Slides for PUBLIC – AIC and CIC 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)

# Chair presentation

2nd Appraisal Committee meeting

Lead team: G.J. Melendez-Torres, Sumithra Maheswaran
ERG: BMJ-TAG
Technical team: Brian Shine, Marcela Haasova, Joanna Richardson, Janet Robertson
Company: BMS

January 2021

# Key issues

- Does committee still prefer the censored to the uncensored indirect comparison analysis?

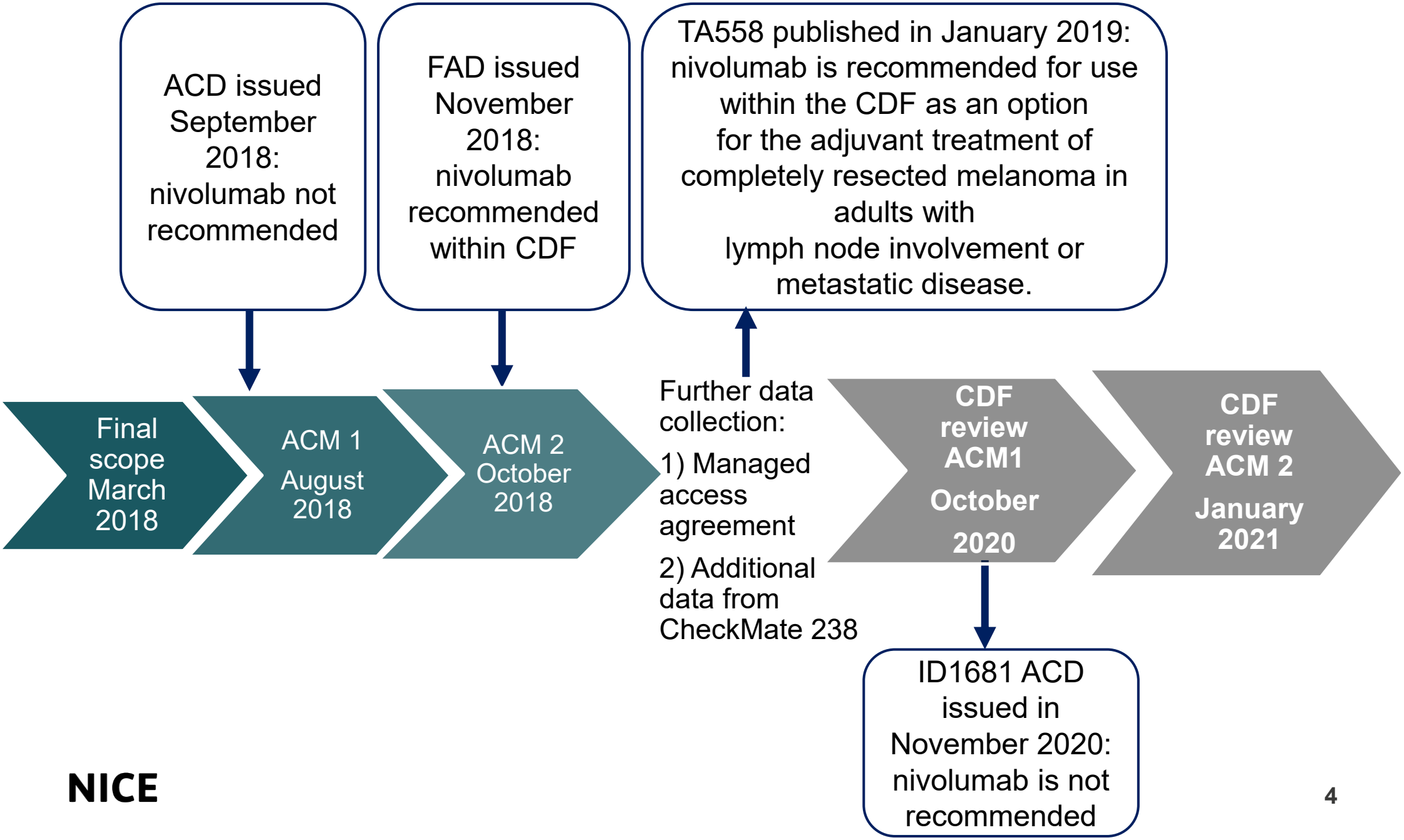
- How long does the effect of nivolumab on overall survival last?

