NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CANCER DRUGS FUND REVIEW

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CDF review of TA558) [ID1681]

Link to TA558
Link to Final Scope and Final Matrix

1. **Company submission** from Bristol-Myers Squibb
2. **Clarification questions and company responses**
3. **Public Health England Data Report**
   a. Subsequent treatments in SACT updated data snapshot
4. **Expert personal perspectives** from:
   a. Prof. Ruth Plummer, Clinical Professor and Consultant Medical Oncologist – clinical expert, nominated by Bristol-Myers Squibb
5. **Evidence Review Group report** prepared by BMJ-TAG
6. **Evidence Review Group – factual accuracy check**
7. **Technical engagement response from Bristol-Myers Squibb**
8. **Technical engagement responses from experts:**
   a. Prof. Ruth Plummer, Clinical Professor and Consultant Medical Oncologist – clinical expert, nominated by Bristol-Myers Squibb
9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ-TAG

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA558

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

Company evidence submission for committee

15 July 2020

File name	Version	Contains confidential information	Date
ID1681_Nivolumab Adjuvant Melanoma CDF review - 100720	1.0	Yes/no	15 July 2020

Contents

Tables and figures

Cancer Drugs Fund review submission

A.1 Background

As per the terms of engagement document[1]:

- Nivolumab is recommended for use within the Cancer Drugs Fund (CDF) as an option for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease. It is recommended only if the conditions in the managed access agreement are followed
- Incremental cost-effectiveness ratios (ICERs) presented to the committee included a simple discount of [redacted]
- The committee noted that the company's ICERs were within the range usually considered a cost-effective use of NHS resources, but was concerned that the ICERs were very uncertain
- The committee highlighted the following key uncertainties during the appraisal:
  - There were no head-to-head trials comparing nivolumab with routine surveillance in the adjuvant setting. An indirect treatment comparison was required, which was considered acceptable for decision making
  - Long-term benefit: The survival data from the clinical trial CheckMate 238 were considered very immature. The committee was therefore unable to identify a range of plausible ICERs
  - Subsequent treatment use: The committee anticipated that the subsequent treatments used after adjuvant treatment in clinical practice could have an impact on the cost effectiveness of nivolumab
- The committee considered that, with the uncertainties highlighted above, all the presented ICERs were associated with substantial uncertainty and nivolumab could not be considered for routine commissioning. No head-to-head trials are planned, but other ongoing trials may allow for a more appropriate indirect treatment comparison. Further evidence for long-term benefit will be collected from the ongoing clinical trial. Further evidence on subsequent treatments could be collected from real-world evidence and from other clinical trials

A.2 Key committee assumptions

Table 1: Key committee assumptions as per the terms of engagement[1]

Assumption subject	Committee preferred assumptions
Model	Following consultation, the company submitted two updated models comparing adjuvant nivolumab with routine surveillance: a partitioned survival model and a Markov model (which was an updated version of the Markov II model in its original submission). The committee concluded that, potentially, both model structures presented were acceptable for decision making. **The company should explore both model structures**
Overall survival	The company estimated overall survival using recurrence-free survival in a surrogacy analysis. The committee considered it was reasonable to expect that the recurrence-free survival benefit seen in CheckMate 238 would be translated to some extent into an overall survival benefit, but the extent is very uncertain. **The overall survival data from CheckMate 238 should be analysed in comparison with routine surveillance in a robust indirect treatment comparison.**
Indirect treatment comparison	The company's updated indirect treatment comparison for recurrence-free survival for the period between 12 weeks and 10 years is suitable to inform decision making. However, the committee considered that differences in the inclusion criteria for CheckMate 238 and CA184-029 about what stage disease people had were potentially not fully accounted for. **The company may consider accounting for these differences in its updated indirect treatment comparison.**
Long-term recurrence-free survival	Overall, the committee considered that the methodologies used to estimate recurrence-free survival after 10 years for the comparison of interest were extremely 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 considering the updated CheckMate 238 data.**
Survival extrapolations	Due to the immaturity of the clinical trial data, the committee concluded it was not able to judge whether any of the extrapolated clinical outcomes predicted by the model were plausible. **The company should re-explore the most appropriate clinical extrapolations.**

Assumption subject	Committee preferred 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 as adjuvant treatment will change the treatment pathway for Stage III melanoma. 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. **The committee concluded that more real-world data on subsequent treatment used after adjuvant nivolumab in clinical practice would help to validate the model assumptions.** The committee noted that the results of the Markov model were highly dependent on the subsequent treatments that patients had, and neither the company's nor the Evidence Review Group's analyses fully captured the true complexity of the post-recurrence treatment pathway. **The company should explore adjusting the results of the CheckMate 238 trial data to reflect the clinical costs and outcomes of the subsequent treatments used in NHS practice.**
Most plausible ICER	It was not possible to specify a plausible incremental cost-effectiveness ratio range at the time of the original appraisal because of the immaturity of the data.
Additional data	Another ongoing trial, Keynote 054 (which is looking at the comparative efficacy of adjuvant pembrolizumab and placebo) may provide useful evidence at the National Institute for Health and Care Excellence (NICE) review.
End of life	Nivolumab does not meet the criteria for end of life treatment.

A.3 Other agreed changes

As per the terms of engagement[1]:

- Where requested changes to the model impact other assumptions, these may also be updated, but should be explicitly highlighted to NICE and the committee (e.g. updating other survival inputs such as progression-free survival in addition to overall survival)
- During their critique of the evidence, NICE and the Evidence Review Group may request that further data be provided or further analyses be conducted if they consider it necessary for committee decision making

- The company should not alter the decision problem, submit additional evidence or make further alterations to the model during the CDF review period unless NICE requests or agrees to this in advance

A.4 The technology

Table 2: Technology being reviewed

UK approved name and brand name	Nivolumab (Opdivo®)
Mechanism of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to PD-1, an immune checkpoint receptor involved in T-cell differentiation and function, and blocks its interaction with its ligands, PD-L1 and PD-L2. Engagement of PD-1 with PD-L1 and PD-L2, which are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2. Malignant tumours may express PD-L1, making them susceptible to PD-1/PD-L1 therapeutic blockade. In the adjuvant setting, nivolumab therefore acts by enhancing the ability of the patient's own immune system to recognize and destroy micrometastases or individual tumour cells at an early stage and prevent further tumour growth and dissemination. This approach, enabling the body's own immune system to target cancer, is novel in resected Stage III or IV melanoma and is viewed by physicians and patient interest groups as a 'step-change' in its management.
Marketing authorisation/CE mark status	The indication which this submission relates to is: 'OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.'
Indications and any restriction(s) as described in the summary of product characteristics	Nivolumab is also indicated in the UK and Europe for the following indications: • As monotherapy or in combination with ipilimumab, for the treatment of advanced (unresectable or metastatic) melanoma in adults • As monotherapy, for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults • As monotherapy, for the treatment of advanced RCC after prior therapy in adults • As monotherapy, for the treatment of adult patients with relapsed or refractory classical Hodgkin's lymphoma after ASCT and treatment with brentuximab vedotin

	• As monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy • As monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy • In combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma
Method of administration and dosage	Intravenous infusion. The recommended dose of nivolumab for the treatment of adjuvant melanoma is 240 mg every 2 weeks or 480 mg every 4 weeks.[a] For adjuvant therapy, the maximum treatment duration is 12 months.
Additional tests or investigations	No additional tests or investigations are needed.
List price and average cost of a course of treatment	£439.00 per 4 ml vial; £1,097.00 per 10 ml vial; £2,633.00 per 24 ml vial. Average cost of a course of treatment [redacted].
Commercial arrangement (if applicable)	A PAS has been approved and comprises a [redacted] from the nivolumab list price. Applying this PAS to the list price, the cost per nivolumab dose is [redacted] with an average cost per course of treatment of [redacted][c]
Date technology was recommended for use in the CDF	November 2018
Data collection end date	The data collection period was anticipated to conclude when the final overall survival data from CheckMate 238 would become available. The final data cut from CheckMate 238 used to inform this submission is 30 January 2020.

Key: ASCT, autologous stem cell transplantation; NSCLC, non-small-cell lung cancer; PAS, patient access scheme; PD-1, programmed cell death protein 1; PDL-1, programmed cell death ligand 1; RCC, renal cell carcinoma.
Notes: [a] The previous TA558 submission used 3 mg/kg in line with CheckMate 238; [b], average cost per dose = £2,633 based on 240 mg x mean number of doses = [redacted] [c], mean number of doses = [redacted]

A.5 Clinical effectiveness evidence

Table 3: Primary source of clinical effectiveness evidence

Study title	CheckMate 238	SACT data cohort study[2]
Study design	A manufacturer-sponsored, multinational, randomized, double-blind, active-controlled Phase III trial.	SACT data cohort study
Population	Patients aged ≥ 15 years of age who were undergoing complete resection of Stage IIIB, IIIC or IV melanoma[a]	Patients with newly diagnosed melanoma that has been staged according to the AJCC 8th edition as having Stage III disease or completely resected Stage IV disease
Intervention(s)	Nivolumab 3 mg/kg Q2W[b]	Nivolumab 240mg Q2W or 480 mg Q4W[b]
Comparator(s)	Ipilimumab 10 mg/kg Q3W for four doses, then Q12W [b,c]	Not applicable
Outcomes collected that address committee's key uncertainties	• **Overall survival** • **Recurrence-free Survival** • Patients retreated with nivolumab in the metastatic setting	• **Subsequent treatments post adjuvant nivolumab** • Time to next treatment

Key: AJCC, American Joint Committee on Cancer Staging Manual; Q12W, every 12 weeks; Q2W, every 2 weeks; Q3W, every 3 weeks; RFS, recurrence-free survival; SACT data, Systemic Anti-Cancer Therapy.
Notes: [a], All enrolled patients were ≥ 18 years old; [b], 1 year maximum treatment duration; [c], this differs from the licensed dose of ipilimumab currently used in advanced or metastatic melanoma although this is the dose approved and licensed in the US for the treatment of adjuvant melanoma; note, ipilimumab is not licensed in the EU for adjuvant melanoma;
Bold text represents outcomes that the model incorporated.

A.6 Key results of the data collection

The latest data cut of the CheckMate 238 trial (30 January 2020) included 48 months minimum follow-up. Recurrence-free survival (RFS), overall survival (OS) and subsequent therapies were collected to address key uncertainties raised in the original submission. In particular, RFS data were consistent with those presented in the original submission and provide long-term evidence to support nivolumab monotherapy in the adjuvant setting.

A.6.1 *CheckMate 238*

Overall survival

One key uncertainty was the long-term survival benefit associated with nivolumab, which was not available in the original appraisal. The overall survival (OS) Kaplan–Meier plots from the latest data cut (48 months minimum follow-up) are presented in Figure 1 and summary statistics are presented in Table 4. The Kaplan–Meier curve displays [redacted] for nivolumab and ipilimumab [redacted] where nivolumab [redacted]. The updated OS data cut remains immature, [redacted] compared with ipilimumab; however, the [redacted] the hazard of death is [redacted] for patients treated with nivolumab compared with those treated with ipilimumab [redacted].

It should be noted that at the time of database lock the updated analyses of OS was underpowered, 302 events were anticipated in order to provide 88% power to detect a HR of 0.7 (critical HR 0.76) under an overall alpha of 0.05 (hierarchical testing after RFS). [redacted]

Despite the increased follow-up, the similarity of OS in both treatment arms may be a result of the immaturity of the data. It may also reflect the fact the impact of subsequent treatments in both treatment groups.

Figure 1: Kaplan–Meier curve for overall survival by treatment arm – CheckMate 238 (48-month minimum follow-up)

Key: ipi, ipilimumab; nivo, nivolumab.

Table 4: Summary statistics for overall survival by treatment arm – CheckMate 238 (48-month minimum follow-up)

Treatment	Subjects	Events	Censored	Median (95% CI)	HR (95% CI)
Ipilimumab	453				
Nivolumab	453				

Key: CI, confidence interval; HR, hazard ratio; NA, not available.
Notes: Hazard ratio <1 favours nivolumab. Hazard ratio >1 favours ipilimumab.

Recurrence-free survival

Consistent with the earlier data cut (minimum 24-month follow-up; presented in Section A.15.1), after a minimum of 48 months of follow-up, patients treated with nivolumab continue to demonstrate a statistically significant and clinically relevant improvement in RFS compared with patients treated with ipilimumab (HR:); see Figure 2 and Table 5. As shown in the Kaplan–Meier curves, the benefit of nivolumab in terms of delaying RFS events also continues in the longer

term, with a greater proportion of patients remaining alive and recurrence-free in the nivolumab arm. In the original submission there was general agreement among the consultees and clinical experts that it was reasonable to expect that the RFS benefit seen in CheckMate 238 would be translated into an OS benefit.[3]

Median RFS was [redacted] months (95% CI: [redacted] in the nivolumab arm, and [redacted] months (95% CI: [redacted] in the ipilimumab arm. Although median RFS [redacted], it should be noted that the data remain immature, with heavy censoring present at the end of the Kaplan–Meier curve, which may change with increased follow-up. The improved RFS with nivolumab compared with that of the ipilimumab group was consistent across subgroups, as presented in Figure 16 in Section A.15.1, with the exception of acral and mucosal melanoma subtype. In these groups the comparisons are based on small patient numbers and results may be confounded by other characteristics meaning the estimated treatment effects may not be reliable.

Figure 2: Kaplan–Meier curve for recurrence-free survival by treatment arm – CheckMate 238 (48-month minimum follow-up)

Key: Ipi, ipilimumab; Nivo, nivolumab.

Table 5: Summary statistics for recurrence-free survival by treatment arm – CheckMate 238 (48-month minimum follow-up)

Treatment	Subjects	Events	Censored	Median (95% CI; months)	HR (95% CI)
Ipilimumab	453	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	453	[redacted]	[redacted]	[redacted]	

Key: CI, confidence interval; HR, hazard ratio; NA, not available.
Notes: Hazard ratio < 1 favours nivolumab. Hazard ratio > 1 favours ipilimumab.

Subsequent treatment

Subsequent treatment was another key area of uncertainty highlighted in the original submission. The update of subsequent treatments from CheckMate 238 (48-month) were derived using the same assumptions as the original submission separating data by local/regional recurrence and distant recurrence (see TA558 Document B, Section B3.5, Page 158). Patients who first have a local/regional recurrence but then have a distant recurrence were included in both groups, i.e. any subsequent treatment records between local and distant recurrence were included in the local recurrence group and any records after the distant recurrence were included in the distant recurrence group. Table 6 presents the latest subsequent treatment data from CheckMate 238.

Subsequent treatment frequencies are similar to those in the original submission and continue to demonstrate that the majority of patients after nivolumab received dabrafenib plus trametinib [redacted] or ipilimumab [redacted] as systemic therapy. In comparison, [redacted] of patients after ipilimumab received dabrafenib plus trametinib [redacted] and pembrolizumab [redacted]

Table 6: Subsequent treatment splits by treatment arm from CheckMate-238 (48-month minimum follow-up)

	Local/regional recurrence		**Distant recurrence***	
	Nivolumab	**Ipilimumab**	**Nivolumab**	**Ipilimumab**
Patients who received subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]

	Local/regional recurrence		Distant recurrence*	
	Nivolumab	**Ipilimumab**	**Nivolumab**	**Ipilimumab**
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent surgery	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Note: * Includes patients who had a distant recurrence following a local recurrence.				

Re-treatment with nivolumab

Another key uncertainty with the original submission was the issue of re-challenging patients with anti-programmed cell death protein 1 (PD-1) treatments in the metastatic setting after receiving an anti-PD-1 treatment in the adjuvant setting. Previous clinical opinion suggested that in practice patients would most likely be re-challenged with PD-1 inhibitors 2 years after relapse.[4] The revised base case model was updated to include this assumption however, uncertainty remained about which treatments patients would receive if their disease recurred after nivolumab.

With longer follow-up data for CheckMate 238, the time from recurrence to first anti-PD-1 subsequent therapy following nivolumab treatment was analysed (see Table 7). The majority of patients in the nivolumab arm are re-treated with anti-PD-1s before the conservative 2 years assumed in the original submission. This is also consistent with the data collected in the Systemic Anti-Cancer Therapy (SACT) dataset, which shows that many patients are treated with an anti-PD-1 as a subsequent therapy after nivolumab in the first year of data collection (see Section A.6.2).

Updated data from the CheckMate 238 study included patients who were re-challenged with anti-PD-1s. This data continues to demonstrate a lower hazard of death compared with other active therapies and therefore it is unlikely that nivolumab

in the adjuvant setting affects the efficacy of subsequent treatments, including subsequent anti-PD-1 usage.

Table 7: Timing of anti-PD-1 re-challenge in the CheckMate 238 trial – nivolumab arm

Time from recurrence to first anti-PD-1 subsequent therapy	Number of patients (%)*	Mean time of 1st anti-PD-1 therapy (months)	Mean line of 1st anti-PD-1 therapy
< 6 months	[redacted]	[redacted]	[redacted]
≥ 6 months to < 12 months	[redacted]	[redacted]	[redacted]
≥ 12 months to < 24 months	[redacted]	[redacted]	[redacted]
≥ 24 months	[redacted]	[redacted]	[redacted]
[redacted] Anti PD-1 treatment includes both monotherapy and anti-PD1 treatment used in combination therapy. * Denominator for the percentage is [redacted] which is the total number of patients who had any systemic subsequent therapy after a recurrence event.			

Summary

With an additional 2 years of follow-up from CheckMate 238, results remain consistent with those previously presented in the original submission, showing statistically significant improvement in RFS of nivolumab versus ipilimumab which is expected to translate into an OS benefit. Despite OS data being immature and underpowered, they demonstrate a lower mortality trend compared with ipilimumab. In addition, subsequent treatment distributions are consistent with the previous data cut in both treatment arms, showing that of the nivolumab patients who received an anti-PD-1 as subsequent therapy, the majority received this within 2 years of their recurrence.

A.6.2 *Systemic Anti-Cancer Therapy dataset*

Systemic Anti-Cancer Therapy patient cohort

Between 30 November 2018 and 29 October 2019, 375 applicants were identified in the Blueteq system.[2] However, 76 patients were excluded due to duplicate applications (n = 20) or previous nivolumab use (n = 56) leaving 299 eligible patients.

Of these 299 patients, 12 did not receive treatment and three patients died before treatment, leaving 284 patients in the SACT cohort. A summary of patient characteristics included in the SACT cohort is presented in the Appendix (Section A.15.2) alongside the nivolumab CheckMate 238 population.

CheckMate 238 patients are slightly older than patients in the SACT cohort (median 63 versus 56 years, respectively). Eastern Cooperative Oncology Group (ECOG) performance status was also marginally worse in the SACT cohort (23% had an ECOG performance status of > 0 versus 9% in the CheckMate 238 cohort). These differences are expected when comparing real-life cohorts to clinical trial cohorts as patients in clinical trials are generally fitter than those treated in practice. BRAF status was also different in the SACT cohort, which may be because dabrafenib plus trametinib is available in clinical practice to patients who are BRAF V600 positive. However, retrospective analyses have confirmed that nivolumab has similar efficacy and safety outcomes regardless of BRAF mutation status[5] and therefore the difference in BRAF status is unlikely to affect outcomes.

Subsequent therapies

Twenty-five unique patients who received nivolumab went on to receive subsequent therapies after their last dose of nivolumab in the SACT cohort. However, 205 patients in the SACT cohort are still on treatment and therefore have not received any subsequent treatment, and given the relatively short follow-up of the SACT cohort, the subsequent treatment data are immature, with only 27 unique records (see Table 8).

The median time from a patient's last nivolumab cycle date in the SACT cohort to receiving their next regimen was 35 days (range: 13–197 days). The snapshot includes SACT activity up to 31 October 2019, and the median follow-up time from a patient's last nivolumab cycle in the SACT cohort was 154 days (range: 28–262 days).

Despite the limited SACT numbers, the data shows that after nivolumab the majority of patients follow on with a PD-L1 treatment, the most common being nivolumab plus ipilimumab. In comparison with the CheckMate 238 data, the majority of patients

went on to have dabrafenib plus trametinib or ipilimumab after nivolumab adjuvant treatment; this was, however, closely followed by anti-PD-L1 treatment (Table 6). CheckMate 238 has a longer follow-up than the SACT cohort and captures patients who have had multiple lines of subsequent treatment, whereas the SACT cohort only has two patients who had multiple treatments (27 subsequent treatment records for 25 patients).

Table 8: Distribution of subsequent treatment in the Systemic Anti-Cancer Therapy data cohort

Regimen	**SACT cohort (n = 284)**
Still on treatment	205 (72%)
Stopped treatment	79 (28%)
Patients receiving at least one subsequent treatment	25 (9%)
Ipilimumab + nivolumab	13 (5%)
Ipilimumab	4 (1%)
Dabrafenib + trametinib	3 (1%)
Binimetinib + encorafenib	2 (1%)
Bleomycin	1 (<1%)
Capecitabine	1 (<1%)
Cisplatin + dacarbazine + vinblastine	1 (<1%)
Pembrolizumab	1 (<1%)
Talimogene laherparepvec	1 (<1%)
Key: n, number; SACT, Systemic Anti-Cancer Therapy.	

A.7 Evidence synthesis

A.7.1 *CA184-029*

As per the original submission, the CA184-029 study (data cut date: 13 May 2016) was used to create an indirect treatment comparison (ITC) between nivolumab, from the CheckMate 238 study, and routine surveillance, via the common comparator of ipilimumab. Within-trial OS and RFS results for CA184-029 were presented in Section B.2.9 of the original submission, and Kaplan–Meier plots and summary statistics are presented in Sections A.15.4 and A.15.5 of this report, respectively.

