]	14,195
Subsequent txt - local	CheckMate 238	CA184-029	[redacted]	[redacted]	[redacted]	11,520
Nivo subseq. txt - distant	CheckMate nivo	SACT data	[redacted]	[redacted]	[redacted]	8,956
OS modelling - applying equal hazard of deaths at [redacted] months (median RFS)		uncensored	[redacted]	[redacted]	[redacted]	18,789
		censored	[redacted]	[redacted]	[redacted]	23,853
State-transition model (STM)						
Base case			[redacted]	[redacted]	[redacted]	**16,171**
Nivolumab dosing	480mg Q4 W	3 mg/kg Q2W	[redacted]	[redacted]	[redacted]	17,919
		240 Q2W	[redacted]	[redacted]	[redacted]	17,120
Subsequent txt - local	CheckMate 238	CA184-029	[redacted]	[redacted]	[redacted]	16,160
Nivo subseq. txt - distant	CheckMate ipi	SACT data	[redacted]	[redacted]	[redacted]	11,248
PRS modelling	Literature	CheckMate	[redacted]	[redacted]	[redacted]	16,064

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Note: results with PAS prices for subsequent treatments are presented in part 2

ERG's scenario analyses (nivolumab & ipilimumab PAS)

ERG base-case:

- **range of ICERs between £17,404 (best scenario) and £52,012 (worst scenario)**

Preferred assumption (deterministic results)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Partitioned survival model (PSM)			
Company base case (CheckMate ipilimumab subsequent txt for routine surveillance [RS])	[redacted]	[redacted]	14,301
1. one-year censoring of ipilimumab OS	[redacted]	[redacted]	17,404
2. Equal hazard of death – 2 years & CheckMate nivolumab subsequent txt for RS	[redacted]	[redacted]	28,809
3. Equal hazard of death – 2 years & nivolumab is subsequent treatment for RS	[redacted]	[redacted]	40,009
4. Scenarios 1 + 2	[redacted]	[redacted]	37,371
5. Scenarios 1 + 3	[redacted]	[redacted]	52,012
6. Threshold analysis assuming additional [redacted] QALY benefit (based on scenario 5)	[redacted]	[redacted]	30,000

NICE

Note: results with PAS prices for subsequent treatments are presented in part 2

Key cost-effectiveness issues

- **Model structure:**
  - Does the committee have a preference for the PSM or STM model
- **Indirect treatment comparison (ITC):**
  - Is the observed or censored OS ITC analysis more appropriate?
- **Hazard of death:**
  - Given the remaining uncertainty with OS, which approach to OS modelling is preferred by committee?