- After the same hazard of death for routine surveillance and adjuvant nivolumab is applied, does the committee prefer the use of subsequent treatments to be taken from nivolumab arm in CheckMate-238?

# 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<br>• Maximum treatment duration 12 months<br>• New flat dose of 240mg every 2 weeks or 480mg every 4 weeks |
| **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 |

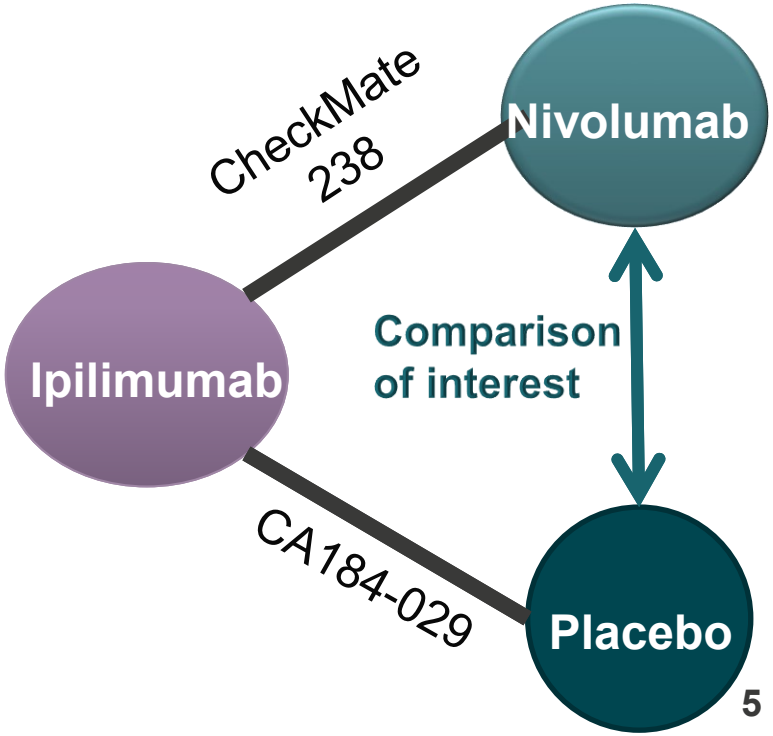
# Summary of original appraisal TA558



# Clinical evidence

- **CheckMate 238**:
  - N=906 patients with **stage IIIB, IIIC, or IV**
  - **Comparison: Nivolumab** up to **1 year** vs. **ipilimumab** up **1 year**
  - When nivolumab entered CDF, estimated completion date was [redacted]
    At 4 years follow-up only 211 deaths out of expected 302 events were observed.
    Completion date was revised. Data cut with a minimum [redacted]

- **CA184-029**:
  - N=951 patients with **stage III**
  - **Comparison: Ipilimumab** up to a maximum of **3 years** vs. **placebo**
  - placebo OS not considered to reflect routine surveillance because of advances in subsequent treatments since the trial started