The primary ITC was performed using a patient level data (PLD) meta-regression and an ITC using the Bucher methodology was performed as a sensitivity analysis.[6]

Differences between studies were consistent with the original submission, with the notable differences between studies detailed below (patient demographics are summarized in Section A.15.3):

- There was no overlap between trials for Stage IIIA and Stage IV patients; the CheckMate 238 study did not include patients with Stage IIIA disease, while the CA184-029 study did not include patients with Stage IV disease
- The CA184-029 study defined disease stage based on the 6th edition of the American Joint Committee on Cancer (AJCC) Staging Manual, while the CheckMate 238 study used the 7th edition AJCC staging
- There were treatment protocol differences with ipilimumab (presented in Table 9). Notably, patients in CA184-029 could receive ipilimumab treatment for up to 3 years, whereas in CheckMate 238 ipilimumab treatment was only permitted for 1 year.

Table 9: Ipilimumab dosage and duration information

CheckMate 238	CA184-029
• Ipilimumab 10 mg/kg every 3 weeks for four doses, then every 3 months up to a maximum of 1 year or until disease recurrence, unacceptable toxicity, major protocol violation or treatment refusal • Median duration = 2.7 months • Median number of doses = 4	• Ipilimumab 10 mg/kg every 3 weeks for four doses, then every 3 months up to a maximum of 3 years or until disease recurrence, unacceptable toxicity, major protocol violation or treatment refusal • Median duration = 2.1 months • Median number of doses = 4 • 25% of patients received ipilimumab beyond 1 year

A.7.2 *Patient level indirect treatment comparison and extrapolation*

Endpoints included in the analysis

To support the cost-effectiveness model, PLD meta-regression analysis was performed for the following endpoints:

- OS
- RFS – censoring ipilimumab patients after 1 year of treatment in CA184-029. This analysis was previously preferred by NICE in the original submission, and

therefore forms the base case RFS analysis. More detail on the within-trial analysis is presented in Section A.15.6.

- RFS – observed (results are presented as a scenario – see Section A.15.17)

For the RFS analyses, in line with the original submission, data were rebased at 12 weeks, as patients are first assessed for recurrence at this time, causing a clustering of events; Kaplan–Meier data were used to directly inform survival estimates prior to 12 weeks.

Analysis methodology

The methodology used in the PLD meta-regression was the same as those used in the original submission and was in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 – namely:

- The same parametric curves were fitted in the meta-regression (exponential, Weibull, Gompertz, log-normal, log-logistic, and generalised gamma)
- For all models, proportional hazards and accelerated failure time were not assumed because PLD were available for both studies. NICE TSD DSU 14 states: 'Generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach'.[7] Note, for completeness, log-cumulative hazard plots to assess proportional hazards and quantile–quantile (QQ)-plots) to assess accelerated failure time are presented in the appendix in Sections A.15.7 and A.15.8 respectively
- The same covariates were appropriate for inclusion in the PLD meta-regression as were included in the original submission:
  - Treatment (nivolumab, ipilimumab or placebo) – note that treatment effect was applied to two parameters for each parametric model (other than the one parameter exponential model), and as such the analysis did not assume proportional hazards or accelerated failure time
  - Sex (male or female)
  - Age (< 65 or ≥ 65 years)

  - Disease stage (Stage IIIA, Stage IIIB, Stage IIIC or Stage IV). Of note, in the CheckMate 238 trial, three patients had unknown/other disease stage, so were excluded from analysis
  - Trial (CA184-029 or CheckMate 238; trial was included as a covariate in the RFS ITC PLD meta-regression analysis only)

  These covariates were applied to the analysis of both OS and RFS and incorporated into the cost-effectiveness model using the corrected group prognosis method
- The same definitions of RFS were used for CheckMate 238 and CA184-029 as were used in the original submission
- RFS data were rebased at 12 weeks due to clustering of events at the time of first disease assessment; Kaplan–Meier data were used directly for the first 12 weeks. Note – clustering of events was not observed for OS, so rebasing was not performed
- The same criteria as in the original submission were used to select the most plausible curve fits

Results – overall survival

Patient characteristics in the PLD meta-regression were set to match the CheckMate 238 and CA184-029 trial populations to produce fitted OS parametric survival curves with Kaplan–Meier curve overlay. The fitted curves for the CheckMate 238 nivolumab arm and the CA184-029 placebo arm are presented in Figure 29 and Figure 30, respectively, in Section A.15.10. The model fit statistics are presented in Table 10. The coefficients used to estimate the curves are presented in Table 25 in Section A.15.9. Each curve was assessed for validity looking at:

- Whether the predicted curves for treatments within trials cross during trial follow up (indicates poor fit as KMs don't cross)
- The time at which the OS and RFS curves meet in the model for the routine surveillance arm

These are presented in Appendix A.15.10.

For OS, the ITC PLD meta-regression model produced a good fit to the Kaplan–Meier data for treatment with nivolumab in the CheckMate 238 trial for all models, with the exception of the Gompertz and exponential curves, which underestimated survival in the first 1.5 years. For the CA184-029 trial, the generalised gamma provided the best visual fit to the CA184-029 placebo arm, with the Gompertz curve underestimating survival in the first 1.5 years and the remaining models overestimating survival between 1 and 4 years.

The goodness-of-fit statistics indicated that the generalised gamma model provided the best statistical fit to the data, as it has the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) values. When considering the extrapolated period for each survival curve, the Gompertz and generalised gamma curves produced the most optimistic estimates for the placebo data, with the generalised gamma, exponential and log-normal curves producing the most optimistic estimates for nivolumab. Of the log-logistic, log-normal and generalised gamma curves, the generalised gamma curve provided the best visual and statistical fit to the data and was therefore selected as the base case for the economic model, consistent with the original submission.

The fitted generalised gamma curves are presented in Figure 3 and Figure 4 for the nivolumab (CheckMate 238) and placebo (CA184-029) arms, respectively. Additional comparisons with the observed trial data are detailed in Section A.15.18 and show that the models demonstrate that the proportion of patients alive at yearly intervals (Table 41) matches well to the Kaplan–Meier data.

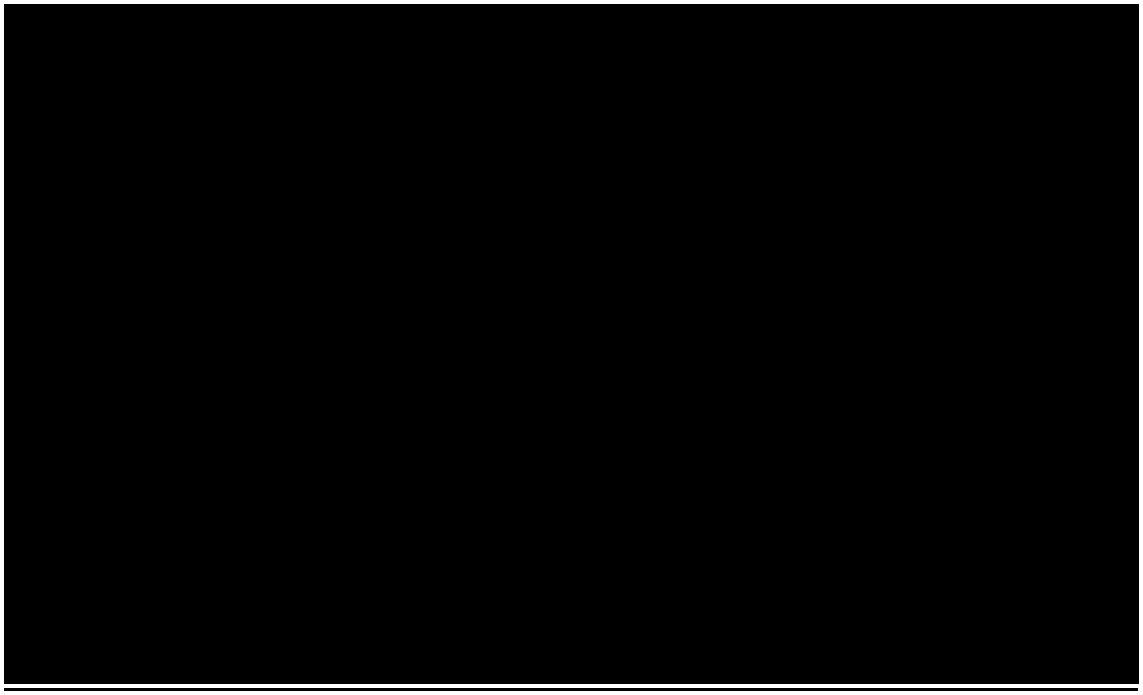
To explore the external validity of the ITC model for OS, exploratory analysis was performed and is presented in Section A.15.18. When patient characteristics were matched to the COMBI-AD study (a Phase III study comparing dabrafenib plus trametinib with placebo in BRAF-positive Stage III melanoma)[8] using a simulated treatment comparison, the model accurately fitted the observed placebo arm (Figure 42 and section A.15.18), indicating that the model provided reasonable estimates outside of the CheckMate 238 and CA184-029 studies for OS.

Table 10: Overall survival – ITC PLD meta-regression model fit statistics

Model	AIC	AIC rank	BIC	BIC rank
Exponential	10931.29	6	10981.01	4
Generalised gamma	**10818.40**	**1**	**10890.23**	**1**
Gompertz	10929.74	5	10996.04	6
Log-logistic	10891.63	3	10957.94	3
Log-normal	10849.68	2	10915.98	2
Weibull	10926.73	4	10993.03	5

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITC, indirect treatment comparison; PLD, patient level data.
Note: Bold distribution represents the base case selection.

Figure 3: CheckMate 238 overall survival ITC PLD meta-regression model – generalised gamma survival extrapolations – nivolumab arm



Key: ITC, indirect treatment comparison; Nivo, nivolumab; PLD, patient level data.

Figure 4: CA184-029 overall survival ITC PLD meta-regression model – generalised gamma survival extrapolations – placebo arm

Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; PBO, placebo; PLD, patient level data.

Once patient demographics for each of the treatment arms were matched to the model population (discussed further in Section A.8) it was observed that patients treated with nivolumab had improved OS compared with patients treated with placebo (Figure 8). Similarly, results of the Bucher comparison indicated that treatment with nivolumab had a significantly reduced hazard of death compared with treatment with placebo ([redacted]) based on the intention-to-treat (ITT) population. These results were also consistent with the Bucher analysis performed on the Stage IIIB/C patient population ([redacted]).

Results – RFS for ipilimumab censored after 1 year of treatment

Patient characteristics in the PLD meta-regression were set to match the CheckMate 238 and CA184-029 trial populations (ipilimumab patients censored after 1 year of treatment in CA184-029) to produce fitted RFS parametric survival curves with Kaplan–Meier curve overlay. The fitted curves for the CheckMate 238 nivolumab arm and the CA184-029 placebo arm are presented in Figure 31 and Figure 32, respectively, in Section A.15.10. The model fit statistics are presented in Table 11.

The coefficients used to estimate the curves are presented in Table 26 in Section A.15.9. Each curve was assessed for validity looking at:

- Whether the predicted curves for treatments within trials cross during trial follow up (indicates poor fit as KMs don't cross)
- The time at which the OS and RFS curves meet in the model for the routine surveillance arm

These are presented in Appendix A.15.10.

Similar to the analysis in the original submission, the ITC PLD meta-regression model produced a good fit to the Kaplan–Meier curve for the nivolumab arm in the CheckMate 238 trial for all models (Figure 31), with the exception of the exponential curve. It is likely that the exponential curve provided a poor fit to the Kaplan–Meier data as it assumes the hazard rate is constant over time, whereas in the nivolumab Kaplan–Meier curve, the rate of events and thus the hazard decreases over time. For the CA184-029 trial (Figure 32), the exponential curve and the Weibull distribution provided a poor fit to the placebo arm. Each of the remaining models provided a reasonable fit to the Kaplan–Meier curve; the log-normal and Gompertz models were the best fitting models to the CA184-029 placebo arm.

The goodness-of-fit statistics indicated that the log-logistic model provided the best statistical fit to the data, as it had the lowest AIC and BIC values. When considering the extrapolated period of each survival curve, the Gompertz model appeared to almost plateau completely, shortly after the end of the Kaplan–Meier curve for each of the treatment arms, and as a result was unsuitable for use. Excluding the Gompertz and exponential curves, the remaining distributions provided similar extrapolations, with the log-logistic and generalised gamma curves providing near identical extrapolations over 10 years for both treatment arms. Out of the log-logistic, log-normal and generalised gamma curves, the log-logistic curve provided the best statistical fit to the data and was therefore selected as the base case for the economic model, consistent with the original submission. The fitted log-logistic curves are presented in Figure 5 and Figure 6 for the nivolumab (CheckMate 238) and placebo (CA184-029) arms, respectively. Additional comparisons with the

observed trial data are detailed in Section A.15.18, demonstrating that the proportion of patients alive at yearly intervals (Table 40) matched well to the Kaplan–Meier data.

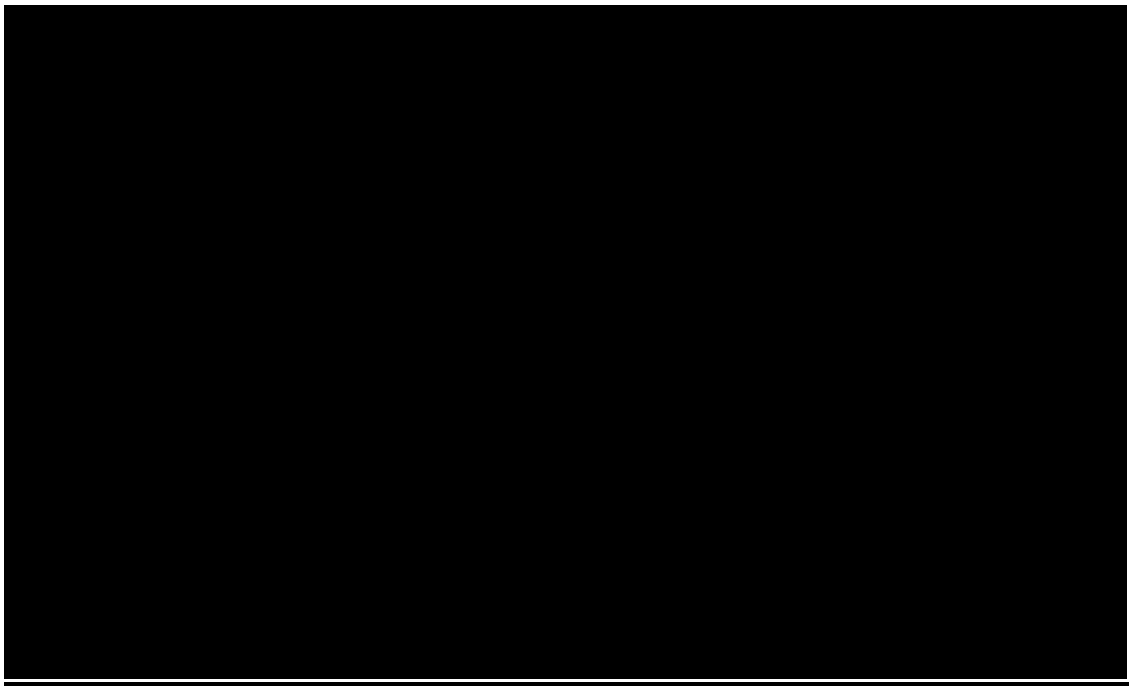
To explore the external validity of the ITC model further for RFS, exploratory analysis was performed and is presented in Section A.15.18. The analysis showed that when patient characteristics were matched to the KEYNOTE-054 (a Phase III study comparing pembrolizumab with placebo in patients with resected Stage III melanoma)[9] and COMBI-AD studies using a simulated treatment comparison, the model accurately fitted the observed placebo arms presented in Figure 41 and Figure 42, respectively, indicating that the model provided reasonable estimates outside the CheckMate 238 and CA184-029 studies for RFS.

Table 11: Recurrence-free survival (ipilimumab patients censored after 1 year of treatment) – ITC PLD meta-regression model fit statistics

Model	AIC	AIC rank	BIC	BIC rank
Exponential	13150.35	6	13198.73	6
Generalised gamma	12792.04	2	12861.92	2
Gompertz	12855.57	5	12920.07	5
Log-logistic	**12783.72**	**1**	**12848.22**	**1**
Log-normal	12798.66	3	12863.16	3
Weibull	12811.97	4	12876.48	4

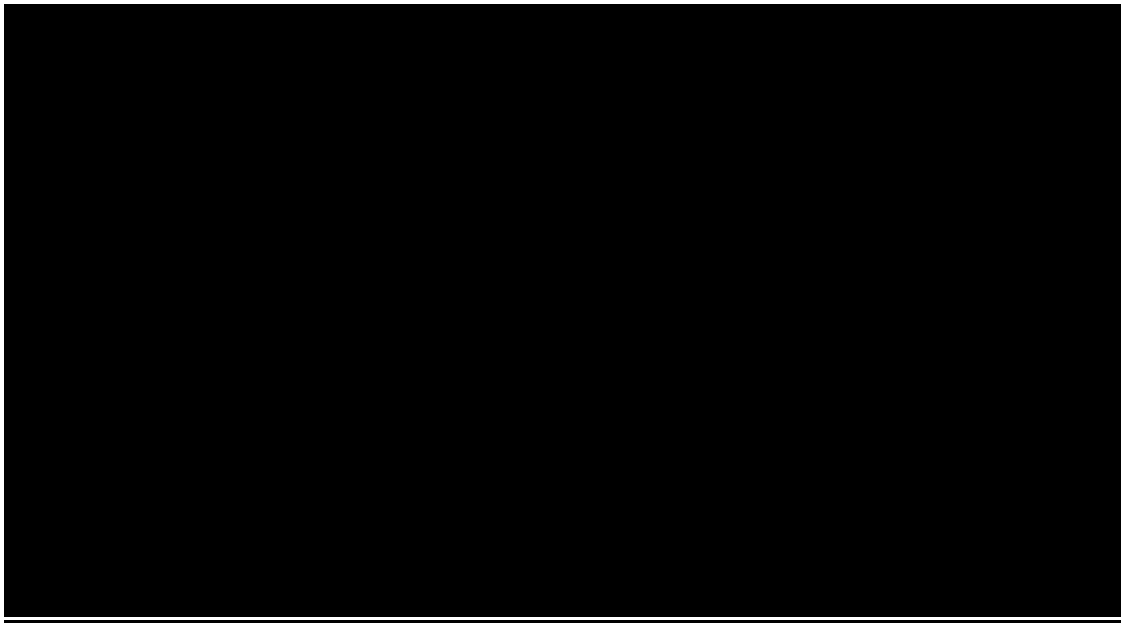
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITC, indirect treatment comparison; PLD, patient level data.
Note: Bold distribution represent the base case selection.

Figure 5: CheckMate 238 recurrence-free survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 – nivolumab arm



Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab; PLD patient level data.
Note: KM from baseline is displayed, log-logistic curve is fitted from 12 weeks onwards.

Figure 6: CA184-029 recurrence-free survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 – placebo arm



Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; PBO, placebo; PLD, patient level data.
Note: KM from baseline is displayed, log-logistic curve is fitted from 12 weeks onwards.

Once the patient demographics for each of the treatment arms were matched to the model population (discussed further in Section A.8) it was observed that patients treated with nivolumab had improved RFS compared with patients treated with placebo (Figure 7). Similarly, the results of the Bucher comparison indicated that treatment with nivolumab had a significantly reduced hazard of an RFS event compared with treatment with placebo (HR: [redacted]) based on the ITT population; the results were also consistent when the Bucher analysis was performed on the population of Stage IIIB/C patients ([redacted]).

Analysis strengths, limitations and discussion

The primary ITC was performed using a PLD meta-regression as it uses PLD from both studies to provide the 'gold standard' in population adjustment. This method represents the most robust estimate of the ITC between nivolumab and placebo, and allows both the ITC and extrapolation of survival curves to be performed within a single analysis.[10] This analysis also produced highly consistent results (same selection of curves and very similar extrapolation) with the analysis performed in the original submission, which assessed RFS with a minimum follow-up of 18 months, indicating that the PLD meta-regression extrapolates the data well (see Appendix A.15.18).

The staging of patients differed between the CheckMate 238 and CA184-029 studies; that is, the CA184-029 study did not recruit Stage IV no evidence of disease (NED) patients, while the CheckMate 238 study did not recruit Stage IIIA patients. Figure 16 and Figure 19 in the Appendix indicate that the relative treatment effect of RFS is consistent within studies across disease stages. The Bucher comparisons presented above show consistent results between the ITT population and Stage IIIB/C patient subgroup for RFS and OS; this is also seen in published results comparing the nivolumab arm of CheckMate 238 and the placebo arm of CA184-029 for other endpoints.[11] These results suggest that including Stage IIIA and Stage IV NED patients does not modify the treatment effect. In addition, the KEYNOTE 054 study showed that for pembrolizumab, which is also a PD-L1 inhibitor, disease stage (Stage IIIA, Stage IIIB and Stage IIIC) was not a significant effect modifier (interaction p-value = 0.69). Furthermore, clinical experts (from the advisory board

used in the original submission) agreed that if resection is possible with Stage IV NED patients, then outcomes would be very similar to those of Stage IIIC patients.[3, 12] Therefore, the covariate adjustment in the meta-analysis is appropriate as it allows for estimation of RFS and OS for the unobserved populations (nivolumab with Stage IIIA disease and placebo with Stage IV NED disease), assuming that disease stage does not change the relative treatment effects within these populations.