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

NICE

# ITC – meta-regression and Bucher method

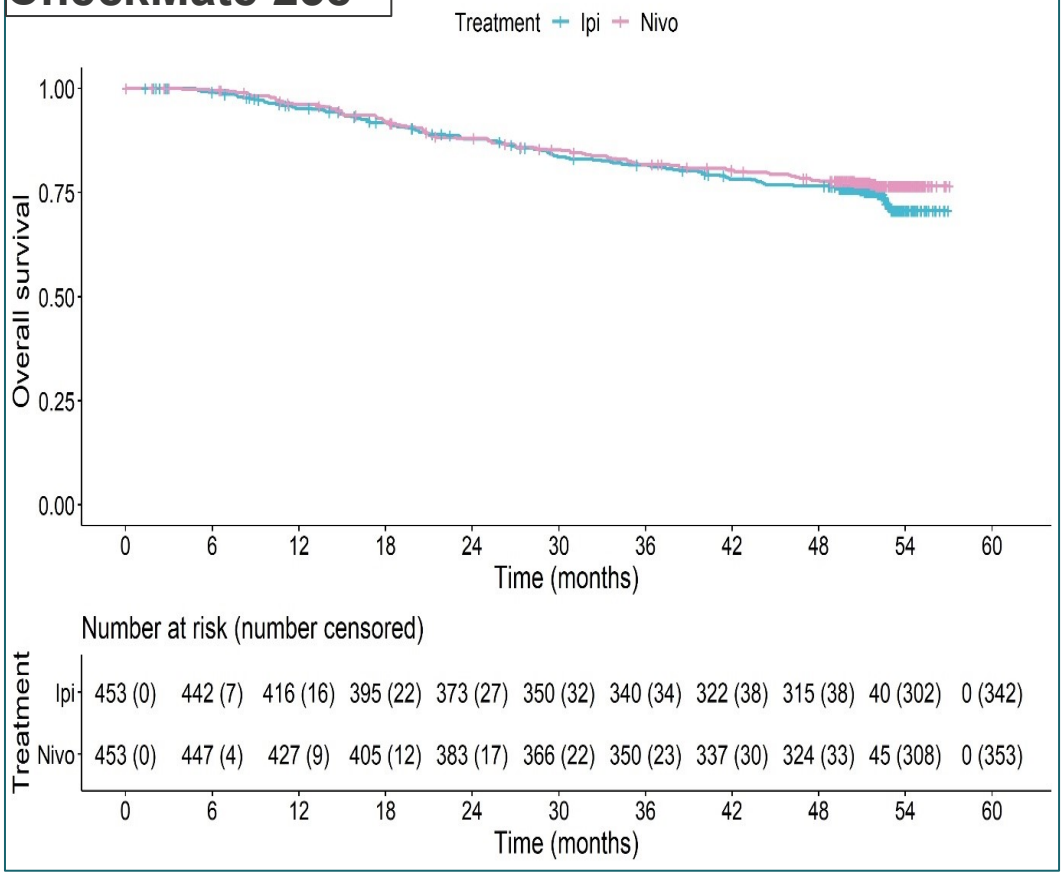
- The company conducted two analyses:
  - individual participant data (IPD) meta-regression used in the model
  - Bucher method used as a sensitivity analysis

| Bucher ITC results 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] |

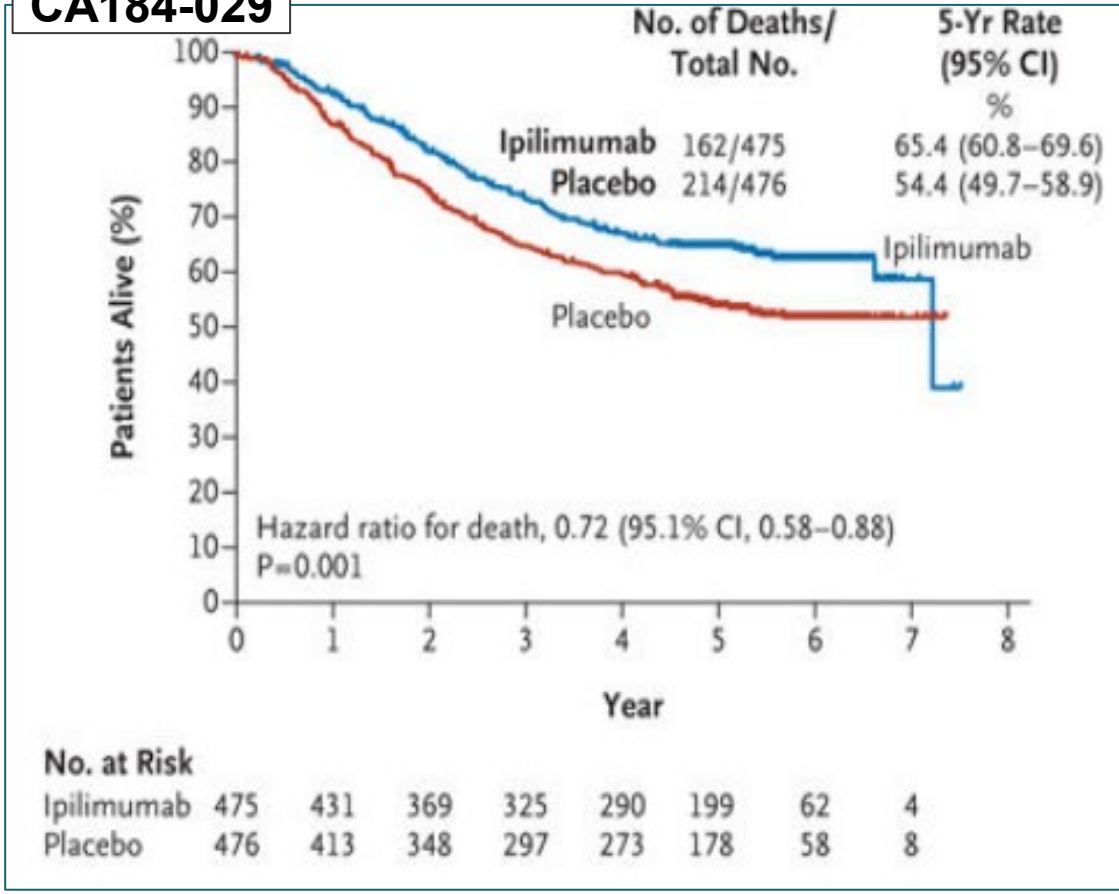
**Committee preferred the censored analysis**