Another source of uncertainty is ipilimumab, which was given for up to 1 year in CheckMate 238 and 3 years in CA184-029. Clinical opinion received at the Advisory Board meeting for the original submission indicated that the difference in dosing would not impact effectiveness.[3] To explore any possible difference in RFS, an analysis was performed where patients who remained on ipilimumab treatment after 1 year were censored for RFS. This analysis showed a slight reduction in the treatment effect compared with the observed RFS analysis. However, the analysis has the limitations discussed in Section A.15.6, notably interval censoring, which may underestimate the true RFS for the ipilimumab arm in CA184-029 and consequently reduce the estimated relative treatment effect between nivolumab and placebo in the ITC.

In the analysis of OS, it is possible that subsequent therapies may have some impact on the results. Since 2014, more active subsequent therapies have become available in the metastatic setting, including nivolumab. As such, the subsequent therapy distribution in the CA184-029 study may not be representative of current clinical practice and may underestimate current overall survival for both treatment arms. However, the inclusion of a trial covariate in the analysis should adjust for this difference to some extent because the relative difference between the ipilimumab arms of the two studies should capture differences in subsequent therapy and other unobserved differences between studies; this is reflected in the coefficient values, which indicate that the trial coefficient value for OS (Table 25 in Section A.15.9) is much larger than that in the RFS analysis (ipilimumab patients censored after 1 year of treatment) (Table 26 in Section A.15.9). Adjustment using this covariate to the CheckMate 238 study from the CA184-029 study, would therefore increase overall survival on both treatment arms but assume that the relative effect between

treatments ipilimumab and placebo remains the same. Additionally, the resulting modelled routine surveillance OS curve was consistent with newer studies once populations were adjusted (see Appendix Section A.15.18), which indicates that the trial covariate successfully accounted for trial age and differences in subsequent treatments.

Other sources of uncertainty in the ITC such as the definition of RFS in CA184-029 and the lack of data collected for BRAF and PD-L1 status in CA184-029 are discussed further in Section B.2.9 of the original submission.

Overall, the analysis used PLD to produce a robust ITC, allowed survival outcomes for nivolumab and placebo to be estimated for matched populations and non-observed populations, and appeared to fit well to both internal data (CheckMate 238 and CA184-029) and to external data (COMBI-AD and KEYNOTE-054). For RFS, the PLD meta-regression gave results that were consistent with the analysis performed in the original submission (based on a minimum of 18 months follow-up in CheckMate 238), indicating that the methodology and chosen distributions are appropriate to model outcomes for adjuvant melanoma. The results of these new analyses show that despite data remaining immature, nivolumab continues to demonstrate a meaningful clinical benefit over routine surveillance and is an important treatment option for achieving long-term RFS and OS improvements in patients with newly resected melanoma.

A.8 Incorporating collected data into the model

The previous submission presented two modelling approaches: a partitioned survival model and a state-transition model. PLD meta-regression with survival analyses were conducted using the latest data from CheckMate 238 (RFS and OS) in order to extrapolate these outcomes over the modelled lifetime horizon.

A.8.1 *Partitioned survival model*

In the final TA558 models, the partitioned survival model used efficacy data mainly from two sources – CheckMate 238 and CA184-029. The RFS curves were derived from an indirect treatment meta-analysis between CheckMate 238 and CA184-029, resulting in parametric survival curves estimated for nivolumab in comparison with

observation (placebo). The ipilimumab arm in CA184-029 (the treatment link) applied censoring to any patients who remained on ipilimumab after 12 months to coincide with the treatment duration seen in CheckMate 238. The OS curves were based on parametric survival curves fitted to the CA184-029 trial where ipilimumab OS was used as a proxy for nivolumab OS. These resulting curves were then manually adjusted upwards such that the resulting nivolumab curve sat in line with the nivolumab OS Kaplan–Meier curve from CheckMate 238. This method relied on the assumption that the treatment effect between ipilimumab and placebo from CA184-029 would be the same as the treatment effect between nivolumab and placebo i.e. nivolumab has the same OS as ipilimumab.

The updated analysis post CDF used an updated indirect meta-analysis for RFS and a new indirect meta-analysis for OS using data from the 48-month data cuts of CheckMate 238 and CA184-029 (see Section A.7).

Recurrence-free survival

The patient level meta-regression for RFS was updated using the 48-month data cut of CheckMate 238. With the exception of updated data, the same approach was used as per the previous submission (see Section A.7). The corrected group prognosis (CGP) method was used to calculate the final parametric survival curves used in the economic model (see TA558 Document B, Section B3.3, Page 114).

In the previous submission, the log-logistic was considered the most plausible distribution based on AIC and BIC values and on clinical plausibility (see TA558 Document B, Section B.2.9, Page 68). On re-evaluation of the parametric curves with the updated CheckMate 238 data, the log-logistic distribution remained the statistically best fitting, giving similar outcomes to the previous log-logistic extrapolations (see Section A.7 and Appendix A.15.18).

Figure 7 shows the final curves using the log-logistic distribution and estimated survival of our matched population of interest (i.e. Stage IIIA – Stage IV NED) using the CGP method.

Figure 7: ITC RFS final curve using matched population

Key: IPD, individual patient-level data; ITC, indirect treatment comparison; RFS, recurrence-free survival.

Overall survival

As presented in Section A.7, given that PLD were available for both studies, a patient level meta-regression was conducted for OS for nivolumab versus routine surveillance using ipilimumab as the treatment link between CheckMate 238 and CA184-029. This was also consistent with the approach used to estimate RFS. The outcome from this analysis was the fitted parametric curves described in Section A.7. The CGP method was used to calculate the final parametric survival curves used in the economic model (see TA558 Document B, Section B3.3, Page 114 for details of how this approach is used).[13]

The generalised gamma was chosen as the base case curve given that it had the best fitting curve statistically and visually, and gave plausible outcomes compared with literature sources (see Section A.7). This was also consistent with the chosen curve used to extrapolate OS from CA184-029 in the previous submission.

Figure 8 shows the final curves using the generalised gamma distribution and estimated survival of our matched population of interest (i.e. Stage IIIA–Stage IV NED) using the CGP method.

Figure 8: ITC OS final curve using matched population

Key: IPD, individual patient-level data; ITC, indirect treatment comparison; OS, overall survival.

Subsequent treatment

Subsequent treatment data using the 48-month data cut from CheckMate 238 were included in the model updates. Details of how these were derived from the data set and the dosing of each treatment can be found in the previous submission (TA558, Document B, Section B.3.5, Page 157).

The proportion of records per subsequent treatment (Table 6) was multiplied by the calculated drug cost (TA558, Document B, Table 49). This cost was then multiplied by the proportion of subsequent treatment records compared with how many patients were in each recurrence type to generate the total subsequent treatment cost per recurrent patient. These overall subsequent treatment costs were then weighted by

the proportion of patients who had each type of recurrence (local/regional recurrence [redacted] and distant recurrence [redacted]), with costs applied to patients upon recurrence (Table 12).

Table 12: Total subsequent treatment cost applied per recurrence in the model per adjuvant treatment

Recurrence type	Nivolumab	Routine surveillance
Local/regional	[redacted]	[redacted]
Distant	[redacted]	[redacted]

A.8.2 *State-transition model*

In the TA558 final model, the state-transition model used the RFS curves derived from the patient-level meta-regression ITC to inform the time dependent transitions from recurrence-free to either post-recurrence or death (see TA558, Appendix N.1, Page 111). Post-recurrence survival was based on weighted survival curves using different treatments in metastatic melanoma (see TA558, Appendix N.2, Page 114). The distributions used to inform the weights in the final Markov model were based on subsequent treatment data from the ipilimumab arm in CheckMate 238 (considered the most reflective of UK practice – see TA558, BMS response to ACD, Page 17). Post-recurrence survival for nivolumab was additionally split into pre-retreatment and post re-treatment at 2 years. After 2 years post-recurrence, patients could be retreated with anti-PD-1s; before this time point it was assumed they were treated with ipilimumab instead.

In the updated analysis post CDF, the distributions used to inform the post-recurrence curves were based on subsequent treatment data collected from the latest CheckMate 238 trial. As per the previous base case, the subsequent treatments of the ipilimumab arm were used to inform the distributions of routine surveillance and nivolumab, as these were shown to be reflective of subsequent treatment use compared with real-world sources (see Section A.15.12).

The subsequent treatment distribution post nivolumab could be informed by the SACT data (see Section A.6.2) as this was the most recent data and reflected the

'adjuvant era'. However, these data were limited due to patient numbers and therefore were used in sensitivity analysis.

For the base case, the state-transition model retained the same settings for re-challenge and assumed that patients are not re-treated with anti-PD-1s for the first 2 years after nivolumab use; instead, patients are treated with ipilimumab. This was shown to be a conservative assumption given that SACT data already show a large proportion of anti-PD-1 use within the year of data collection. Therefore, for the scenario using SACT data to inform post-nivolumab subsequent treatment distribution, it was assumed that patients have these treatments straight after recurrence without a 2-year gap.

Details of the subsequent treatment weightings used to inform the new base case and scenarios are presented in Appendix A.15.12.

A.8.3 *Long-term survival*

As per the original submission, long-term survival estimates were estimated from the AJCC 8th edition registry data applied at 10 years (see TA558, Document B, Section B.3.3, Page 123). In addition to registry data, all OS projections were adjusted for background mortality so that the estimated hazard of mortality was never less than that of the age-adjusted general population.[14] The 10-year time point was selected as this is approximately when long-term melanoma survival outcomes begin to plateau[15, 16], suggesting that the risk of death due to melanoma is reduced at this time.

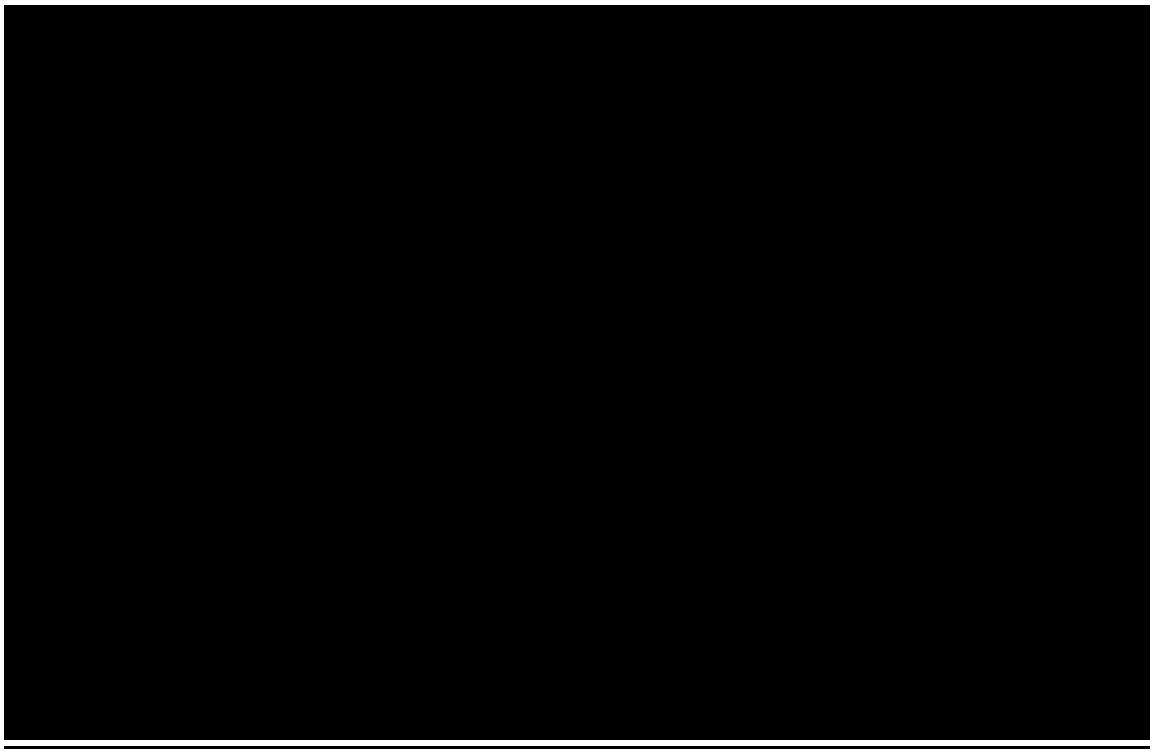
To estimate the long-term RFS curve, a HR was calculated comparing RFS and OS. Pseudo PLD were created from digitized observational OS and RFS curves from the E1697 trial (HR: 1.98 (95% CI: 1.62, 2.43).[16] This HR was applied to the long-term OS curve to produce the long-term RFS curve. The committee considered that these methodologies used to estimate long-term RFS were complex and relied too much on potentially inappropriate data sources. To account for these concerns, the ITC extrapolations for RFS have been used for the whole time horizon instead of adjusting at 10 years in the sensitivity analysis (see Section A.12).

A.8.4 *Final model projections*

Figure 9 and Figure 10 present the final model projections for the partitioned survival model and state-transition model, respectively, after incorporating the new data post-CDF.

Validation of the final model outcomes is presented in Section A.15.18.

Figure 9: Partitioned survival model – final model projections for RFS and OS



Key: OS, overall survival; RFS, recurrence-free survival.

Figure 10: State-transition model – final model projections for RFS and OS

Key: OS, overall survival; RFS, recurrence-free survival.

A.9 Key model assumptions and inputs

Analyses were conducted using the committee's preferred assumptions from the original submission, but using the more mature CheckMate 238 data. The 'original' assumptions described the latest models that were considered appropriate by the committee and are detailed in TA558, BMS response to ACD.

The long-term (48 month) and more mature data from the CheckMate 238 trial provide additional evidence that the assumptions and survival extrapolations used in the original submission were appropriate. Scenario analyses have also been conducted to explore alternative extrapolations (for OS and RFS) and subsequent therapy assumptions (SACT data and real-world evidence).

Table 13 presents the key changes in the model inputs from the previous submission compared with the post-CDF submission. In addition to the updated data from CheckMate 238, the dose of nivolumab has also been changed to be consistent with

the summary of product characteristics and uses 240 mg twice per week instead of 3 mg/kg twice per week.[17] As 3 mg/kg twice per week was the dose used in the original submission and CheckMate 238 trial, this has been presented in scenario analysis as well as the alternative flat dosing option of 480 mg four times per week. As a result of the dose change, the administration cost has also been changed to reflect a simpler infusion based on flat dosing: this now uses NHS reference code 'SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance'.

Table 13: Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/justification
Recurrence-free survival source B2.9, Page 46. BMS ACD response, Page 9.	ITC with CheckMate 238 (24-month data cut) and CA184-029. Ipilimumab patients in CA184-029 censored if on treatment beyond 12 months	ITC with CheckMate 238 (48-month data cut) and CA184-029. Ipilimumab patients in CA184-029 censored if on treatment beyond 12 months	Further follow-up data from the pivotal trial (CheckMate 238) were incorporated into the clinical model
Recurrence-free survival extrapolation B.2.9, Page 68.	KM for 12 weeks, followed by log-logistic parametric curve	KM for 12 weeks followed by log-logistic parametric curve	As per the original submission, goodness of fit statistics and visual inspection suggest that the log-logistic remained the best fitting extrapolation for the updated clinical data.
Nivolumab dose	3 mg/kg Q2W	240 mg Q2W	Dose has changed to be consistent with the licensed nivolumab dose for adjuvant melanoma.[17]
Administration cost	SB13Z: 'Deliver more Complex Parenteral Chemotherapy at First Attendance'	SB12Z: 'Deliver Simple Parenteral Chemotherapy at First Attendance'	Changed to reflect the simpler dosing of nivolumab based on flat dosing instead of weight based dosing.
Partitioned survival model			
Overall survival source. BMS response to ACD, Page 11.	Parametric curves fitted to CA184-029 and manually shifted to match the CheckMate 238 OS KM data. Assumed that ipilimumab and nivolumab have equal efficacy.	ITC with CheckMate 238 (48-month data cut) and CA184-029.	Further follow-up data from the pivotal trial (CheckMate 238) have been incorporated into the clinical model.

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/justification
Overall survival extrapolation. BMS response to ACD, Page 11.	Generalised gamma	Fully fitted generalised gamma parametric curve	Goodness of fit statistics and visual inspection suggest that the generalised gamma was the best fitting extrapolation for the updated clinical data.
State-transition model			
Subsequent treatment distributions. BMS response to ACD, Page 5 and 18.	Based on the ipilimumab subsequent treatment data from 24 months CheckMate 238. Pre 2 years, no anti-PD-1s used and instead assumed ipilimumab was given.	Based on the ipilimumab subsequent treatment data from 48 months CheckMate 238. Pre 2 years, no anti-PD-1s used and instead assumed ipilimumab was given.	Further follow-up data from the pivotal trial (CheckMate 238) have been incorporated into the clinical model.
Key: ACD, appraisal consultation document; KM, Kaplan–Meier; OS, overall survival; Q2W, twice per week; RFS, recurrence-free survival.			

A.10 Cost-effectiveness results (deterministic)

A.10.1 *Replication of the key cost-effectiveness result(s) considered by the committee to demonstrate plausible potential for cost effectiveness at entry to the CDF*

The key cost-effectiveness results considered by the committee to demonstrate plausible potential for cost effectiveness at entry to the CDF have been replicated in Table 14 and Table 15.

An error in the model has been identified in the CGP sheet of the original model. This has now been corrected, alongside some minor corrections in the calculation of subsequent treatments (see Section A.15.13). These changes have increased the incremental ICERs slightly, but have little impact on the overall conclusions. Table 14 presents the results of the analysis upon entry to the CDF for both the partitioned survival and state-transition models with the corrected values.

Table 14: Cost-effectiveness results (deterministic): replication of the analysis that demonstrated plausible potential for cost effectiveness at CDF entry

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							
Routine surveillance	[redacted]	17.83	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,423
Partitioned survival model – corrected							
Routine surveillance	[redacted]	17.83	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,870
State-transition model							
Routine surveillance	[redacted]	14.19	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,018
State-transition model – corrected							
Routine surveillance	[redacted]	17.62	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,235

Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

A.10.2 *Cost-effectiveness results incorporating the data collected during the CDF data collection period, with all model inputs and parameters unchanged from the cost-effectiveness analysis in Section A.10.1*

The cost-effectiveness results that incorporate the updated CheckMate 238 data collected during the CDF, with all model inputs and parameters (aside from correction of errors) unchanged from the original cost-effectiveness analysis, are presented in Table 15. All analyses include a patient access scheme (PAS) discount of [redacted] off the list price of nivolumab.

The addition of long-term CheckMate 238 data including OS data has resulted in a reduction in the ICERs of both models presented in the original submission. This is a result of decreasing incremental costs and increasing QALYs and life years gained.

A variety of assumptions was explored in these analyses in addition to those explored in the original submission (presented in scenario analysis, Section A.12) including:

- No long-term adjustments for RFS
- Nivolumab subsequent treatment (distant) based on the SACT data
- Nivolumab dosing

Table 15: Cost-effectiveness results (deterministic): analysis demonstrating plausible potential for cost effectiveness at CDF entry – incorporating updated clinical evidence

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							
Routine surveillance	[redacted]	18.65	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,263
State-transition model							
Routine surveillance	[redacted]	14.27	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,299
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

A.10.3 *Cost-effectiveness results incorporating data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions*

As discussed in Section A.9, in addition to including the updated CheckMate 238 data in the base case, the dosing of nivolumab has changed to 240 mg twice per week instead of 3 mg/kg to align with nivolumab's summary of product characteristics and clinical practice. In addition to this, the administration cost has been revised from a complex cost code to a simple cost code from NHS references to account for this simplification in dosing.

The revised dosing and administration cost reduces the ICER further to £14,195 per QALY compared with routine surveillance using the partitioned survival model, and £17,120 per QALY using the state-transition model. Both model structures are presented in the company base case to reduce any uncertainty associated with structural error. Both models demonstrate that nivolumab is still cost effective versus routine surveillance with the addition of longer follow-up CheckMate 238 data, OS data from CheckMate 238, conservative assumptions around re-challenge, and revision of drug costs based on clinical practice.

Details of the impact of each change are presented in Section A.15.14.

Table 16: Cost-effectiveness results (deterministic): new company base-case

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							
Routine surveillance	[redacted]	18.65	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,195
State-transition model							
Routine surveillance	[redacted]	14.27	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,120
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

A.11 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed for 1,000 iterations. In each iteration, the model inputs were randomly drawn from the specified distributions, as summarized in Section A.15.15.

The average (mean) incremental QALYs gained from nivolumab with the PAS applied across the 1,000 iterations are displayed in Table 17. The visual results of the probabilistic sensitivity analysis runs are presented in Figure 11 for the partitioned survival model and Figure 12 for the state-transition model. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability of nivolumab being the most cost-effective treatment option was [redacted] in the partitioned survival model and [redacted] with the state-transition model (with the PAS applied – see Section A.15.16). The results of the probabilistic analysis were similar to those of the deterministic analysis.

Table 17: Updated base-case results (probabilistic) – B.3.8 (Page 169)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							
Routine surveillance	[redacted]	19.37	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,930
State-transition model							
Routine surveillance	[redacted]	14.46	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,136
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 11: Cost-effectiveness plane: partitioned survival model

Key: QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 12: Cost-effectiveness plane: state-transition model

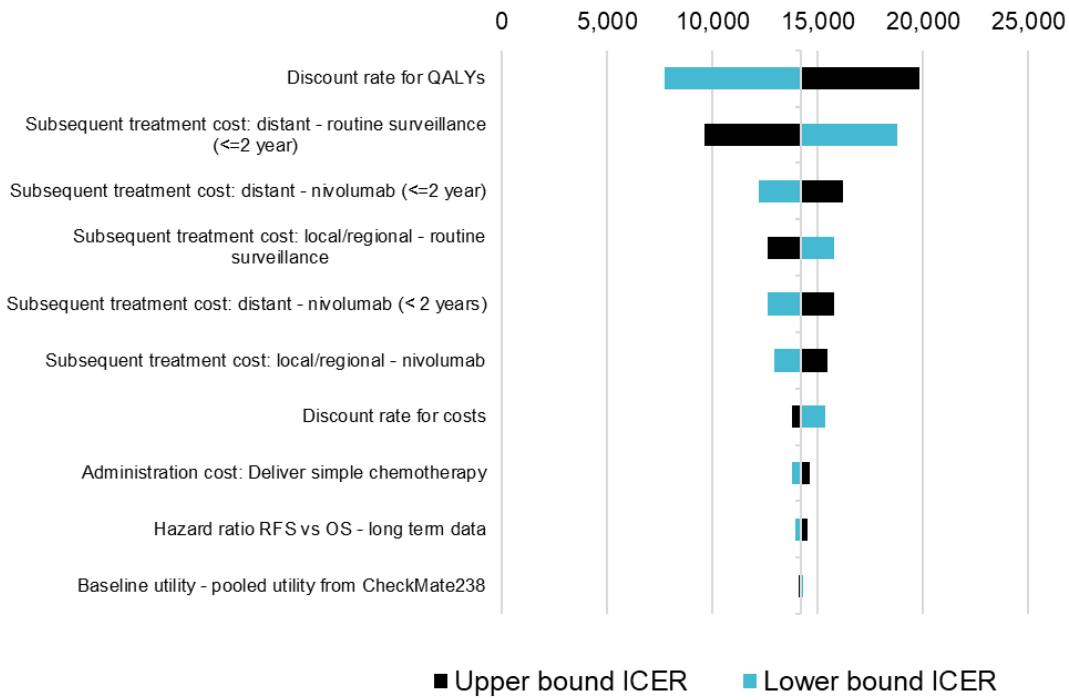
Key: QALY, quality-adjusted life year; WTP, willingness to pay.

A.12 Key sensitivity and scenario analyses

Figure 13 and Figure 14 present tornado diagrams showing the top 10 drivers of cost effectiveness with descending sensitivity from the one-way sensitivity analysis when nivolumab is provided with the PAS discount. The ICERs for both models were most sensitive to the discount rate applied to QALYs and subsequent treatment costs. All ICERs remained below the £30,000 willingness-to-pay threshold for each parameter tested.

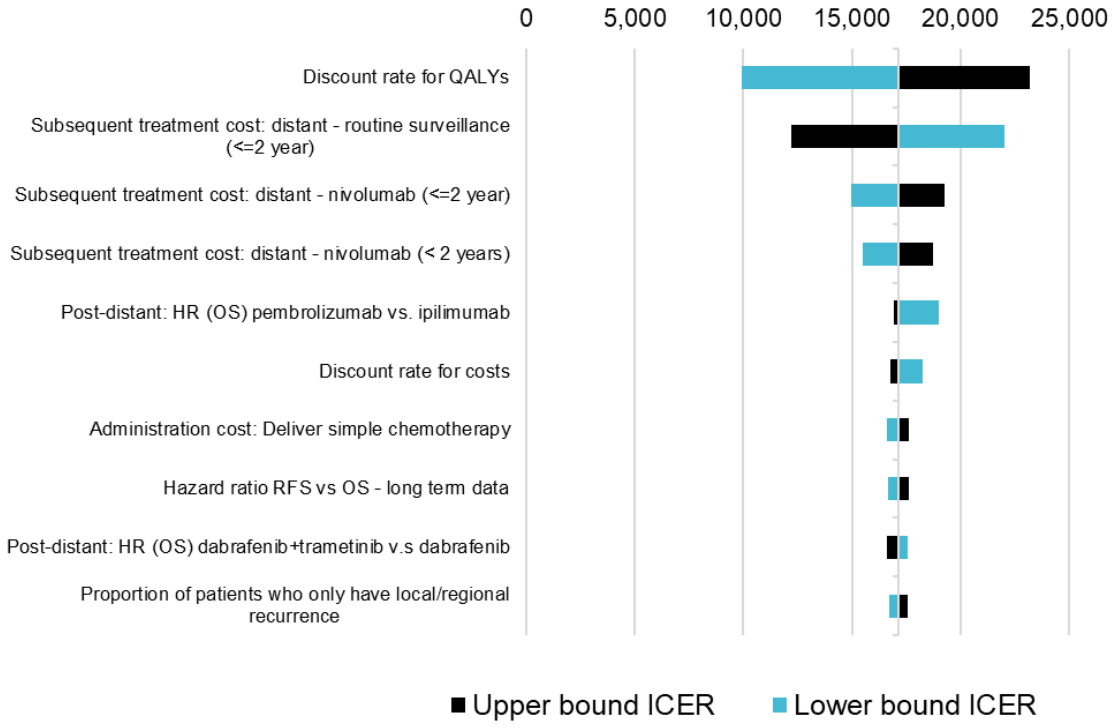
The parameters with the greatest impact in the one-way sensitivity analysis were consistent with the original submission (TA558, company response to ACD).The addition of long-term, more mature data from CheckMate 238 has reduced the uncertainty surrounding the long-term benefit of nivolumab, as the aforementioned parameters have a reduced impact on the ICERs. The one-way sensitivity analysis demonstrated that varying parameters by their upper and lower bounds did not impact the cost effectiveness of nivolumab versus routine surveillance and this was consistent with the previous submission.

Figure 13: Tornado diagram – partitioned survival model - B.3.8 (Page 172)



Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life-year; RFS, recurrence-free survival.

Figure 14: Tornado diagram – state-transition model



Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life-year; RFS, recurrence-free survival.

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis. The key scenario analyses are presented in Table 18 and Table 19 for the partitioned survival and state-transition models, respectively (where nivolumab is provided with the PAS discount). The key scenarios summarize the top five plausible scenarios that had the greatest impact on the ICER. As shown in Table 18 and Table 19, all scenarios with the exception of one in the state transition model were associated with an ICER of less than £30,000 per QALY gained versus routine surveillance. The one scenario which exceeds £30,000 per QALY is using the exponential distribution for the RFS extrapolation, however this can be dismissed as implausible given the poor fit to the data (see Appendix A.15.10 and A.15.17).

Scenarios that had the biggest impact revolve around different assumptions in the long-term estimates. Using AJCC 7th edition data (Balch et al, 2009) at year 5 has the biggest impact on both models. However, this data is largely outdated based on

predictions using newer AJCC data are more reflective of melanoma survival and changes to clinical practice.

A full comprehensive list of all scenarios is presented in Section A.12. Based on committee comments on the complexity of the RFS long-term adjustment, a scenario has also been added that does not adjust the RFS at 10 years but uses the ITC estimations for the full-time horizon. Additionally, scenarios were tested that used the SACT data to inform the subsequent treatment distribution for the nivolumab arm in the state-transition model. These scenarios further reduced the ICERs (see Appendix A.15.17).

Table 18: Key scenario analyses – partitioned survival model

Scenario and cross reference	Scenario detail	Brief rationale	ICER	Impact on base-case ICER
Base case			**£14,195**	**NA**
Long-term survival adjustment [Gershenwald, applied after 10 years & OS vs RFS HR from E1697]	Balch, 5 years	The ICER is sensitive to adjustments made to long-term survival (source used, cut off and extrapolation applied). Balch is an older study; additionally a cut off of 5 years has been analysed.	£26,157	+£11,962
Nivolumab subsequent treatment (distant) [CheckMate 238]	SACT data	The ICER is sensitive to subsequent treatment data applied. SACT provides UK nivolumab subsequent treatment data from clinical practice (the SACT dataset only provides follow-up of 1 year)	£7,604	-£6,591

Long-term survival adjustment [Generalised gamma distribution, Gershenwald, applied after 10 years & OS vs RFS HR from E1697]	Log-normal	The ICER is sensitive to adjustments made to long-term survival (source used, cut off and extrapolation applied). Alternative extrapolations have been analysed.	£19,841	+£5,645
	Log-logistic		£19,802	+£5,607
	Gershenwald, 5 years	The ICER is sensitive to adjustments made to long-term survival (source used, cut off and extrapolation applied). An alternative cut off has been analysed.	£18,397	+£4,202
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NA, not applicable; OS, overall survival; RFS, recurrence-free survival; SACT, Systemic Anti-Cancer Therapy.				

Table 19: Key scenario analyses – state-transition model

Scenario and cross reference	Scenario detail	Brief rationale	ICER	Impact on base-case ICER
Base case			**£17,120**	**NA**
Long-term survival adjustment [Gershenwald, applied after 10 years & OS vs RFS HR from E1697]	Balch, 5 years	The ICER is sensitive to adjustments made to long-term survival (source used, cut-off and extrapolation applied). Balch is an older study, additionally a cut off of 5 years has been analysed.	£29,687	+£12,567
Nivolumab subsequent treatment (distant) [CheckMate 238]	SACT data	The ICER is sensitive to subsequent treatment data applied. SACT provides UK nivolumab subsequent treatment data from clinical practice (the SACT dataset only provides follow-up of 1 year)	£10,275	-£6,845
Long-term survival adjustment [Generalised gamma distribution, Gershenwald, applied after10 years & OS vs RFS HR from E1697]	Log-normal	The ICER is sensitive to adjustments made to long-term survival (source used, cut off and extrapolation applied). Alternative extrapolations have been analysed.	£22,667	+£5,547
	Log-logistic		£22,658	+£5,538
	Balch 2009, OS/RFS HR from 029	The ICER is sensitive to adjustments made to long-term survival (source used, cut off and extrapolation applied). Balch is an older study; additionally an alternative hazard ratio has been applied.	£21,819	+£4,699

Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NA, not applicable; OS, overall survival; RFS, recurrence-free survival; SACT data, Systemic Anti-Cancer Therapy data.

A.13 Key issues and conclusions based on the data collected during the CDF review period

The additional data now available from CheckMate 238 provides additional evidence of the long term benefit of nivolumab monotherapy for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease. The updated data cut (48 months) continues to demonstrate a significant RFS improvement for nivolumab compared with another active comparator (ipilimumab). Additional OS data from CheckMate 238 remains immature making it [redacted] compared with ipilimumab; however, [redacted] for patients treated with nivolumab compared with those treated with ipilimumab (hazard ratio [HR]: [redacted] [95% confidence interval [CI]: [redacted]

The ITC for RFS was updated using the longer follow-up data from CheckMate 238 to enable the comparison of nivolumab with routine surveillance with results remaining consistent with the original ITC performed (24-month data). The updated RFS ITC continues to demonstrate a significant benefit for nivolumab compared with placebo despite using the ipilimumab censored analysis, which biased against nivolumab.

OS data were not available in the original submission, so a new ITC analysis for OS was conducted using the longer follow-up data from CheckMate 238 and CA184-029. These results were consistent with the RFS ITC and [redacted]

Data collected from the SACT cohort study data were collected mainly to address the uncertainty associated with subsequent treatment after adjuvant treatment with nivolumab. As expected patients in the Checkmate 238 trial were younger and had a lower ECOG status when compared with the SACT cohort. The availability of dabrafenib plus trametinib in clinical practice may have also affected the proportion of patients who are BRAF V600 positive, but retrospective have confirmed that nivolumab has similar efficacy and safety outcomes regardless of BRAF mutation status. The subsequent treatment data from the SACT cohort are immature, but do

show that patients are re-treated with anti-PD-1s sooner than the modelled 2 year time point, suggesting that the state-transition model is conservative, given that it assumes that patients cannot receive an anti-PD-1 before 2 years.

Evidence demonstrating the clinical- and cost-effectiveness of nivolumab has been provided as part of this appraisal in line with the terms of engagement document. The results showing that nivolumab would be a cost-effective option for the adjuvant treatment of newly resected patients.

The new data from CheckMate 238 incorporated into the cost-effectiveness model reduced the ICERs for both the partitioned survival and state-transition models. The results of both models validate the conclusions of the previous submission in that nivolumab is cost effective compared with routine surveillance at the £30,000 willingness to pay threshold. In addition, the incorporation of longer follow-up from CheckMate 238, including OS, results in more clinically plausible estimates for routine surveillance, where previous results looked pessimistic compared with what would be expected. More recent adjuvant trials, which include a placebo arm, also validated these results once the patient characteristics had been adjusted to match those trials.

Sensitivity analyses demonstrated that the results were robust, with the probabilistic sensitivity analysis results being very similar to the deterministic results, and the deterministic scenarios resulting in no plausible scenarios in which the ICER was above £30,000. Further scenarios investigating subsequent treatments using the SACT data showed that the ICER was actually reduced assuming these inputs.

As per the nature of melanoma treated at the adjuvant stage, despite further follow-up, the OS data are still relatively immature. However, the state transition model, which does not rely on CheckMate 238, also shows that nivolumab is cost effective. SACT data did not provide robust survival data from which to draw conclusions about patients who are retreated with anti-PD-1s, but did show that patients in practice are using anti-PD-1s once their disease has recurred.

In conclusion, the new analysis validates the conclusions of the previous submission: that nivolumab demonstrates improved RFS and OS compared with routine surveillance, and is a cost-effective adjuvant treatment for the NHS at a willingness to pay threshold of £30,000 and should be available to patients in England through routine commissioning. In addition, nivolumab provides the only adjuvant treatment option for Stage IV patients, which, based on the SACT data, is the largest proportion of patients by disease stage using nivolumab in practice (35% Stage IV vs 9%, 26%, 29% and 2% for Stage IIIA, B, C and D, in CM238 respectively).

A.14 References

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A.15 Appendices

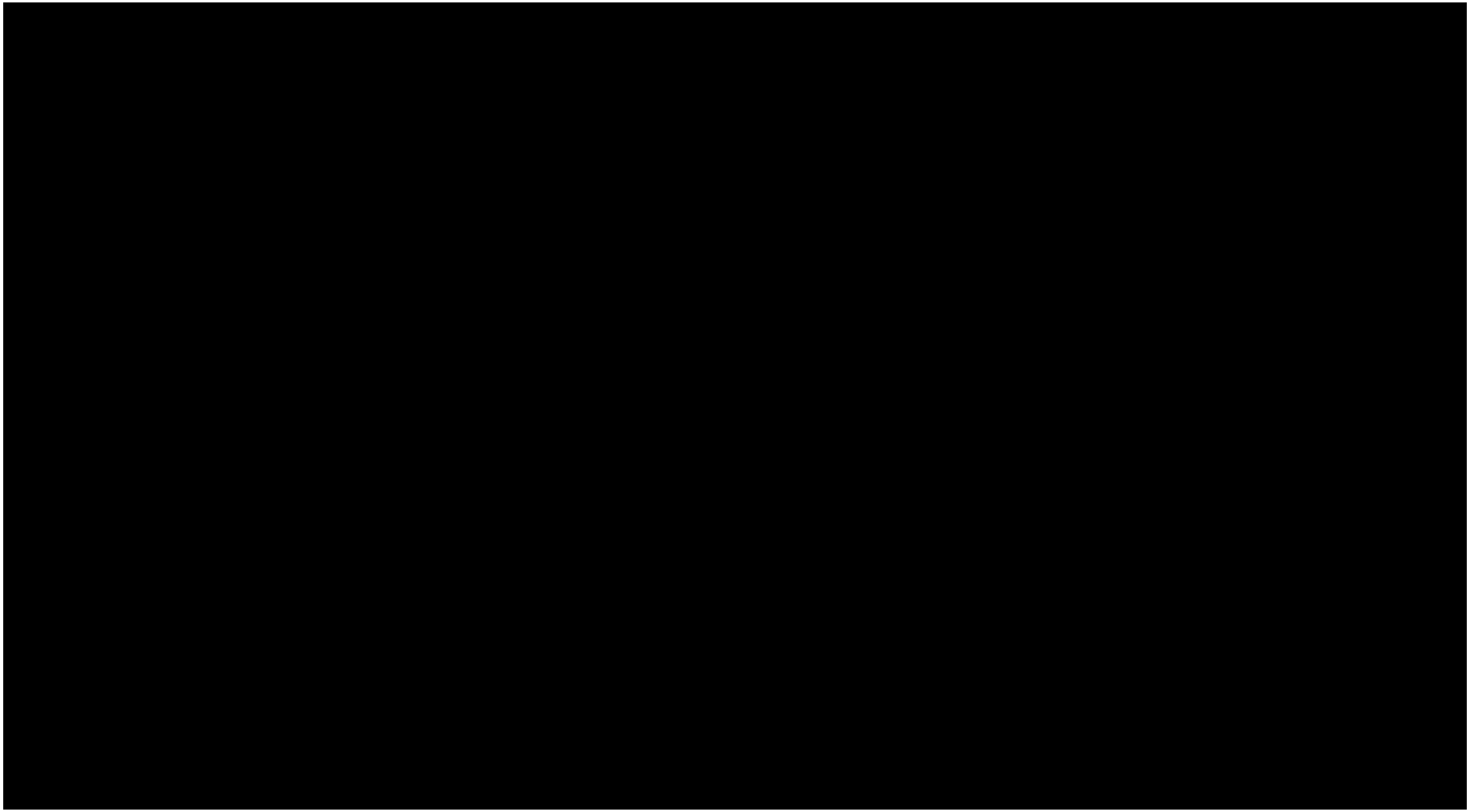
A.15.1 *Recurrence-free survival – CheckMate 238*

The RFS data presented in the original submission had a minimum of 24-months follow-up. This data demonstrated that patients treated with nivolumab had a statistically significant and clinically relevant improvement in RFS compared with patients treated with ipilimumab (HR: [redacted]), as presented in Figure 15.

Figure 15: Kaplan–Meier curve for recurrence-free survival by treatment arm – CheckMate 238 (24-month minimum follow-up)

Key: Ipi, ipilimumab; Nivo, nivolumab.

Figure 16: Forest plot of RFS in subgroups: CheckMate 238 (48-month minimum follow-up)



Notes: Plot 1 of 3.

Notes: Plot 2 of 3.

Key: CI, confidence interval; F, female; HR, hazard ratio; Ipi, ipilimumab; M, male; NA, not available; Nivo, nivolumab.
Notes: Plot 3 of 3. Hazard ratio < 1 favours nivolumab; hazard ratio > 1 favours ipilimumab.

A.15.2 *Summary of patient baseline characteristics – CheckMate 238 and SACT cohort*

Table 20: Systemic Anti-Cancer Therapy data cohort patient characteristics versus CheckMate 238

Patient characteristic	SACT cohort (n = 284)	CheckMate 238 - Nivolumab (n = 453)
Median age, n (range)	63 (Not reported)	56 (19-83)
Age category, n (%)		
< 40 years	25 (9%)	[redacted]
40-49 years	32 (11%)	[redacted]
50-59 years	63 (22%)	[redacted]
60-69 years	81 (29%)	[redacted]
70-79 years	69 (24%)	[redacted]
≥80 years	14 (5%)	[redacted]
Sex, n (%)		
Male	157 (55%)	258 (57%)
Female	127 (45%)	195 (43%)
ECOG performance status, n (%)		
0	199 (70%)	413 (91%)
1	62 (22%)	40 (9%)
2	2 (1%)	0 (0%)
3	0 (0%)	0 (0%)
4	0 (0%)	0 (%)
Unknown/missing	21 (7%)	0 (%)
BRAF mutation status, n (%)		
V600 negative	222 (78%)	197 (44%)
V600 positive	62 (22%)	187 (41%)
Unknown/missing	0 (0%)	69 (15%)
Melanoma stage, n (%) [a]		
Stage IIIA	25 (9%)	[redacted]
Stage IIIB	73 (26%)	[redacted]
Stage IIIC	83 (29%)	[redacted]
Stage IIID	5 (2%)	[redacted]
Stage IV	98 (35%)	[redacted]
Not reported	0 (0%)	[redacted]

Key: ECOG, Eastern Cooperative Oncology Group; n, number; SACT, Systemic Anti-Cancer Therapy data.
Notes: [a] CheckMate 238 data have been reclassified to the American Joint Committee on Cancer Staging Manual (AJCC) 8th edition for this Table. See A.15.11 for details of the Stage re-classification. [b] Assuming all patients with Stage IV disease remain in Stage IV and are not reclassified using the AJCC 8th edition.