# Key trials: OS results

## CheckMate 238




## CA184-029




| Treatment | Subjects | Events | Median (95% CI) | HR (95% CI) |
|---|---|---|---|---|
| **CheckMate 238- 48-month follow up** | | | | |
| **Ipilimumab** | 453 | 111 (24.5%) | NA | **0.87 (0.66, 1.14)** |
| **Nivolumab** | 453 | 100 (22.1%) | NA | |
| **CA184-029** | | | | |
| **Ipilimumab** | 475 | 162 (34.1%) | NR | **0.72 (0.58, 0.88)** |
| **Placebo** | 476 | 214 (45.0%) | NR | |

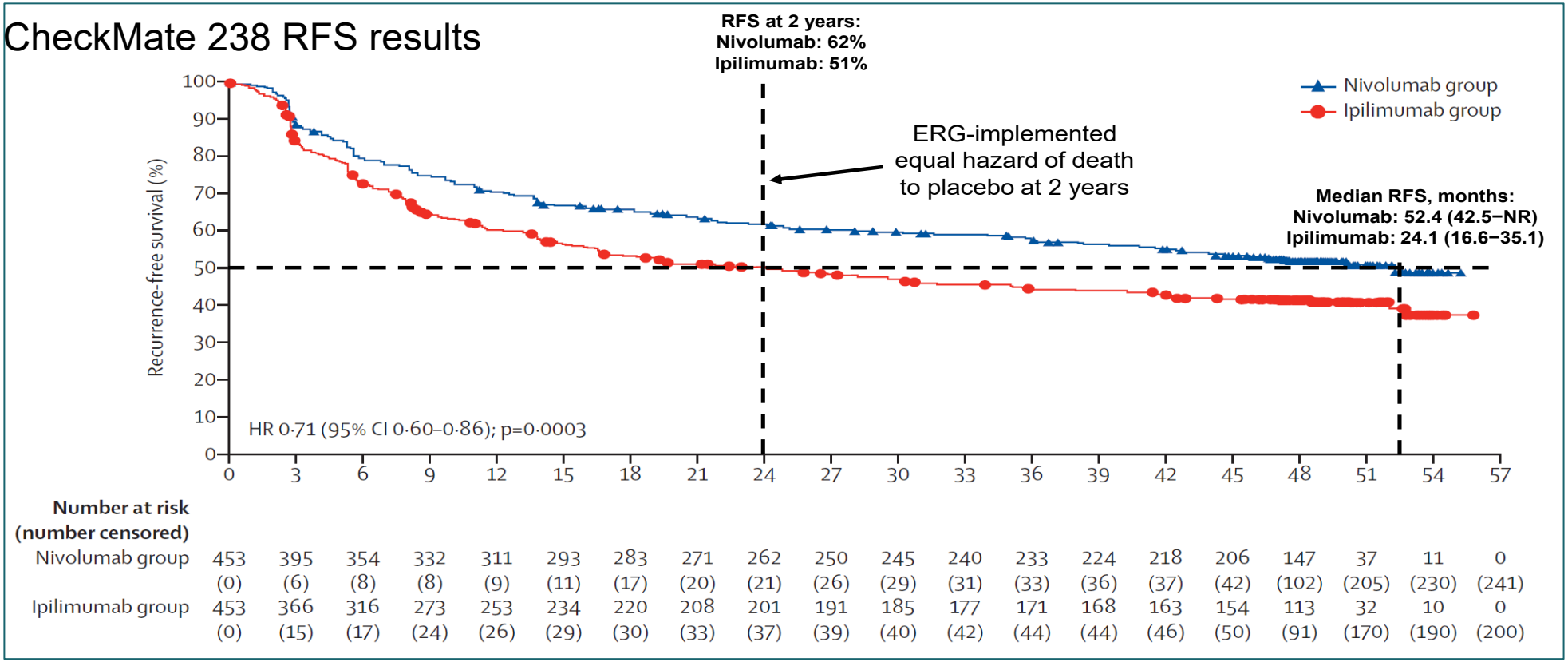
**NICE**

# CheckMate 238: equal hazard of death

The ERG explored scenarios assuming same hazard of death for nivolumab and routine surveillance to explore advancements in subsequent treatments:

- **Company**: Post TE suggested 4.36 years based on nivolumab median RFS
- **ERG:** 2 years (1.61 years) surveillance median RFS, more appropriate.

CheckMate 238 RFS results



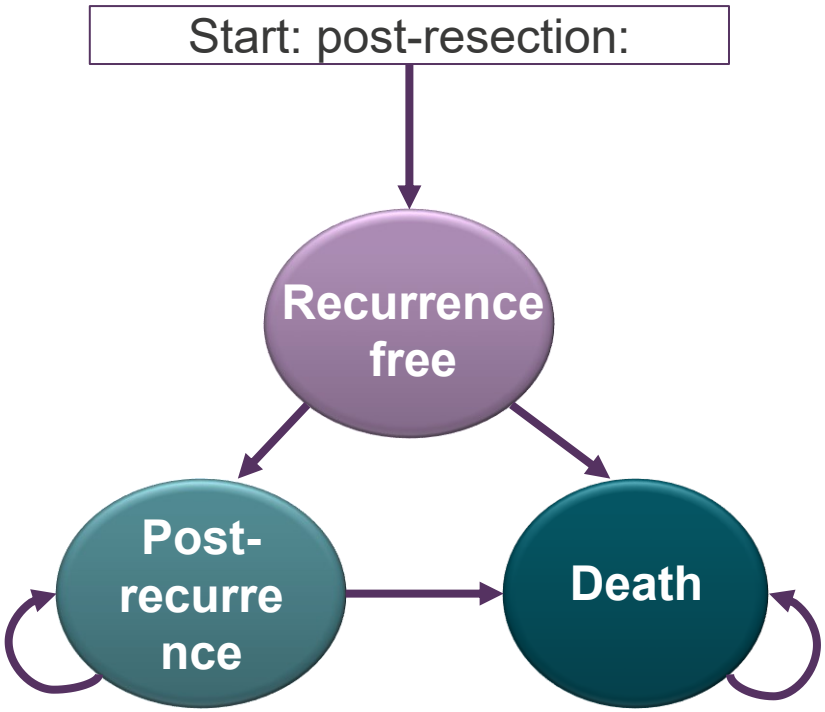

**Committee preferred ERG's more conservative approach of 2 years**

NICE

# 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
- **Post-recurrence** & **Death states** based on weighted subsequent treatment-specific survival data obtained from published sources.

**Committee preferred the partitioned survival model (PSM)**

# Cost-effectiveness analyses presented at ACM1 (nivolumab & ipilimumab PAS)

| ERG's preferred assumptions (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 treatment 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 |

**Committee considered scenarios 4 and 5 in its decision making**

NICE



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

# ACD preliminary recommendation

1.1 Nivolumab is not recommended, within its marketing authorisation, for the adjuvant treatment of melanoma with lymph node involvement or metastatic disease that has been completely resected in adults.

# ACD consultation responses

| | |
|---|---|
| **Professional organisations / groups** | • Melanoma UK<br>• Testimonials from 145 patients submitted to Melanoma UK<br>• NCRI-ACP-RCP-RCR (National Cancer Research Institute - Association of Cancer Physicians - Royal College of Physicians - Royal College of Radiologists) |
| **Company** | • BMS |
| **Public (web) comments** | • 2 patients<br>• Joint submission from 55 UK Consultant Melanoma Oncologists<br>• Consultant medical oncologist<br>• East Midlands Skin Cancer Expert Clinical Advisory Group (ECAG)<br>• Melanoma Focus<br>• Skin Cancer Special Interest Group BAPRAS (British Association Plastic Reconstructive Surgeons) |

# Summary of consultation responses (1)

**NCRI-ACP-RCP-RCR**

- The recommendation to discontinue adjuvant nivolumab funding is based on uncertainty of the resulting QALYs generated by immature treatment outcome data.
- More data will be forthcoming,
- Withdrawal of funding will cause significant harm to patients.
- Therefore, we urge the committee to reconsider and to commend continued CDF funding of nivolumab in resected high risk melanoma.

**Melanoma UK**

- We feel that in this case, the decision really is not in the best interest of patients
- There is a very clear unmet medical need for stage four patients and this treatment is the only approved and reimbursed treatment for this section of patients. We are concerned that this recommendation would be extremely traumatic for the patient community and a backward step in the treatment of melanoma.

# Summary of consultation responses (2)

**Patients feedback - summarised by Melanoma UK**

- Utter devastation
- Please don't take away the hope
- This decision is breaking my heart
- This could be the difference between life & death
- This is now another worry – what about my children?
- Just reading this news is having a huge psychological impact on me
- I am sick to my stomach
- This will remove a lifeline for so many patients
- This drug is currently keeping me alive

# Summary of consultation responses (3)

## Web comments

- [joint submission] Withdrawal of funding will cause significant harm to patients. … Of particular concern is the withdrawal of adjuvant nivolumab funding for the resected stage IV patients. These patients, ..., are the ones at highest risk of recurrence.
- There are more younger people being diagnosed with melanoma. These people and myself deserve a chance. This is not an old persons disease. You're not talking about giving a person a few more years. At 38, I hope that I would live a lot longer
- Please reconsider. Give time for evidence to show that it does work to reduce recurrence.
- [ECAG] My colleagues and I are very concerned that you appear in this uncertainty to presume that it is not cost effective despite not having all the necessary data yet
- How can it be that we will soon be telling our patients that a treatment that literally halves their chance of recurrence will no longer be available to them, but instead they can only be treated when their cancer returns? How can it be that we will be telling our patients in England that if they lived in Scotland they could have this potentially life-saving treatment
- [Skin Cancer Special Interest Group BAPRAS] This recommendation appears to be based on a 'worse case scenario' set of data' rather than something akin to real world data and risks depriving patients … receiving treatment that on balance clearly improves their survival.
- Patients …would rather have treatment when they are fit and healthy and have single agent immunotherapy rather than combination immunotherapy when diagnosed with metastatic disease

# Summary of new evidence

**Company:** ICERs discussed at ACM1 not based on clinically plausible assumptions, no changes made to PSM preferred base, but a range of ICERs based on more plausible assumptions is introduced:

- **ITC censoring**: does not consider that censoring is needed, but have included a range of ICERs based on OS ITC both with, and without censoring of ipilimumab.
- **Same hazard of death**: applying the same hazard of death for routine surveillance and adjuvant nivolumab after 2 years is not clinically plausible.
  - Presented analyses exploring assumptions for censoring and the company's post TE ITC adjusted for post-recurrence survival of placebo in CA184-029 to reflect subsequent treatments used in CheckMate 238 exploring same hazard assumption
  - Results assuming same hazard of death at 3 - 10 years are included.
- **Subsequent treatments:** assuming that subsequent treatment for routine surveillance is nivolumab after same hazard of death is applied is not clinically plausible. Subsequent treatments for routine surveillance and nivolumab after same hazard of death should be the same - based on nivolumab in CheckMate 238.
- **Model:** disagrees with the rationale to reject STM but in line with the committee preference presents PSM as the primary analysis

# Survival data

**Company:**

- Agree with committee that immature OS is positive for patients. 77.9% of CheckMate 238 patients are alive at 4 years after initiating adjuvant nivolumab therapy and 51.7% were recurrence free. Other outcomes also showed nivolumab improvements vs. ipilimumab.
- ACD: The clinical experts explained that usually if a treatment has a clinically meaningful difference in RFS then it was likely that this would be reflected in OS
- If nivolumab and ipilimumab are assumed to have same OS - such an assumption is clinically unlikely given CheckMate238 and thus is conservative - then based on CA184-029, nivolumab has improved OS vs routine surveillance

**ERG:**

- [redacted]
- The comparison of interest is nivolumab vs routine surveillance and the evidence for this is from ITC using CheckMate 238 and CA184-029
- The  model validation is useful, however, the ERG was not able to fully critique the curves.
- Because the data are immature the OS gain with nivolumab is highly uncertain.