A.15.3 *Summary of patient baseline characteristics – CheckMate 238 and CA184-029*

Table 21: Summary of patient baseline characteristics – CheckMate 238 and CA184-029

Characteristic	CheckMate 238		CA184-029	
	Nivo (n = 453)	Ipi (n = 453)	Ipi (n = 475)	PBO (n = 476)
Gender				
Male (%)	258 (57.0)	269 (59.4)	296 (62.3)	293 (61.6)
Age				
Median (range)	56 (19–83)	54 (18–86)	51 (20–84)	52 (18–78)
< 65 years old (%)	333 (73.5)	339 (74.8)	395 (83.2)	389 (81.7)
Disease stage[a]				
IIIA (%)	0 (0.0)	0 (0.0)	98 (20.6)	88 (18.5)
IIIB (%)	165 (36.4)	147 (32.5)	213 (44.8)	207 (43.5)
IIIC (%)	203 (44.8)	219 (48.3)	164 (34.5)	181 (38.0)
IV (%)	82 (18.1)	87 (19.2)	0 (0.0)	0 (0.0)
Other/Not reported (%)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Disease stage[a] (IIIB/C subgroup)				
IIIB (%)	165/368 (44.8)	147/366 (40.2)	213/377 (56.5)	207/388 (53.4)
IIIC (%)	203/368 (55.2)	219/366 (59.8)	164/377 (43.5)	181/388 (46.6)
Stage III lymph node involvement				
Microscopic (%)	126/368 (34.2)	134/366 (36.6)	210/475 (44.2)	193/476 (40.5)
Macroscopic (%)	217/368 (59.0)	214/366 (58.5)	265/475 (55.8)	283/476 (59.5)
Not reported (%)	25/368 (6.8)	18/366 (4.9)	0/475 (0.0)	0/476 (0.0)
Stage III tumour ulceration				
Present (%)	155/368 (42.1)	137/366 (37.4)	197/475 (41.5)	203/476 (42.6)
Absent (%)	199/368 (54.1)	213/366 (58.2)	257/475 (54.1)	244/476 (51.3)
Not reported (%)	14/368 (3.8)	16/366 (4.4)	21/475 (4.4)	29/476 (6.1)
Melanoma subtype				
Cutaneous (%)	404 (89.2)	395 (87.2)	475 (100.0)	476 (100.0)
Acral (%)	16 (3.5)	18 (4.0)	0 (0.0)	0 (0.0)
Extracutaneous (%)	49 (10.8)	58 (12.8)	0 (0.0)	0 (0.0)
Mucosal (%)	16 (3.5)	13 (2.9)	0 (0.0)	0 (0.0)
Other (%)	33 (7.3)	45 (9.9)	0 (0.0)	0 (0.0)

Characteristic	CheckMate 238		CA184-029	
	Nivo (n = 453)	Ipi (n = 453)	Ipi (n = 475)	PBO (n = 476)
ECOG PS				
0 (%)	413 (91.2)	405 (89.4)	445 (93.7)	448 (94.1)
1 (%)	40 (8.8)	48 (10.6)	29 (6.1)	28 (5.9)
2 (%)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
BRAF				
Wild type (%)	197 (43.5)	212 (46.8)	25 (5.3)	41 (8.6)
Mutant (%)	187 (41.3)	194 (42.8)	39 (8.2)	33 (6.9)
Not reported (%)	69 (15.2)	47 (10.4)	411 (86.5)	402 (84.5)
PD-L1 status				
<5% / Indeterminate (%)	300 (66.2)	299 (66.0)	0 (0.0)	0 (0.0)
≥5%(%)	153 (33.8)	154 (34.0)	0 (0.0)	0 (0.0)
Not reported (%)	0 (0.0)	0 (0.0)	475 (100.0)	476 (100.0)

Key: ECOG PS, Eastern Cooperative Oncology Group performance status; Ipi, ipilimumab; Nivo, nivolumab; n, number of patients; PBO, placebo; PD-L1, programmed cell death ligand 1.
Notes: [a], CA184-029 define disease stage using the American Joint Committee on Cancer Staging Manual 6th edition, while CheckMate 238 uses the 7th edition.

A.15.4 *Overall survival – CA184-029*

Figure 17: Kaplan–Meier curve for overall survival by treatment arm – CA184-029

Key: Ipi, ipilimumab.

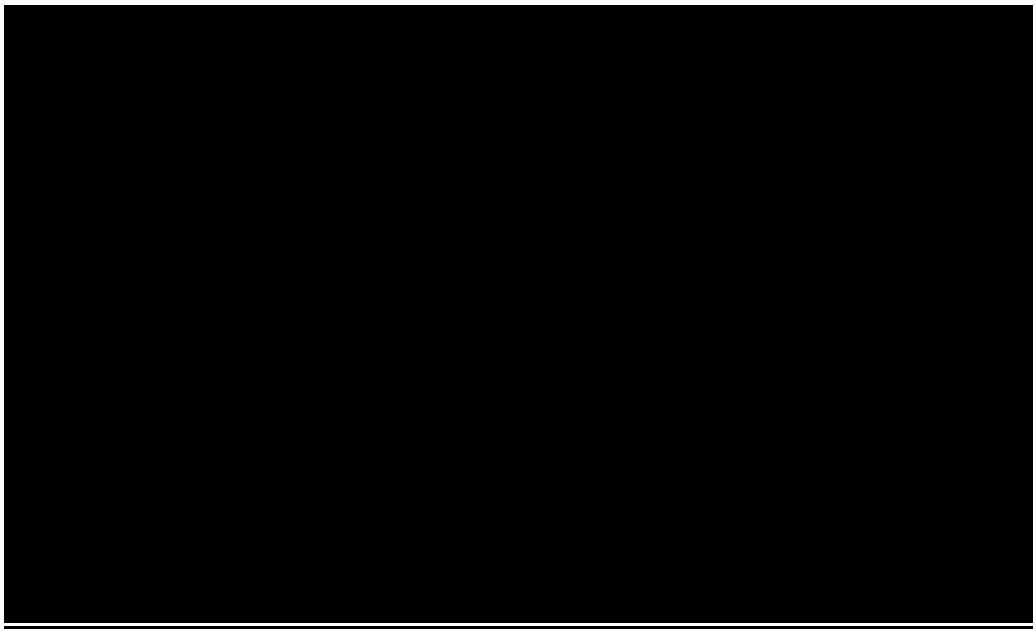
Table 22: Summary statistics for overall survival by treatment arm – CA184-029

Treatment	Subjects	Events	Censored	Median (95% CI; months)	HR (95% CI)
Ipilimumab	475	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	476	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; HR, hazard ratio; NA, not reached.
Notes: Hazard ratio <1 favours ipilimumab. Hazard ratio >1 favours placebo.

A.15.5 *Recurrence-free survival – CA184-029*

Figure 18: Kaplan–Meier curve for recurrence-free survival by treatment arm – CA184-029



Key: Ipi, ipilimumab

.

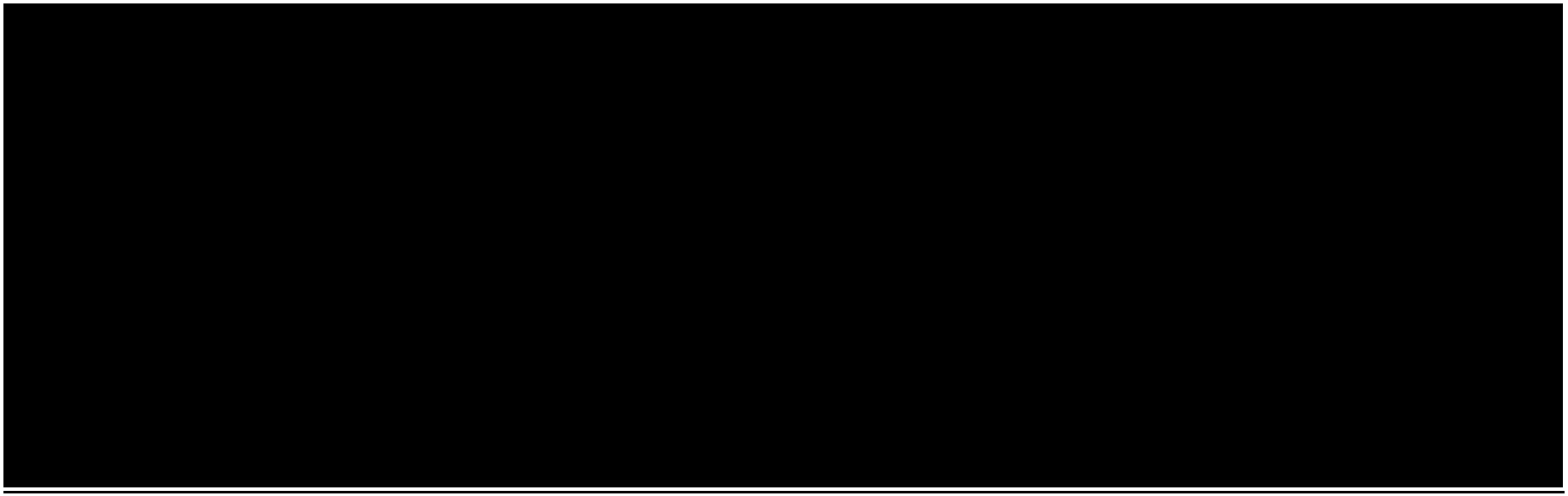
Table 23: Summary statistics for recurrence-free survival by treatment arm – CA184-029

Treatment	Subjects	Events	Censored	Median (95% CI; months)	HR (95% CI)
Ipilimumab	475	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	476	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; HR, hazard ratio.
Notes: Hazard ratio < 1 favours ipilimumab; hazard ratio > 1 favours placebo.

Figure 19: Forest plot of RFS in subgroups-CA184-029

Notes: Plot 1 of 2



Key: CI, confidence interval; F, female; HR, hazard ratio; Ipi, ipilimumab; M, male; RFS, recurrence-free survival.
Notes: Plot 2 of 2. Hazard ratio <1 favours ipilimumab. Hazard ratio >1 favours placebo. Hazard ratios are unstratified.

A.15.6 *Recurrence-free survival – censoring ipilimumab patients after 1 year of treatment – CA184-029*

Given the differences in ipilimumab treatment between the two trials (detailed in Table 9), an alternative RFS analysis was performed. In this analysis, patients treated with ipilimumab were censored after 1 year of treatment if still on treatment. This analysis was previously preferred by NICE, and therefore forms the base case RFS analysis.

However, the limitations of this analysis should be also be acknowledged, most notably informative censoring. The Kaplan–Meier method assumes non-informative censoring, meaning there is no dependence between the time to event (in this case RFS) and the process that causes the censoring. Selective censoring due to treatment duration clearly violates the assumption of non-informative censoring. Patients who are informatively censored are likely those with the best prognosis at 1 year, which would bias the results against ipilimumab. The NICE Evidence Review Group (ERG) also made the statement quoted below. Given this, the observed RFS was considered in a sensitivity analysis.

> 'Patients from CA184-029 censored at one year are likely to be those that are healthier than patients who stop receiving ipilimumab. The ERG considers that an analysis where these patients are censored is likely to underestimate RFS in the ipilimumab group compared with placebo. The subsequent ITC would, therefore, potentially underestimate the difference in RFS between nivolumab and routine surveillance. The ERG considers this analysis to be a 'worst case' scenario based on the current data available.' [18]

The RFS data censoring ipilimumab patients after 1 year of treatment in CA184-029 are presented in Figure 20) and summary statistics are presented in Table 24. These data continue to demonstrate that patients treated with ipilimumab had a statistically significantly better RFS compared with patients treated with placebo [redacted] Median RFS was [redacted] months in the ipilimumab arm, and [redacted] months on the placebo arm.

Figure 20: Kaplan–Meier curve for recurrence-free survival by treatment arm – CA184-029 – ipilimumab patients censored after 1 year of treatment

Key: Ipi, ipilimumab.
Notes: Dashed line indicates 1 year after randomization; patients typically started treatment a few days after randomization.

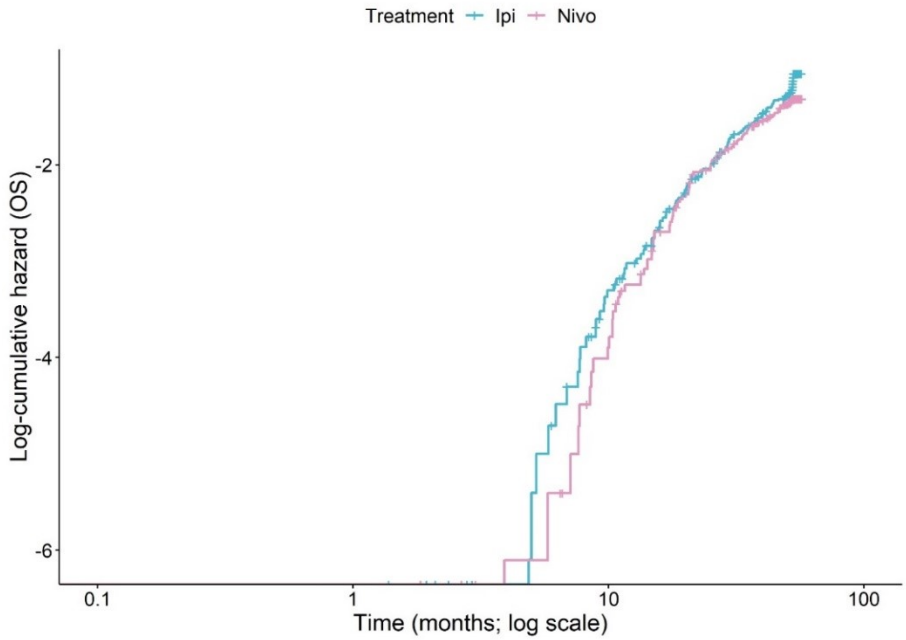
Table 24: Summary statistics for recurrence-free survival by treatment arm – CA184-029 – ipilimumab patients censored after 1 year of treatment

Treatment	Subjects	Events	Censored	Median (95% CI; months)	HR (95% CI)
Ipilimumab	475	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	476	[redacted]	[redacted]	[redacted]	

Key: CI, confidence interval; HR, hazard ratio.
Notes: Hazard ratio < 1 favours ipilimumab; hazard ratio > 1 favours placebo.

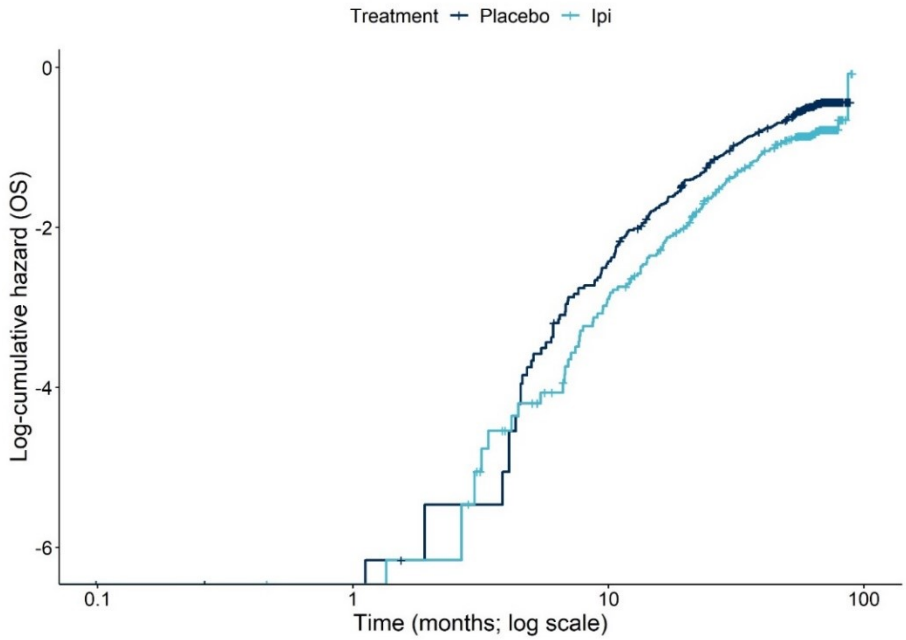
A.15.7 *Log-cumulative hazard plots by study and endpoint*

Figure 21: CheckMate 238 Overall survival log-cumulative hazard plot



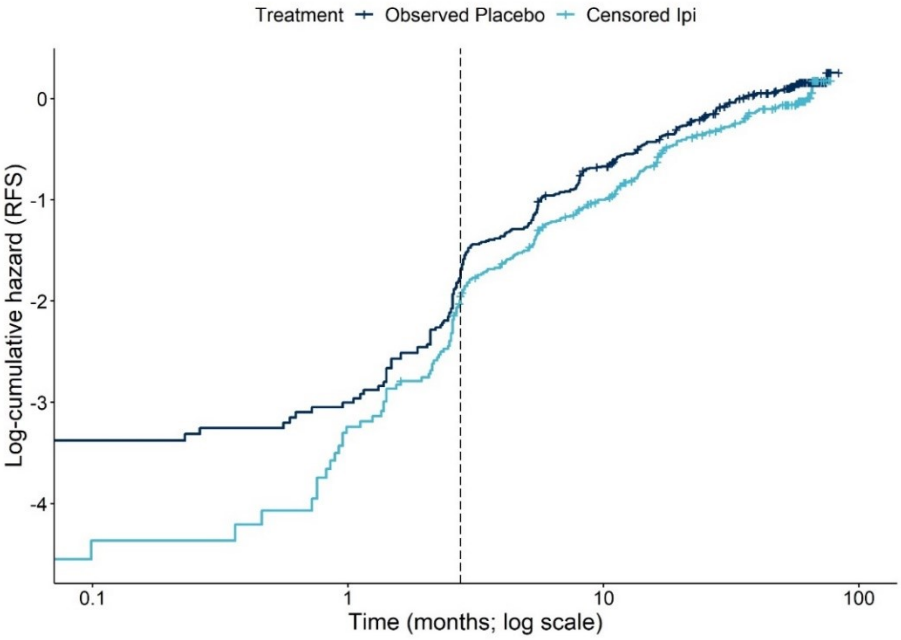
Key: Ipi, ipilimumab; Nivo, nivolumab; OS, overall survival.

Figure 22: CA184-029 Overall survival log-cumulative hazard plot



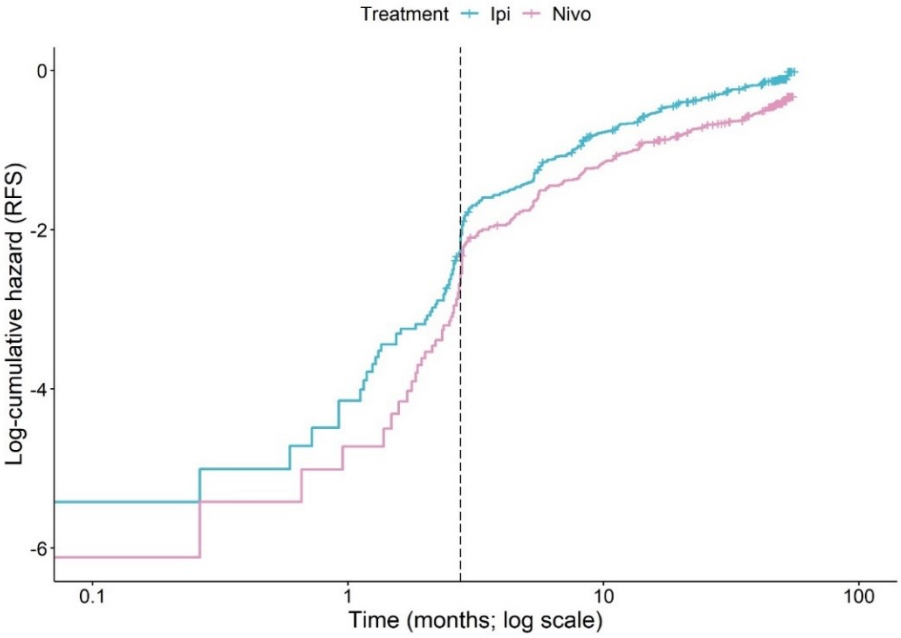
Key: Ipi, ipilimumab; OS, overall survival.

Figure 23: CA184-029 Recurrence-free survival (ipilimumab patients censored after 1 year of treatment) log-cumulative hazard plot



Key: Ipi, ipilimumab; RFS, recurrence-free survival.
Notes: Dashed line indicates first assessment time (12 weeks).

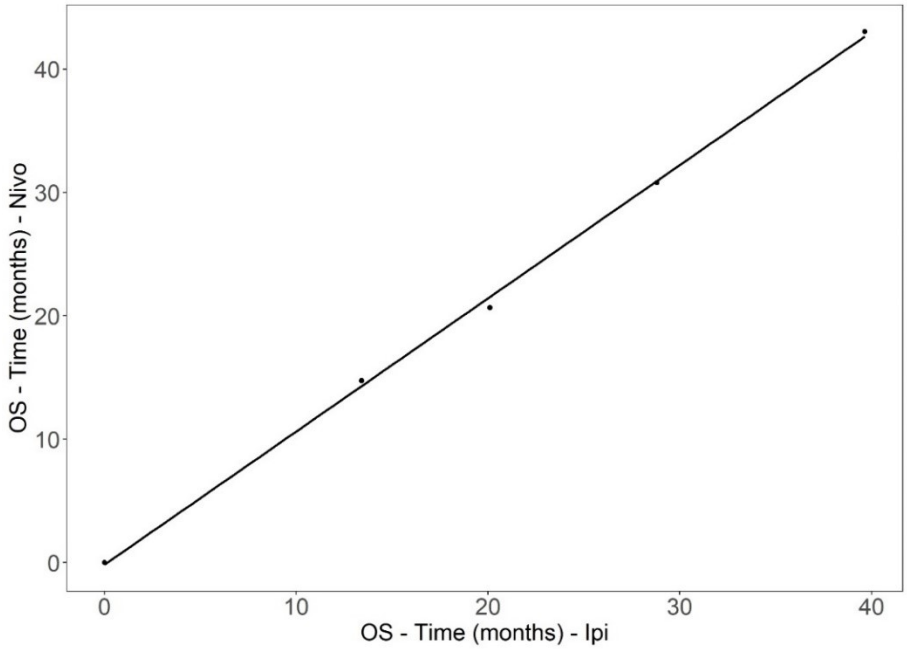
Figure 24: CheckMate 238 Recurrence-free survival log-cumulative hazard plot



Key: Ipi, ipilimumab; Nivo, nivolumab; RFS, recurrence-free survival.
Notes: Dashed line indicates first assessment time (12 weeks).