# Issue 1: ITC censoring

**Company:**

- Censored OS ITC is biased against nivolumab.
- Post-TE adjusted analysis of CA184-029 for CheckMate 238 subsequent therapies estimated increase of 63% in post-recurrence survival (PRS) in CheckMate 238 vs. CA184-029 and resulted in adjusted ITC HR of 0.65 (95%CI 0.45-0.91). This in line with uncensored ITC HR of [redacted] The adjusted ITC is now explored in company's scenario analyses.
- Provided routine surveillance model validation using placebo data from KEYNOTE 054 (pembrolizumab vs placebo in Stage III melanoma) and COMBI-AD (dabrafenib + trametinib vs placebo in BRAF positive Stage III melanoma).

**ERG:**

- Agree that censored OS ITC is biased against nivolumab but best approach
- 25% of patients receiving ipilimumab beyond 1 year is significant proportion
- The adjusted ITC analysis was not fully critiqued as more detail on methods was needed. However, the various adjustments to PRS have [redacted] HR for OS.
- The  model validation is useful, however, the ERG was not able to critique the curves fully

Does the committee still prefer the censored ITC?

# Company's new analysis - hazard of death

**Estimated HR and 95% CI - Nivolumab vs adjusted routine surveillance from CA184-029:**

**Company:** After [redacted] the HR is decreasing and only starts to increase after [redacted], Confidence interval does not cross the HR of 1 - equal hazard in both arms – until [redacted]

- [redacted] was the minimum when hazards became non-significant in 90% of (median was [redacted] months ~[redacted]) when considering the flexible models and those with 3+ parameters

# Company's new analysis - hazard of death (2)

**Estimated HR and 95% CI - Nivolumab vs routine surveillance censored ipilimumab:**

**Company:** confidence interval does not cross the HR of 1 - equal hazard in both arms – until [redacted].

# Issue: hazard of death (1)

**Company response to ACD:**

- CheckMate 238: All data needs to be considered. At 2 years, model shows [redacted] are recurrence-free in nivolumab vs. [redacted] in routine surveillance arm – evidence that is not confounded by subsequent treatments. Assuming equal hazard at 2 years ignores fact that more patients in the nivolumab arm are recurrence-free.
- Smoothed hazard plots show:
  - Difference in hazards in CheckMate 238 [redacted]
  - Nivolumab KM data are below modelled nivolumab from 2 years
  - Equal hazard at 2 years means placebo has a lower hazard than ipilimumab.
  - Smoothed hazard plots of the company's adjusted and censored ITC do not cross for at least 4 years (max trial data for CheckMate 238 – and likely to continue to ≥6.5 years)
- Treatment waning time points previously considered by committees for other immune checkpoint inhibitor appraisals started the earliest at 3 years.
- Additional analyses provided after ACD response suggest that the minimum timepoint should be 4 years ([redacted])

# Issue: hazard of death (2)

**ERG response:**

- CheckMate 238: KM data for nivolumab and ipilimumab overlap until approximately 52 months, and, there is heavy censoring from 48 months onwards - OS data beyond 48 months (4 years) are likely to be unreliable
- Based on the company's new analyses, assuming equal hazard of death at 2 years may be overly conservative.
- The maximum time point for the equal hazard of death assumption should be 5 years as
  - [redacted]
  - [redacted]
- The timepoint that limits the uncertainty with cost-effectiveness analysis (though does not eliminate the uncertainty) is 3 years
- The ERG considers the company's absolute minimum time point of 3 years, with exploratory analyses up to 5 years (which covers the most recent data cut for CheckMate 238) to be a plausible range.
- Presented illustrative scenarios exploring increased immunotherapy use. All ERG's scenarios include ITC censoring.