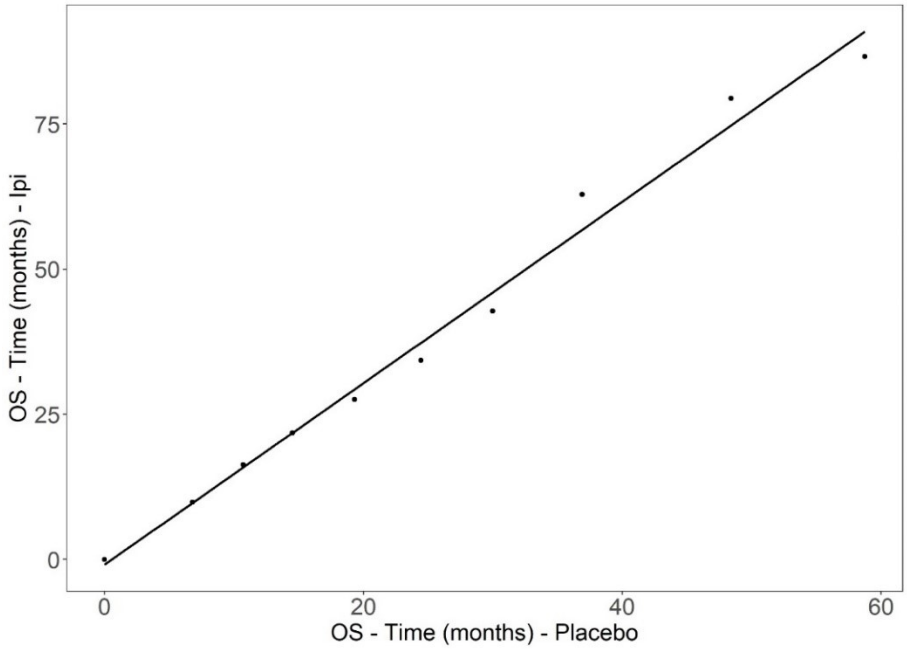
A.15.8 *Quantile–quantile plots by study and endpoint*

Figure 25: CheckMate 238 overall survival QQ-plot



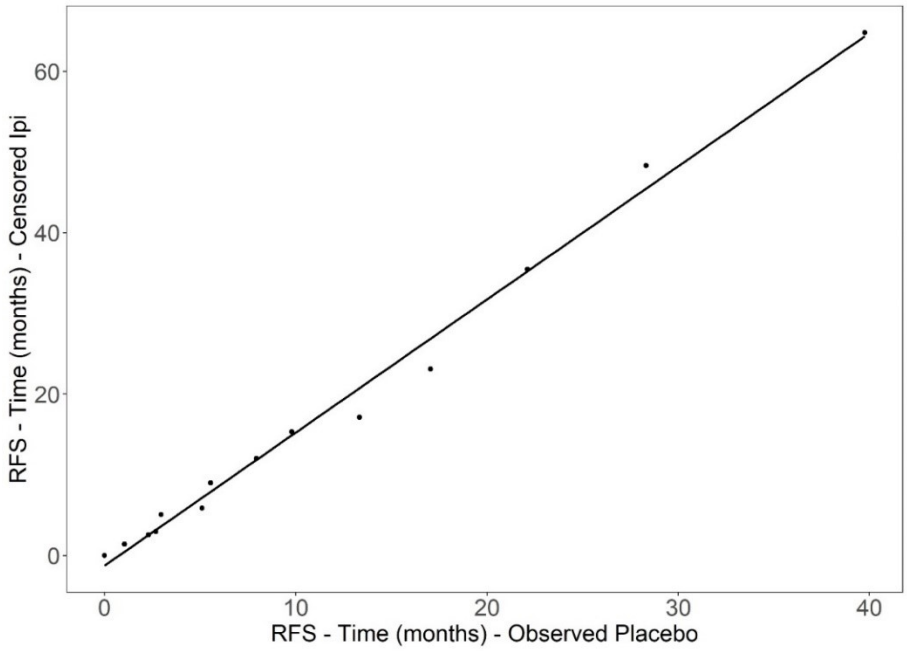
Key: Ipi, ipilimumab; Nivo, nivolumab; OS, overall survival; QQ, quantile–quantile.

Figure 26: CA184-029 overall survival QQ-plot



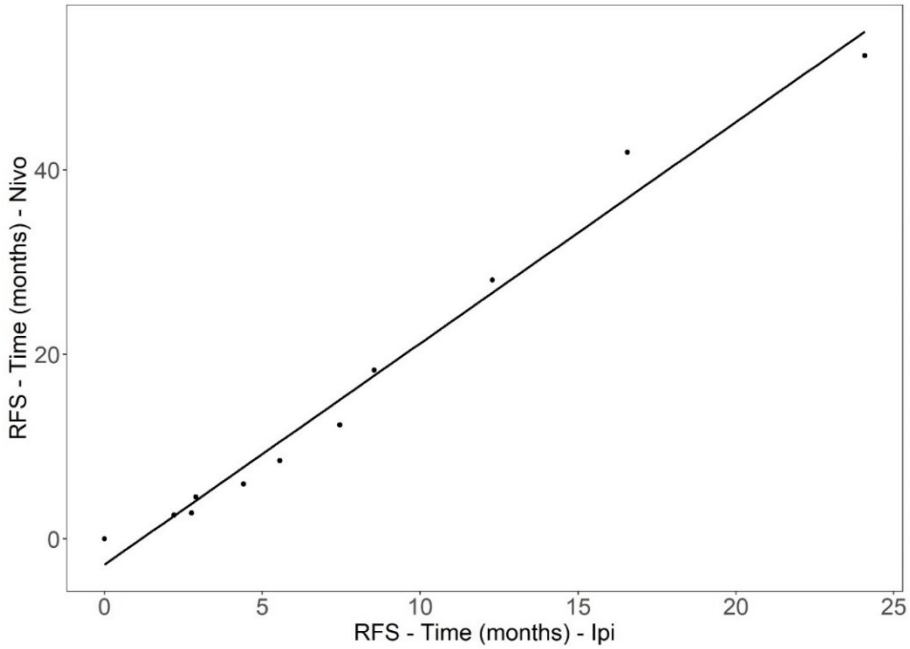
Key: Ipi, ipilimumab; OS, overall survival; QQ, quantile–quantile.

Figure 27: CA184-029 Recurrence-free survival (ipilimumab patients censored after 1 year of treatment) QQ-plot



Key: Ipi, ipilimumab; RFS, recurrence-free survival; QQ, quantile–quantile.

Figure 28: CheckMate 238 Recurrence-free survival QQ-plot



Key: Ipi, ipilimumab; Nivo, nivolumab; RFS, recurrence-free survival; QQ, quantile–quantile.

A.15.9 *Patient level data meta-regression – model coefficient values by endpoint*

Table 25: Overall survival – ITC PLD meta-regression model coefficient values

Coefficient	Exp	GG	Gom	LL	LN	Wei
TRT: PBO (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TRT: Nivo (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage: IIIA (ref: IIIB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage: IIIC (ref: IIIB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage: IV (ref: IIIB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex: Female (ref: male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age: ≥ 65 (ref: < 65)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial: 029 (ref: 238)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape TRT: PBO (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape TRT: Nivo (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sigma TRT: PBO (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sigma TRT: Nivo (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sdlog TRT: PBO (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sdlog TRT: Nivo (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Meanlog	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sdlog	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sigma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: Exp, exponential; GG, generalised gamma; Gom, Gompertz; Ipi, ipilimumab; ITC, indirect treatment comparison; LL, log-logistic; LN, log-normal; Nivo, nivolumab; PBO, placebo; PLD, patient level data; TRT, treatment; Wei, Weibull.
Note: To interpret the stage, sex and age coefficients for the exponential and Gompertz distributions, a negative value indicates improved outcomes and a positive value indicates reduced outcomes relative to the reference category. For the generalised gamma, log-logistic, log-normal and Weibull distributions the converse is true.

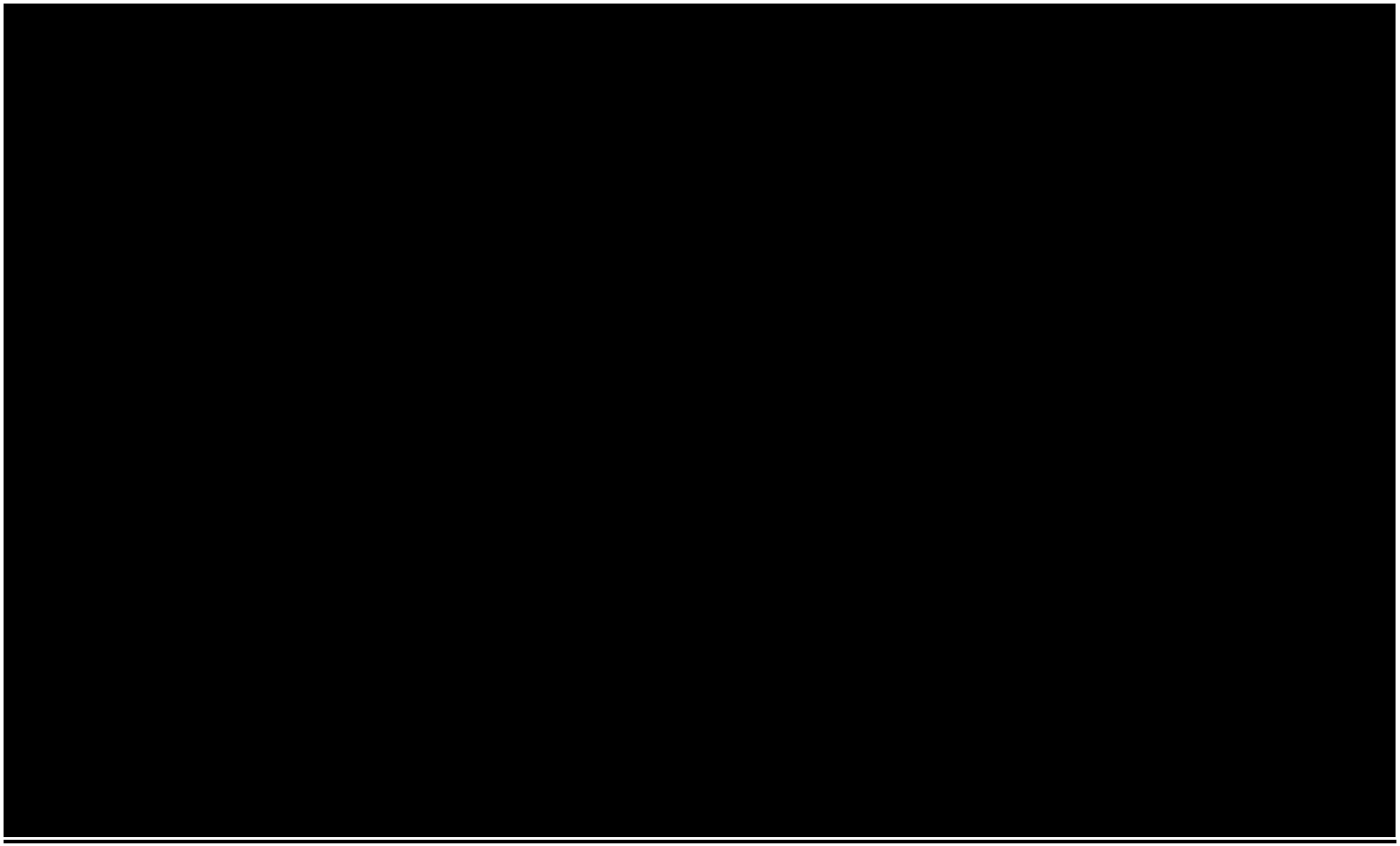
Table 26: Recurrence-free survival (ipilimumab patients censored after 1 year of treatment)) – ITC PLD meta-regression model coefficient values

Coefficient	Exp	GG	Gom	LL	LN	Wei
TRT: PBO (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TRT: Nivo (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage: IIIA (ref: IIIB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage: IIIC (ref: IIIB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage: IV (ref: IIIB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex: Female (ref: male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age: ≥ 65 (ref: < 65)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial: 029 (ref: 238)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape TRT: PBO (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape TRT: Nivo (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sigma TRT: PBO (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sigma TRT: Nivo (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sdlog TRT: PBO (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sdlog TRT: Nivo (ref: ipi)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Meanlog	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sdlog	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sigma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: Exp, exponential; GG, generalised gamma; Gom, Gompertz; Ipi, ipilimumab; ITC, indirect treatment comparison; LL, log-logistic; LN, log-normal; Nivo, nivolumab; PBO, placebo; PLD, patient level data; TRT, treatment; Wei, Weibull.
Notes: To interpret the stage, sex and age coefficients for the exponential and Gompertz distributions, a negative value indicates improved outcomes and a positive value indicates reduced outcomes relative to the reference category. For the generalised gamma, log-logistic, log-normal and Weibull distributions the converse is true.

A.15.10 *Patient level data meta-regression – fitted survival models*

Figure 29: CheckMate 238 overall survival ITC PLD meta-regression model – long-term survival extrapolation from parametric survival curves – nivolumab arm



Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab; PLD, patient level data.

Figure 30: CA184-029 overall survival ITC PLD meta-regression model – long-term survival extrapolation from parametric survival curves – placebo arm

Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; PBO, placebo; PLD, patient level data.

Table 27: Overall survival – model fit statistics and validation

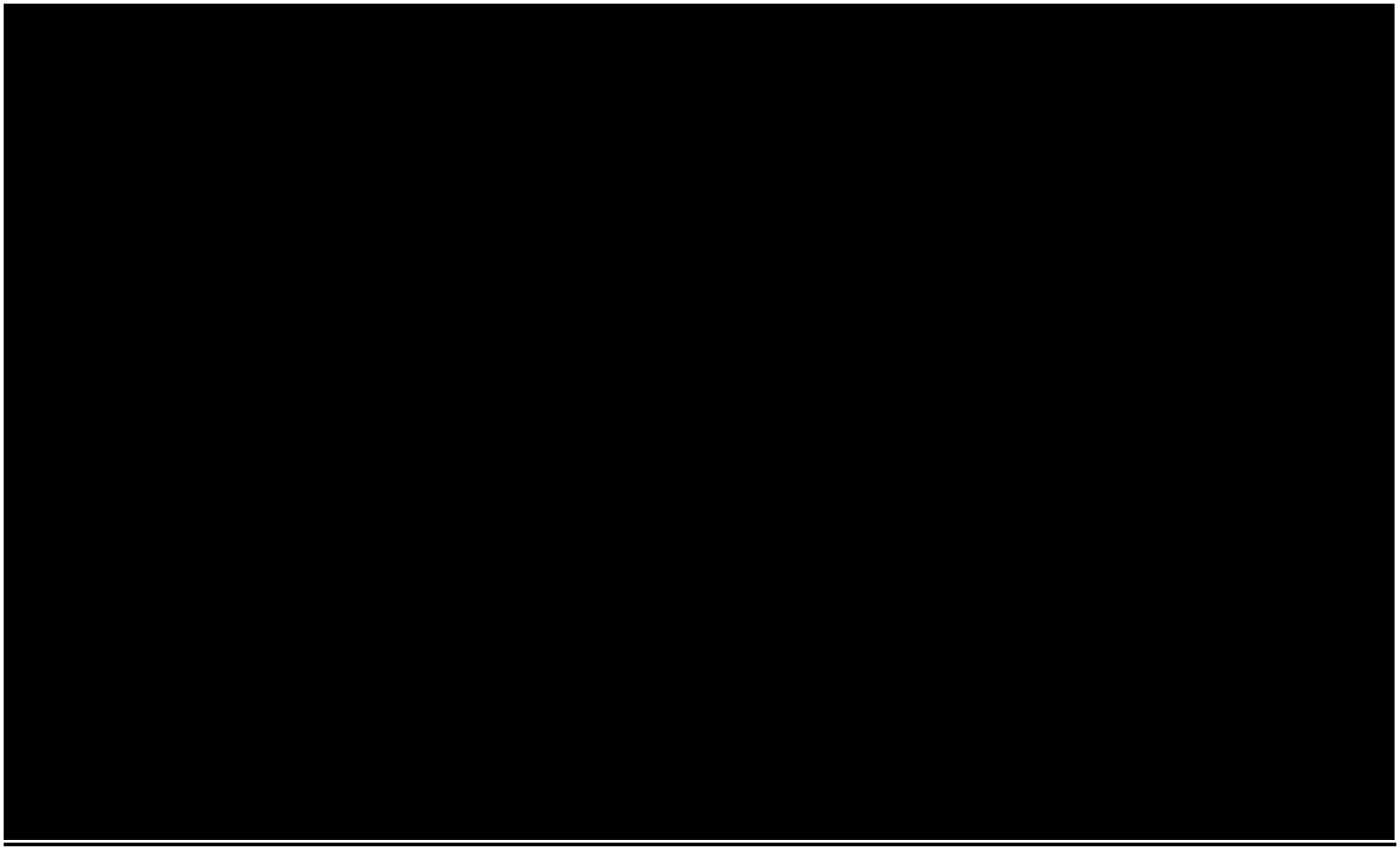
Model	AIC	AIC rank	BIC	BIC rank	Arms cross within trial		Time RFS and OS curves meet (years)*	
					CheckMate 238	CA184-029	Nivolumab	Routine surveillance
Exponential	10931.29	6	10981.01	4	×	×	22.5	27.1
Generalised gamma	**10818.40**	**1**	**10890.23**	**1**	×	×	**NA**	**NA**
Gompertz	10929.74	5	10996.04	6	✓ 8.6 years	×	15.6	NA
Log-logistic	10891.63	3	10957.94	3	×	×	22.8	NA
Log-normal	10849.68	2	10915.98	2	×	×	33.9	NA
Weibull	10926.73	4	10993.03	5	×	×	14.8	23.3

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; NA, not available.
Notes: Bold distribution represent the base case selection.
*Post 20 years a patient who remains recurrence-free should be more or less similar to general population mortality.

Figure 31: CheckMate 238 recurrence-free survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – long-term survival extrapolation from parametric survival curves rebased at Week 12 – nivolumab arm

Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab; PLD, patient level data.
Notes: KM from baseline is displayed; parametric curves are fitted from 12 weeks onwards.

Figure 32: CA184-029 recurrence-free survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – long-term survival extrapolation from parametric survival curves rebased at Week 12 – placebo arm



Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; PBO, placebo; PLD, patient level data.
Notes: KM from baseline is displayed; log-logistic curve is fitted from 12 weeks onwards.

Table 28: Recurrence-free survival – model fit statistics and validation

Model	AIC	AIC rank	BIC	BIC rank	Arms cross within trial		Time RFS and OS curves meet (years)*	
					CheckMate 238	CA184-029	Nivolumab	Routine surveillance
Exponential	13150.35	6	13198.73	6	×	×	NA	NA
Generalised gamma	12792.04	2	12861.92	2	×	×	NA	NA
Gompertz	12855.57	5	12920.07	5	×	×	19.9	33.5
Log-logistic	**12783.72**	**1**	**12848.22**	**1**	×	×	**NA**	**NA**
Log-normal	12798.66	3	12863.16	3	×	×	NA	NA
Weibull	12811.97	4	12876.48	4	×	×	NA	NA

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; NA, not available.
Notes: Bold distribution represent the base case selection.
*Post 20 years a patient who remains recurrence-free should be more or less similar to general population mortality.

A.15.11 *CheckMate 238 reclassification of Stage III disease*

Figure 33: AJCC 7th edition and AJCC 8th edition stage classifications[15, 19]

AJCC 7th edition										AJCC 8th edition									
N Category	T Category									N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b		T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A/B	A/B	A/B	A/B	A/B	A/B	A/B	B	N1a	N/A	A	A	A	B	B	C	C	C
N1b	N/A	B/C	B/C	B/C	B/C	B/C	B/C	B/C	C	N1b	B	B	B	B	B	B	C	C	C
N1c	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A/B	A/B	A/B	A/B	A/B	A/B	A/B	B	N2a	N/A	A	A	A	B	B	C	C	C
N2b	N/A	B/C	B/C	B/C	B/C	B/C	B/C	B/C	C	N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C	N2c	C	C	C	C	C	C	C	C	C
N3a	C	C	C	C	C	C	C	C	C	N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	C	N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	C	N3c	C	C	C	C	C	C	C	C	D

Key: AJCC, American Joint Committee on Cancer; N/A, not available.

Table 29: CheckMate 238 – stage reclassification from AJCC 7th edition to 8th edition – nivolumab

7th edition stage	8th edition				
	Stage IIIA	Stage IIIB	Stage IIIC	Stage IIID	Not reported
Stage IIIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IIIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AJCC, American Joint Committee on Cancer.					

Table 30: CheckMate 238 – stage reclassification from AJCC 7th edition to 8th edition – ipilimumab

7th edition stage	8th edition				
	Stage IIIA	Stage IIIB	Stage IIIC	Stage IIID	Not reported
Stage IIIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IIIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AJCC, American Joint Committee on Cancer.					

Table 31: CheckMate – stage classifications from AJCC 7th edition to AJCC 8th edition – total

Stage classifications	AJCC 7th edition		AJCC 8th edition	
	Ipilimumab (n = 453)	Nivolumab (n = 453)	Ipilimumab (n = 453)	Nivolumab (n = 453)
Stage IIIA	NA	NA	[redacted]	[redacted]
Stage IIIB	147 (32.5%)	165 (36.4%)	[redacted]	[redacted]
Stage IIIC	219 (48.3%)	203 (44.8%)	[redacted]	[redacted]
Stage IIID	NA	NA	[redacted]	[redacted]
Stage IV	87 (19.2%)	82 (18.1%)	[redacted]	[redacted]
Not reported	0 (0.00%)	1 (0.22%)	[redacted]	[redacted]
Other	0 (0.00%)	2 (0.44%)	[redacted]	[redacted]
Key: AJCC, American Joint Committee on Cancer Staging Manual; NA, not available.				

A.15.12 *State-transition model subsequent treatments*

Comparison to real-world sources

Table 32 summarizes the data on subsequent treatments post routine surveillance obtained from Ipsos and Wilmington Health Care at the time of the original submission and compares it to the data collected in the updated CheckMate 238 ipilimumab arm. The real-world data used in the previous submission showed similar trends to that of the ipilimumab arm in CheckMate 238 (see TA558, company response to ACD, Page 6). Based on the updated data in CheckMate 238, this still appears to be the case.

The proportion of use of anti-PD-1s in the metastatic setting (the committee's main area of concern) was consistent within the ipilimumab arm from the CheckMate 238 trial and data sources from the UK (CheckMate 238 trial = [redacted] Ipsos data = [redacted] Wilmington data = [redacted] Use of BRAF/MEK inhibitors was also consistent within the trial and UK data sources.

In practice, individual clinicians use different treatments and each facility will have different usages; however, the real-word metastatic treatment data suggest that use of the post-recurrence treatment data from CheckMate 238 in the ipilimumab arm as a proxy for routine surveillance is generally reflective of average usage in England and Wales. We have therefore kept the data from the ipilimumab arm of CheckMate 238 in the state-transition model base case post routine surveillance.

The SACT data represent the most recent subsequent treatment distribution for England after adjuvant use and demonstrate that there is high usage of immunotherapies, mainly nivolumab plus ipilimumab. However, patient numbers were small and therefore comparisons are limited.

Table 32: Subsequent treatment data in the metastatic setting

Treatment	IPSOS			Wilmington	SACT	CheckMate 238		
	1L	2L	All	All	All	Ipi – 1L	Ipi – 2L	Ipi – all
Total immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	76.6%	[redacted]	[redacted]	[redacted]
Anti-PD-1s	[redacted]	[redacted]	[redacted]	[redacted]	58.1%	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	3.7%	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	48.1%	[redacted]	[redacted]	[redacted]
Other immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	18.5%	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	14.8%	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]	3.7%	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
BRAF/MEK inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	18.5%	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]	18.5%	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy	[redacted]	[redacted]	[redacted]	[redacted]	11.1%	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	11.1%	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]

Key: 1L, first line; 2L, second line; Ipi, ipilimumab; PD-1, programmed cell death protein 1; SACT, Systemic Anti-Cancer Therapy.

Weighted survival curves

The proportions of patients who receive metastatic treatments, were based on the first-line subsequent treatment data from the updated CheckMate 238 trial described in Section A.6.1 to inform the weighting of the curves. Before re-challenge at 2 years, it was assumed that, after nivolumab, patients have ipilimumab instead of the anti-PD-1s; after 2 years, the distributions are the same between treatment arms.

The weightings for each of the treatments are shown in Table 33.

Table 33: Weightings for state-transition curves

Subsequent drug	Nivolumab		Routine surveillance
	Pre- re-challenge	Post re-challenge	
Palliative chemotherapy*	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]
Ipilimumab plus nivolumab	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]
Local recurrence	[redacted]	[redacted]	[redacted]

Note: *Includes no treatment, dacarbazine, temozolomide, fotemustine, interleukin, interferon, paclitaxel and cisplatin. This category follows the dacarbazine survival curve.

A.15.13 *Cost-effectiveness model corrections and changes*

The economic model used in the previous submission ('ID1316 Nivo_post_CQ_ERG_model v0.1 23.07.18 (ACiC)_amendment_postACM 18.09.2018') was used as a base for the revised model for the CDF review submission. The following changes were made to ensure model transparency and ease of use:

- Revision of the subsequent treatment sheet:
  - Based on the multiple rounds of scenarios, this sheet has been tidied with all switches to inform scenarios now moved to the control sheet. This sheet has also been restructured to make it easier to understand the flow of calculations
- Additions to the controls sheet:
  - The scenarios created by the ERG and company have been moved onto the control sheet and reformatted so they are in line with the rest of the switches in the model

Upon revising the model, two minor errors were identified that, when corrected, slightly changed the original ICERs presented in the previous submission:

- In the CGP sheet, the trial covariate for CA184-029 was applied to estimate the extrapolations for the routine surveillance arm from the RFS ITC. This was incorrect as this should reflect the CheckMate 238 trial to be comparable with nivolumab
- In the subsequent treatment sheet, the calculations for the nivolumab arm subsequent treatment total (pre-re-challenge) did not take into account the second-line subsequent treatments for the cost calculations

These errors have now been revised in the model and Table 34 shows the impact of each on the original ICERs.

Table 34: Impact of model corrections

Model correction	Partitioned survival model	State-transition model
Previous base case ICER	£18,423	£18,018
(1) Corrected CGP sheet	£18,870	£18,992
(2) Corrected subsequent treatment calculations	NA	£18,250
(1) + (2) corrected	£18,870	£19,235

Key: CGP, corrected group prognosis; ICER, incremental cost-effectiveness ratio; NA, not applicable.

A.15.14 *Deterministic results per model update*

Table 35: Deterministic results implementing each change separately – partitioned survival model

Model update	Nivolumab			Routine surveillance			Incremental			
	Total costs (£)	**Total LYG**	**Total QALYs**	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER**
Original final base case	[redacted]	[redacted]	[redacted]	[redacted]	***17.83***	[redacted]	[redacted]	[redacted]	[redacted]	***£18,423***
Corrected original base case	[redacted]	[redacted]	[redacted]	[redacted]	***17.83***	[redacted]	[redacted]	[redacted]	[redacted]	***£18,870***
(1) Using updated 48 month RFS (ipi censored)	[redacted]	[redacted]	[redacted]	[redacted]	17.83	[redacted]	[redacted]	[redacted]	[redacted]	£19,535
(2) Using new 48 month OS ITC	[redacted]	[redacted]	[redacted]	[redacted]	18.65	[redacted]	[redacted]	[redacted]	[redacted]	£16,132
(3) Using new 48 month subsequent treatment data	[redacted]	[redacted]	[redacted]	[redacted]	17.83	[redacted]	[redacted]	[redacted]	[redacted]	£17,246
(4) Nivolumab dosing changed to 240 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	17.83	[redacted]	[redacted]	[redacted]	[redacted]	£18,005
(5) Administration cost code changed to SB12Z	[redacted]	[redacted]	[redacted]	[redacted]	17.83	[redacted]	[redacted]	[redacted]	[redacted]	£18,490
(1+2) RFS + OS ITC	[redacted]	[redacted]	[redacted]	[redacted]	18.65	[redacted]	[redacted]	[redacted]	[redacted]	£16,677
(1+2+3) RFS + OS + new subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	18.65	[redacted]	[redacted]	[redacted]	[redacted]	£15,263
(1+2+3+4+5) RFS + OS + subsequent treatment + nivo dose+admin cost	[redacted]	[redacted]	[redacted]	[redacted]	**18.65**	[redacted]	[redacted]	[redacted]	[redacted]	**£14,195**

Key: LYG, life-year gained; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OS, overall survival; Q2W, twice per week; QALY, quality-adjusted life-year; RFS, recurrence-free survival.

Table 36: Deterministic results implementing each change separately – state-transition model

Model update	Nivolumab			Routine surveillance			Incremental			
	Total costs (£)	**Total LYG**	**Total QALYs**	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER**
Original final base case	[redacted]	[redacted]	[redacted]	[redacted]	***14.19***	[redacted]	[redacted]	[redacted]	[redacted]	***£18,018***
Corrected original base case	[redacted]	[redacted]	[redacted]	[redacted]	***14.34***	[redacted]	[redacted]	[redacted]	[redacted]	***£19,235***
(1) Using updated 48 month RFS (ipi censored)	[redacted]	[redacted]	[redacted]	[redacted]	14.52	[redacted]	[redacted]	[redacted]	[redacted]	£20,080
(2) Using new 48 month subsequent treatment data	[redacted]	[redacted]	[redacted]	[redacted]	14.09	[redacted]	[redacted]	[redacted]	[redacted]	£17,493
(3) Nivolumab dosing changed to 240 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	14.34	[redacted]	[redacted]	[redacted]	[redacted]	£18,452
(4) Administration cost code changed to SB12Z	[redacted]	[redacted]	[redacted]	[redacted]	14.34	[redacted]	[redacted]	[redacted]	[redacted]	£18,844
(1+2) RFS + 48 month subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	14.27	[redacted]	[redacted]	[redacted]	[redacted]	£18,299
(1+2+3+4) RFS + 48 month subsequent treatment + nivo dose + nivo admin	[redacted]	[redacted]	[redacted]	[redacted]	**14.27**	[redacted]	[redacted]	[redacted]	[redacted]	**£17,120**

Key: LYG, life-year gained; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; nivo, nivolumab; OS, overall survival; QALY, quality-adjusted life-year; RFS, recurrence-free survival.

A.15.15 *Base case inputs and distributions*

Table 37: List of base case parameters

Parameter	Distribution	Mean	Lower bound	Upper bound	Source of distribution
Patient characteristics					
Proportion of females	Beta	39.9%	37.7%	42.1%	CheckMate 238 and CA184-029
Efficacy					
Proportion of patients who have local/regional recurrence from recurrence-free	Dirichlet	[redacted]	[redacted]	[redacted]	CheckMate 238
Proportion of patients who have distant recurrence from recurrence-free		[redacted]	[redacted]	[redacted]	CheckMate 238
Proportion of patients who die from recurrence-free		[redacted]	[redacted]	[redacted]	CheckMate 238
Proportion of patients with BRAF V600 positive mutation	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
Proportion of patients who only have local/regional recurrence	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
Proportion of local/regional recurrence patients who are unresectable	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
Long term survival – proportion of patients who have recurrence from recurrence-free	Dirichlet	86.9%	88.95%	85.03%	Agarwala et al. 2017
Long term survival – proportion of patients who die from recurrence-free		13.1%	11.05%	14.97%	Agarwala et al. 2017
Proportion of patients who have Stage IIIA disease	Dirichlet	16.5%	28.23%	27.58%	±10%
Proportion of patients who have Stage IIIB disease		33.2%	21.88%	22.51%	±10%
Proportion of patients who have Stage IIIC disease		34.7%	21.32%	22.06%	±10%
Proportion of patients who have Stage IV NED		15.6%	28.57%	27.85%	±10%

Parameter	Distribution	Mean	Lower bound	Upper bound	Source of distribution
Hazard ratios					
RFS: Bucher comparison – HR nivo vs routine surveillance	Log-normal	[redacted]	[redacted]	[redacted]	CheckMate 238 and CA184-029 PLD
CheckMate 238 observed HR nivo vs ipi (RFS)	Log-normal	0.650	0.510	0.830	Weber et al. 2017
Post-distant: HR (OS) dabrafenib+trametinib vs dabrafenib	Log-normal	0.710	0.550	0.920	COMBI-d
Post-distant: HR (OS) pembrolizumab vs ipilimumab	Log-normal	0.790	0.510	0.820	Bucher comparison
Post-distant: HR (OS) ipilimumab vs dacarbazine	Log-normal	0.640	0.560	0.850	Hodi et al. 2010
Post-distant: HR (OS) vemurafenib vs dacarbazine	Log-normal	0.760	0.630	0.930	BRIM-3
OS: HR ipilimumab vs routine surveillance	Log-normal	0.720	0.580	0.890	CA184-029
Correlation equation – constant	Normal	[redacted]	[redacted]	[redacted]	±10%
Correlation equation – beta	Normal	[redacted]	[redacted]	[redacted]	±10%
Hazard ratio (029 ipi vs 238 ipi) – censored after 12 weeks	Log-normal	[redacted]	[redacted]	[redacted]	CheckMate 238 and CA184-029
Hazard ratio RFS vs OS – long term data	Log-normal	1.984	1.632	2.412	±10%
Hazard ratio PRS vs OS – ipi	Log-normal	[redacted]	[redacted]	[redacted]	CA184-029
Hazard ratio PRS vs OS – placebo	Log-normal	[redacted]	[redacted]	[redacted]	CA184-029
Utility values					
Utility parameter – observed: intercept	Multivariate normal	[redacted]			CheckMate 238
Utility parameter – observed: baseline	Multivariate normal	[redacted]			CheckMate 238
Utility parameter – observed: ipilimumab	Multivariate normal	[redacted]			CheckMate 238
Utility parameter – observed: post-recurrence	Multivariate normal	[redacted]			CheckMate 238

Parameter	Distribution	Mean	Lower bound	Upper bound	Source of distribution
Utility parameter - observed: Stage IIIC	Multivariate normal	[redacted]			CheckMate 238
Utility parameter – observed: Stage IV	Multivariate normal	[redacted]			CheckMate 238
Utility parameter – observed: ipilimumab:post-recurrence	Multivariate normal	[redacted]			CheckMate 238
Baseline utility – nivolumab	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
Baseline utility – ipilimumab	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
Baseline utility – pooled (CheckMate 238)	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
Utility for RF based on Middleton et al. 2016	Beta	0.890	0.664	0.994	±10%
Utility for recurrence based on Middleton et al. 2016	Beta	0.620	0.495	0.737	±10%
Disutility due to immune-related AEs – nivolumab	Beta	-0.111	-0.134	-0.090	±10%
Disutility due to diarrhoea – nivolumab	Beta	-0.090	-0.108	-0.073	±10%
Disutility due to other AEs based – nivolumab	Beta	-0.137	-0.165	-0.111	±10%
Disutility due to immune-related AEs – routine surveillance	Beta	-0.111	-0.134	-0.090	±10%
Disutility due to diarrhoea – routine surveillance	Beta	-0.090	-0.108	-0.073	±10%
Disutility due to other AEs based – routine surveillance	Beta	-0.137	-0.165	-0.111	±10%
Costs and resource use					
Administration cost: deliver complex chemotherapy	Normal	310.00	249.24	370.75	±10%
Administration cost: deliver oral chemotherapy	Normal	197.16	158.52	235.81	±10%
Administration cost: deliver simple chemotherapy	Normal	259.76	208.85	310.67	±10%
Subsequent treatment cost: local/regional - nivolumab	Normal	[redacted]	[redacted]	[redacted]	±10%
Subsequent treatment cost: distant - nivolumab	Normal	[redacted]	[redacted]	[redacted]	±10%

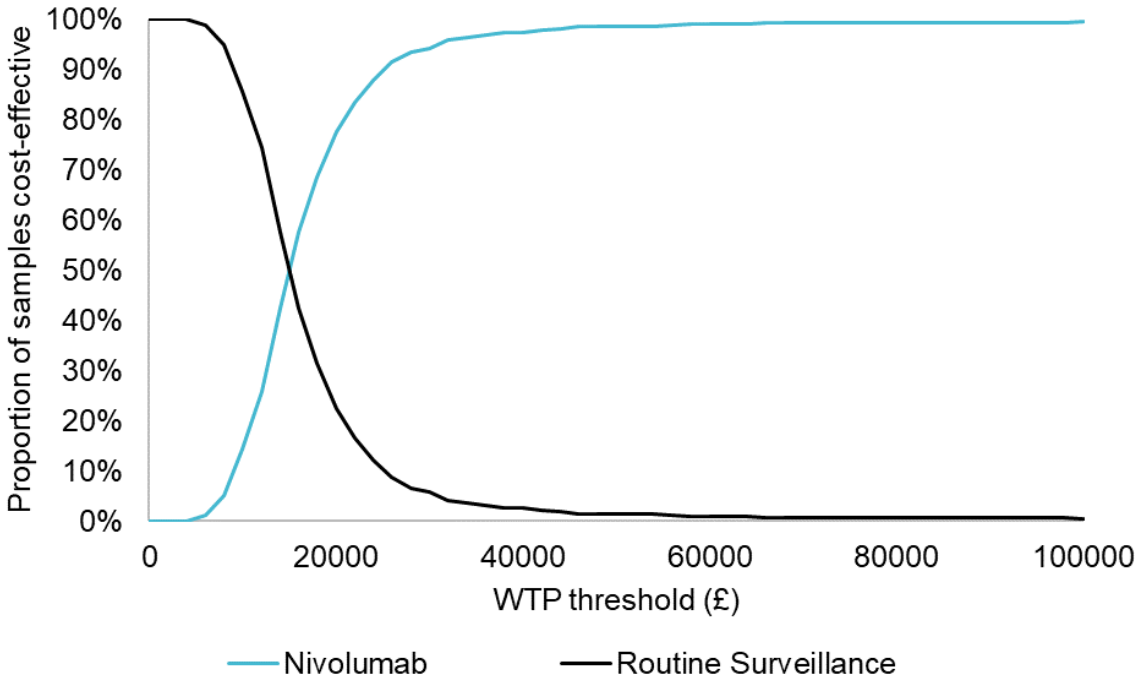
Parameter	Distribution	Mean	Lower bound	Upper bound	Source of distribution
Subsequent treatment cost: local/regional - routine surveillance	Normal	[redacted]	[redacted]	[redacted]	±10%
Subsequent treatment cost: distant – routine surveillance	Normal	[redacted]	[redacted]	[redacted]	±10%
Unit cost: subsequent surgery	Normal	100.72	80.98	120.46	±10%
Unit cost: subsequent radiotherapy	Normal	297.09	238.86	355.31	±10%
Monitoring cost – recurrence free – Year 1	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – recurrence free – Year 2	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – recurrence free – Years 3–5	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – recurrence free – Year 5+	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – local unresectable recurrence – Year 1	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – local unresectable recurrence – Year 2	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – local unresectable recurrence – Years 3–5	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – local unresectable recurrence – Year 5+	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – local resectable recurrence – Year 1	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – local resectable recurrence – Year 2	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – local resectable recurrence – Years 3–5	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – local resectable recurrence – Year 5+	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – distant recurrence – Year 1	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – distant recurrence – Year 2	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – distant recurrence – Years 3–5	Normal	[redacted]	[redacted]	[redacted]	±10%
Monitoring cost – distant recurrence – Year 5+	Normal	[redacted]	[redacted]	[redacted]	±10%
End of life: average health care costs for all cancers (Round et al.)	Normal	4,475.12	3,598.01	5,352.23	±10%
End of life: average social care costs for all cancers (Round et al.)	Normal	1,924.07	1,546.96	2,301.18	±10%

Parameter	Distribution	Mean	Lower bound	Upper bound	Source of distribution
Adverse events					
AE costs nivolumab	Normal	[redacted]	[redacted]	[redacted]	±10%
AE costs routine surveillance	Normal	[redacted]	[redacted]	[redacted]	±10%
% Immune-related AEs – nivolumab (CheckMate 238)	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
% Immune-related AEs – ipilimumab (CheckMate 238)	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
% Immune-related AEs – routine surveillance	Beta	[redacted]	[redacted]	[redacted]	±10%
% Diarrhoea – nivolumab (CheckMate 238)	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
% Diarrhoea – ipilimumab (CheckMate 238)	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
% Diarrhoea – routine surveillance	Beta	[redacted]	[redacted]	[redacted]	±10%
% Other AEs – nivolumab (CheckMate 238)	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
% Other AEs – ipilimumab (CheckMate 238)	Beta	[redacted]	[redacted]	[redacted]	CheckMate 238
% Other AEs – routine surveillance	Beta	[redacted]	[redacted]	[redacted]	±10%
Duration of immune-related AEs	Log-normal	[redacted]	[redacted]	[redacted]	±10%
Duration of diarrhoea	Log-normal	[redacted]	[redacted]	[redacted]	±10%
Duration of other AEs	Log-normal	[redacted]	[redacted]	[redacted]	±10%

Key: AE, adverse event; CI, confidence interval; D+T, dabrafenib+ trametinib; HR, hazard ratio; ipi, ipilimumab; NED, no evidence of disease; nivo, nivolumab; OR, odds ratio; OS, overall survival; PLD, patient-level data; PRS, post-recurrence survival; RF, relapse-free; RFS, relapse-free survival.

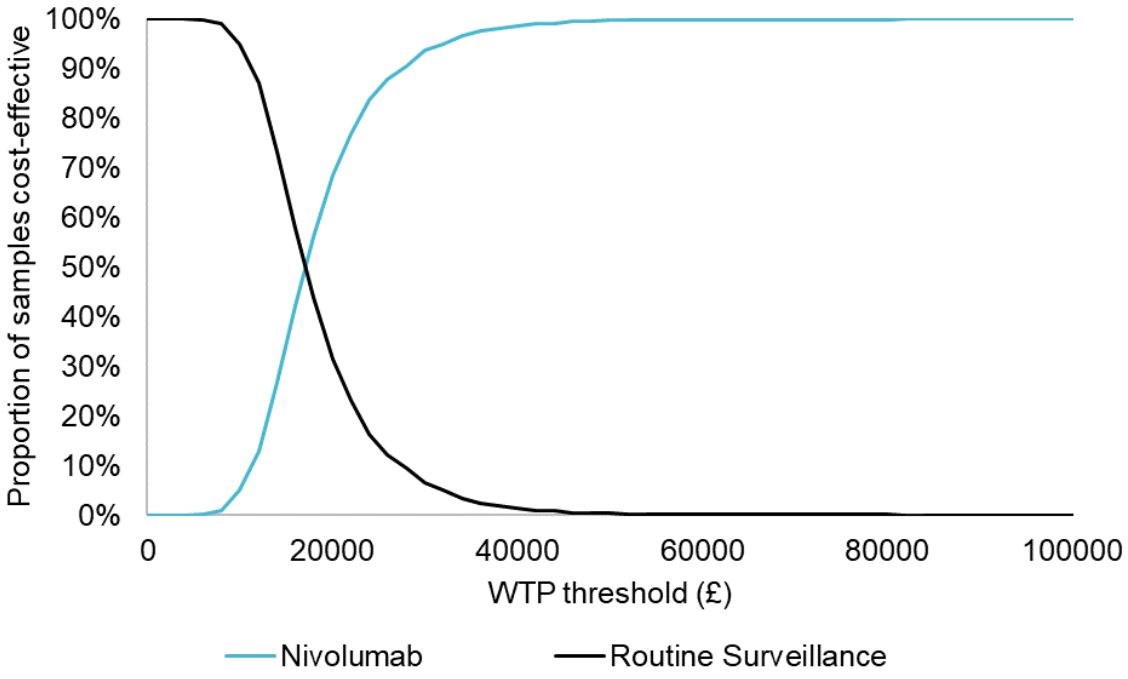
A.15.16 *Cost-effectiveness acceptability curves*

Figure 34: Cost-effectiveness acceptability curve – partitioned survival model



Key: WTP, willingness-to-pay.