NICE

What is the most plausible hazard of death to accept in the model?

# Issue: subsequent treatments

- ACD: committee concluded that CheckMate data 238 reflect clinical practice.

**Company:**

- ERG scenario assuming that subsequent treatment for routine surveillance is nivolumab after same hazard of death is applied is not clinically plausible.
- The rationale for equal hazard scenarios was to investigate the impact of improved survival based on improved subsequent treatments for routine surveillance compared to those available in CA184-029. Therefore, at the point of equal hazard of death, the costs of the subsequent treatments received in nivolumab arm in CheckMate 238 were also applied to the routine surveillance arm - the same costs and benefits are applied to both arms.

**ERG response:**

- Using nivolumab subsequent treatment costs after the equal hazard of death time point is methodologically correct, as costs are aligned with the associated survival benefit.
- Agrees with company's choice of subsequent treatment based on committee's preference. However, in clinical practice, use of immunotherapies for patients relapsing on routine surveillance is likely to be higher than for patients relapsing on nivolumab. This was explored in 2 illustrative scenarios.

NICE

Does the committee prefer subsequent treatments, after same hazard of death is applied, to be taken from nivolumab arm of CheckMate-238?

# Company's results (nivolumab & ipilimumab PAS)

- PSM model as per committee preference with clinically plausible ICERs including ITC censoring and equal hazard time point

Conservative assumptions

Conservative assumptions

| Equal hazard time point | Uncensored OS | One-year censoring of ipilimumab OS patients |
|---|---|---|
| Company base case – 10 years | **£14,301** | £17,404 |
| 9 years | £14,640 | £17,899 |
| 8 years | £15,088 | £18,550 |
| 7 years | £15,679 | £19,405 |
| 6 years | £16,486 | £20,568 |
| 5 years | £17,647 | £22,230 |
| 4.36 years (median RFS) | £18,789 | £23,853 |
| 4 years | £19,431 | £24,760 |
| 3 years | £22,487 | **£29,011** |

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

# Company's ITC scenario analyses (nivolumab & ipilimumab PAS)

- Scenarios exploring company's adjusted ITC analyses that estimated an increase of 63% in post-recurrence survival in CheckMate 238 vs. CA184-029
  - the average increase was varied by -10%, +10% and +20% for the placebo arm

| Adjusted post-recurrence survival increase in CA184-029 | | OS HR (96% CI), nivolumab versus placebo | ICER using the uncensored OS ITC | ICER using the censored OS ITC |
|---|---|---|---|---|
| Ipilimumab | Placebo | | | |
| +63% | +53% | 0.63 (0.44-0.89) | £12,300 | £12,231 |
| +63% | +63% | **0.65 (0.45-0.91)** | **£13,087** | **£13,013** |
| +63% | +73% | 0.66 (0.47-0.94) | £13,508 | £13,431 |
| +63% | +83% | 0.69 (0.49-0.98) | £14,894 | £14,808 |
| Company's base-case | | | | |
| OS HR from uncensored ITC | | [redacted] | **£14,301** | £17,404 |

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

# ERG's scenarios (nivolumab & ipilimumab PAS)

- The ERG considers the minimum time point of 3 years, with exploratory analyses up to 5 years to be a plausible range
  - illustrative scenarios 1 & 2 explore increased immunotherapy use, specifically subsequent nivolumab

| Scenario | Equal hazard | OS ITC | Subsequent treatments | ICER |
|---|---|---|---|---|
| **Company's base-case** | 10 years | uncensored | Nivolumab arm of CheckMate 238 | £14,301 |
| **ERG's most plausible ICER** | 3 years | censored | Nivolumab arm of CheckMate 238 | **£29,011** |
| • **Scenario 1** | 3 years | censored | Ipilimumab arm of CheckMate 238 | 29,126 |
| • **Scenario 2** | 3 years | censored | 50% nivolumab usage and 50% Ipilimumab arm of CheckMate 238 redistributed | 30,997 |

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

# Key issues

- Does committee still prefer the censored to the uncensored indirect comparison analysis?

- How long does the effect of nivolumab on overall survival last?

- After the same hazard of death for routine surveillance and adjuvant nivolumab is applied, does the committee prefer the use of subsequent treatments to be taken from nivolumab arm in CheckMate-238?