Figure 35: Cost-effectiveness acceptability curve – state-transition model



Key: WTP, willingness-to-pay.

A.15.17 *Scenario analysis results*

Table 38: Partitioned survival model (scenario analysis results)

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs routine surveillance
			Costs (£)	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	14,195
Population	Patient characteristics: (CA184-029 and CheckMate 238) Stage proportions: CA184-029 & CheckMate 238 adjusted RFS for nivolumab and routine surveillance: ITC (CA184-029 and CheckMate 238)	CheckMate 238 CheckMate 238 Nivo: CheckMate 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	12,301
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	13,500
Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	14,719
		50 years	[redacted]	[redacted]	[redacted]	14,296
Nivolumab dosing	240 Q2W	3mg/kg Q2W	[redacted]	[redacted]	[redacted]	14,935
		480mg Q4W	[redacted]	[redacted]	[redacted]	14,301
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	14,195
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	14,199
Nivolumab administration cost reference	SB12Z	SB13Z	[redacted]	[redacted]	[redacted]	14,524
Subsequent treatment (local/regional)	CheckMate 238	CA184-029	[redacted]	[redacted]	[redacted]	12,358
Nivolumab subsequent treatment (distant)	CheckMate 238	SACT data	[redacted]	[redacted]	[redacted]	7,604
RFS ITC method	ITC 48-month DBL (subgroup 1-year ipi treatment in 029)	ITC 48-month DBL	[redacted]	[redacted]	[redacted]	13,677
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	18,432
		Gompertz	[redacted]	[redacted]	[redacted]	14,394
		Log-normal	[redacted]	[redacted]	[redacted]	13,428
		Generalised gamma	[redacted]	[redacted]	[redacted]	13,814
		Weibull	[redacted]	[redacted]	[redacted]	14,827
Long-term survival adjustment	Gershenwald, applied after10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	12,646
		No long-term adjustment to RFS	[redacted]	[redacted]	[redacted]	13,369
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	18,397
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	12,829

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs routine surveillance
			Costs (£)	LYs	QALYs	
		Balch, 5 years	[redacted]	[redacted]	[redacted]	26,157
		Balch, 10 years	[redacted]	[redacted]	[redacted]	17,214
		Balch, 20 years	[redacted]	[redacted]	[redacted]	13,723
		OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	14,548
		Balch, OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	17,812
OS distribution (all)	Generalised gamma	Exponential*	[redacted]	[redacted]	[redacted]	12,612
		Gompertz*	[redacted]	[redacted]	[redacted]	29,731
		Log-normal	[redacted]	[redacted]	[redacted]	14,537
		Log-logistic	[redacted]	[redacted]	[redacted]	14,894
		Weibull	[redacted]	[redacted]	[redacted]	15,056
Long-term-data curve selection	Gershenwald, Generalised gamma	Balch, Exponential**	[redacted]	[redacted]	[redacted]	24,422
		Balch, Generalised gamma	[redacted]	[redacted]	[redacted]	17,214
		Balch, Gompertz	[redacted]	[redacted]	[redacted]	14,004
		Balch, log-normal	[redacted]	[redacted]	[redacted]	19,841
		Balch, log-logistic	[redacted]	[redacted]	[redacted]	19,802
		Balch, Weibull**	[redacted]	[redacted]	[redacted]	21,221
		Exponential**	[redacted]	[redacted]	[redacted]	18,023
		Gompertz	[redacted]	[redacted]	[redacted]	13,624
		Log-normal	[redacted]	[redacted]	[redacted]	15,792
		Log-logistic	[redacted]	[redacted]	[redacted]	16,203
		Weibull**	[redacted]	[redacted]	[redacted]	16,990
End-of-life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	14,080
Utilities source	Observed EQ-5D Apply same utility to across treatments Separate stage covariate Include AE disutilities: yes	Include AE disutilities: No	[redacted]	[redacted]	[redacted]	14,171
		Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	14,332
		Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	14,357
		Middleton et al.	[redacted]	[redacted]	[redacted]	11,660
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	14,409
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	14,576
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	14,195
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	14,357
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	14,342

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs routine surveillance
			Costs (£)	LYs	QALYs	

Key: AE, adverse event; HR, hazard ratio; DBL, database lock; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; ipi, ipilimumab; ITC, indirect treatment comparison; LY, life year; nivo, nivolumab; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival; SACT, Systemic Anti-Cancer Therapy.
Note: The curve fits that are indicated (*) are those that fit the data poorly.

Table 39: State-transition model (scenario analysis results)

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	17,120
Population	Patient characteristics: (CA184-029 and CheckMate 238) Stage proportions: CA184-029 & CheckMate 238 adjusted RFS for nivolumab and routine surveillance: ITC (CA184-029 and CheckMate 238)	CheckMate 238 CheckMate 238 Nivo: CheckMate 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	14,254
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	16,549
Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	17,547
		50 years	[redacted]	[redacted]	[redacted]	17,208
Nivolumab dosing	240 Q2W	3mg/kg Q2W	[redacted]	[redacted]	[redacted]	17,919
		480mg Q4W	[redacted]	[redacted]	[redacted]	16,171
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	17,120
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	17,123
Nivolumab administration cost reference	SB12Z	SB13Z	[redacted]	[redacted]	[redacted]	17,499
Subsequent treatment (local/regional)	CheckMate 238	CA184-029	[redacted]	[redacted]	[redacted]	17,109
Nivolumab subsequent treatment (distant)	CheckMate 238	SACT data	[redacted]	[redacted]	[redacted]	10,275
		Wilmington	[redacted]	[redacted]	[redacted]	18,740
		IPSOS	[redacted]	[redacted]	[redacted]	18,031
RFS ITC method	ITC 48-month DBL (subgroup 1-year ipi treatment in CA184-029)	ITC 48-month DBL	[redacted]	[redacted]	[redacted]	15,708
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	32,536
		Gompertz	[redacted]	[redacted]	[redacted]	17,870

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
		Log-normal	[redacted]	[redacted]	[redacted]	15,449
		Generalised gamma	[redacted]	[redacted]	[redacted]	16,334
		Weibull	[redacted]	[redacted]	[redacted]	18,900
Long-term survival adjustment	Gershenwald, applied after 10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	15,913
		No long-term adjustment to RFS	[redacted]	[redacted]	[redacted]	15,903
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	21,173
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	16,005
		Balch, 5 years	[redacted]	[redacted]	[redacted]	29,687
		Balch, 10 years	[redacted]	[redacted]	[redacted]	20,569
		Balch, 20 years	[redacted]	[redacted]	[redacted]	16,955
		OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	17,698
		Balch, OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	21,819
Long-term-data curve selection	Gershenwald, Generalised gamma	Balch, exponential*	[redacted]	[redacted]	[redacted]	24,815
		Balch, Generalised gamma	[redacted]	[redacted]	[redacted]	20,569
		Balch, Gompertz	[redacted]	[redacted]	[redacted]	16,632
		Balch, log-normal	[redacted]	[redacted]	[redacted]	22,667
		Balch, log-logistic	[redacted]	[redacted]	[redacted]	22,658
		Balch, Weibull*	[redacted]	[redacted]	[redacted]	23,372
		Exponential*	[redacted]	[redacted]	[redacted]	21,334
		Gompertz	[redacted]	[redacted]	[redacted]	16,046
		Log-normal	[redacted]	[redacted]	[redacted]	19,183
		Log-logistic	[redacted]	[redacted]	[redacted]	19,632
		Weibull*	[redacted]	[redacted]	[redacted]	20,409
End-of-life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	16,957
Utilities source	Observed EQ-5D Apply same utility to across treatments Separate stage covariate Include AE disutilities: Yes	Include AE disutilities: No	[redacted]	[redacted]	[redacted]	17,088
		Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	17,263
		Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	17,296
		Middleton et al.	[redacted]	[redacted]	[redacted]	14,630
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	17,292
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	17,472

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	17,119
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	17,296
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	17,282
Data used for Markov model curves	CheckMate 067 and other sources	Metastatic NMA	[redacted]	[redacted]	[redacted]	14,023
Post-distant long-term dataset	Balch 2009	Balch 2001	[redacted]	[redacted]	[redacted]	16,556
Dacarbazine hazard ratio applied	HR (OS) vemurafenib vs dacarbazine	HR (OS) ipi vs gp100	[redacted]	[redacted]	[redacted]	17,523
OS HR pembrolizumab vs ipilimumab source	Bucher comparison	KEYNOTE 006	[redacted]	[redacted]	[redacted]	17,731
Re-challenge scenario	Yes	No	[redacted]	[redacted]	[redacted]	15,909
Re-challenge scenario time-point	2.00	0.50	[redacted]	[redacted]	[redacted]	16,503
		1.00	[redacted]	[redacted]	[redacted]	16,806
		60.00	[redacted]	[redacted]	[redacted]	18,083

Key: AE, adverse event; DBL, database lock; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; ipi, ipilimumab; LY, life year; nivo, nivolumab; NMA, network meta-analysis; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival; SACT, Systemic Anti-Cancer Therapy.
Note: The curve fits that are indicated (*) are those that fit the data poorly.

A.15.18 *Validation*

Internal validation

Internal validation was explored using the updated RFS Kaplan–Meier data from CheckMate 238 and CA184-029 to compare the RFS outputs from the model. Table 40 shows the model-projected RFS compared with the Kaplan–Meier-projected RFS from the trial. Median RFS for CA184-029 is stated as reported in the clinical study report[20]; median RFS for CheckMate 238 was [redacted] however, it should be noted that the data were still immature, with heavy censoring present at the end of the Kaplan–Meier curve. Figure 36 and Figure 37 show the Kaplan–Meier RFS from the trials compared with the model RFS when patient characteristics were changed to reflect the trial specific population (i.e. when comparing to data from a given trial only patient characteristics from that trial were used). The modelled RFS appears to be a good estimate when overlaid with the actual trial data. In addition, the modelled RFS using the new data cut contnues to show consistency with the previous model projections.

Table 40: Trial RFS versus model RFS

	Data median (years)	Year 1	Year 2	Year 3	Year 4
CA184-029					
Trial '029 RFS – placebo (KM)	1.43	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – routine surveillance*	1.69	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – routine surveillance (previous model results)*	1.46	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 238					
Trial CheckMate 238 RFS – nivolumab (KM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – nivolumab**	4.37	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – nivolumab (previous model results)**	4.29	[redacted]	[redacted]	[redacted]	[redacted]

Key: KM, Kaplan–Meier; RFS, recurrence-free survival; NA, not available.
Notes: Trial data medians were sourced from trial clinical study report.
* Patient characteristics were based on CA184-029.
** Patient characteristics were based on CheckMate 238.

Figure 36: CheckMate 238 Kaplan–Meier versus model RFS

Key: KM, Kaplan–Meier; RFS, recurrence-free survival.
Note: Patient characteristics were based on CheckMate 238 for this validation assessment.

Figure 37: CA184-029 Kaplan–Meier versus model RFS

Key: KM, Kaplan–Meier; RFS, recurrence-free survival.
Note: Patient characteristics were based on CA184-029 for this validation assessment.

Table 41 shows the proportion of patients alive at each year based on the CA184-029 and CheckMate 238 trial data compared with the projected proportions based on the model. Figure 38 and Figure 39 show the Kaplan–Meier curves from CheckMate 238 and CA184-029 overlaid with the projected OS from the model, respectively. This modelled OS appears to be a good fit compared with the trial data when patient characteristics were changed to reflect the trial population.

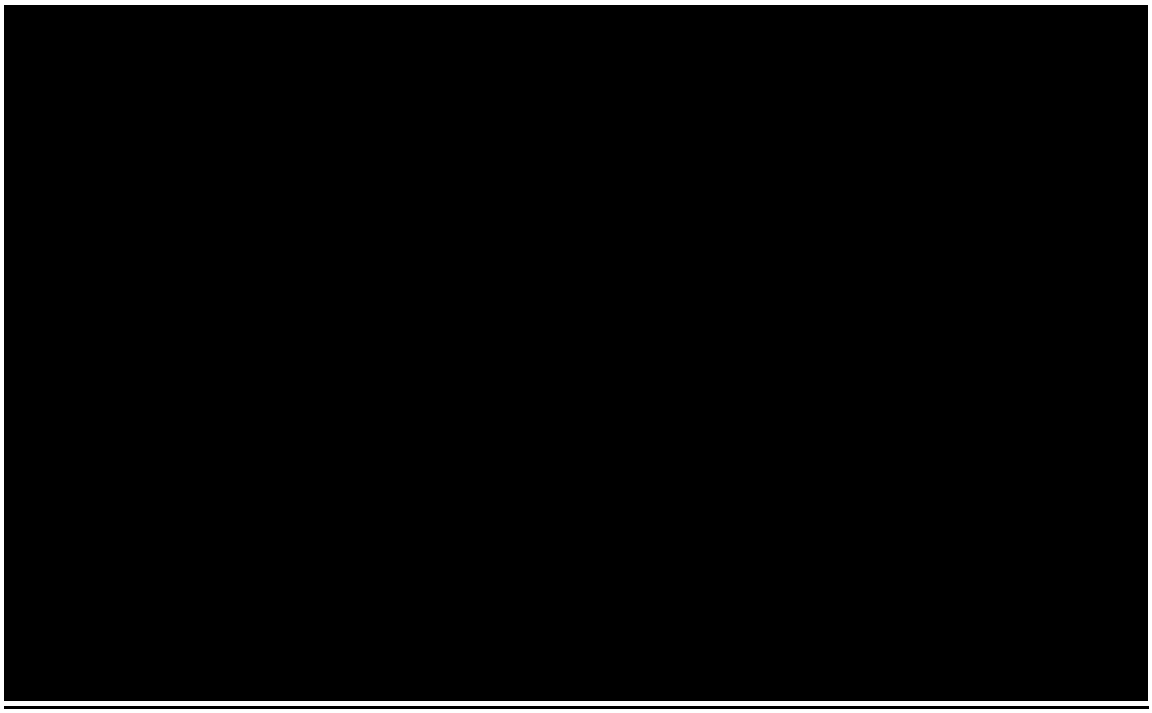
Both the RFS and OS comparisons show that the modelled outcomes, regarding absolute predictions and comparable benefit, appear plausible and in line with observed clinical trial data.

Table 41: Trial OS versus model OS (partitioned survival model)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
CA184-029							
Trial CA184-029 OS – placebo (KM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model OS – routine surveillance*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 238							
Trial CheckMate 238 OS – nivolumab (KM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model OS – nivolumab**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: KM, Kaplan–Meier; OS, overall survival.
Notes: * Patient characteristics were based on CA184-029.
** Patient characteristics were based on CheckMate 238.

Figure 38: CheckMate 238 Kaplan–Meier versus model overall survival



Key: KM, Kaplan–Meier; OS, overall survival.
Note: Patient characteristics were based on CheckMate 238 for this validation assessment

Figure 39: CA184-029 Kaplan–Meier versus model overall survival

Key: KM, Kaplan–Meier; OS, overall survival.
Note: Patient characteristics were based on CA184-029 for this validation assessment.

External validation – partitioned survival model

Long-term OS data were sourced for routine surveillance using AJCC 7th edition data (Balch et al., 2009[15]) and AJCC 8th edition data (Gershenwald et al., 2017[19]). These data sources were compared with the active routine surveillance survival from the model by comparing the proportion of patients alive at different time points (Table 42) and plotting survival curves (Figure 40).

The final modelled OS for routine surveillance compared with the long-term survival of external sources show lower estimates in comparison to the AJCC v8 Stage III data. This is due to the following:

- The long-term data available are not entirely reflective of the intended population, making comparisons with the model results difficult
- It is unknown what treatments these patients in the long-term data would have received and whether adjuvant therapy was given
- The modelled results sit below the Stage III curve from Gershenwald et al., which is expected given the inclusion of Stage IV NED patients in our population

Despite predicting lower estimates compared with the AJCC v8 data, the OS projected from the ITC meta-regression predicts better outcomes for the placebo arm compared with the previous analysis where the projections were considered conservative.

The nivolumab OS predictions would be expected to be greater than AJCC v7 predictions and more in line with the AJCC v8 given the age of the data; however, nivolumab OS projections in the model are currently slightly lower than the AJCC v8 predictions, suggesting that the model OS predictions are still conservative (as is the routine surveillance prediction).

Table 42: Long-term OS data for external validation

	Year 1	Year 2	Year 5	Year 10	Year 15
Balch 2009 Stage IIIA	97.8%	91.6%	77.3%	67.7%	66.5%
Balch 2009 Stage IIIB	95.5%	83.0%	58.4%	42.6%	37.1%
Balch 2009 Stage IIIC	85.5%	64.5%	40.3%	25.3%	22.6%
Balch 2009 Stage III (weighted) – AJCC 7v	**89.0%**	**74.4%**	**52.9%**	**38.9%**	**32.1%**
Balch 2009 Stage IV abnormal LDH	33.3%	19.4%	9.7%	7.5%	NA
Balch 2009 Stage IV normal LDH	69.4%	44.1%	24.2%	18.8%	NA
Gershenwald 2017 Stage III – AJCC v8	**97.8%**	**91.3%**	**79.3%**	**71.7%**	**NA**
Nivolumab OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Routine surveillance OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AJCC, American Joint Committee on Cancer Staging Manual; LDH, lactate dehydrogenase; NA, not available; OS, overall survival.
Note: Data not collected after 10 years for Gershenwald et al. (2017).

Figure 40: Long-term OS data for external validation – partitioned survival model

Key: LDH, lactate dehydrogenase; OS, overall survival.

RFS and OS data from the model were also compared with data from other trials in the same disease area. KEYNOTE 054 is a Phase III trial comparing pembrolizumab with placebo in patients with resected Stage III melanoma[9], and COMBI-AD is a Phase III trial comparing dabrafenib plus trametinib with placebo in patients with BRAF positive Stage III melanoma.[8]

In comparison to KEYNOTE-054, the modelled routine surveillance arm and nivolumab arm look in line with the observed data in the trial once patient characteristics were adjusted to match the KEYNOTE-054 trial (Figure 41). The difference between the nivolumab arm and routine surveillance arm predicted from the ITC is consistent with the difference observed between pembrolizumab and placebo, but the nivolumab predicted RFS sits slightly under pembrolizumab's RFS data, suggesting that the difference may be slightly underestimated from the ITC. OS data have not been presented from KEYNOTE-054, so only RFS has been used.

Figure 41: KEYNOTE-054 RFS compared with modelled RFS data

Key: RFS, recurrence-free survival.
Note: Modelled data have been adjusted to reflect patient characteristics from KEYNOTE-054.

Similarly, in comparison to COMBI-AD, the modelled routine surveillance arm looks consistent with the observed placebo arm from the trial when patient characteristics have been adjusted to match the COMBI-AD trial population (Figure 42).

Figure 42: COMBI-AD RFS and OS compared with modelled data

Key: PBO, placebo; OS, overall survival; RFS, recurrence-free survival.
Note: Modelled data have been adjusted to reflect patient characteristics from COMBI-AD.

External validation – state-transition model

The final modelled OS for the state-transition model shows lower estimates for routine surveillance in comparison to the partitioned survival model but slightly higher estimates compared with the final weighted AJCC v7 Stage III curve.

Table 43: Long-term OS data for external validation – state-transition model

	Year 1	Year 2	Year 5	Year 10	Year 15
Balch 2009 Stage IIIA	97.8%	91.6%	77.3%	67.7%	66.5%
Balch 2009 Stage IIIB	95.5%	83.0%	58.4%	42.6%	37.1%
Balch 2009 Stage IIIC	85.5%	64.5%	40.3%	25.3%	22.6%
Balch 2009 Stage III (weighted) – AJCC 7v	**89.0%**	**74.4%**	**52.9%**	**38.9%**	**32.1%**
Balch 2009 Stage IV abnormal LDH	33.3%	19.4%	9.7%	7.5%	NA
Balch 2009 Stage IV normal LDH	69.4%	44.1%	24.2%	18.8%	NA
Gershenwald 2017 Stage III – AJCC 8v	97.8%	91.3%	79.3%	71.7%	NA
Nivolumab OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Routine surveillance OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AJCC, American Joint Committee on Cancer Staging Manual; LDH, lactate dehydrogenase; NA, not available; OS, overall survival.
Note: Data not collected after 10 years for Gershenwald et al. (2017).

Figure 43: Long-term OS data for external validation – state-transition model

Key: OS, overall survival.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Review of TA558 Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

Clarification questions

August 2020

File name	Version	Contains confidential information	Date
ID1681 Nivo adjuvant melanoma CDF-R questions to PM for clarification AIC_final_OSipi	**2.0**	**Yes**	**10th August 2020**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Priority question. Please provide details of when:

a) the next data cut is expected for OS and RFS from CheckMate 238 and how long minimum follow-up is expected to be at this data-cut.
b) the estimated date of study completion for CheckMate 238.

Previously, the estimated study completion date for CheckMate 238 was [redacted]. However, the number of OS events were lower than anticipated in the 4-year database lock. We continue to observe that the rate of death is slower than expected and future plans for subsequent database locks and study completion are being revised. The trend observed in the data available shows that, with increased follow-up, nivolumab continues to demonstrate robust and meaningful improvements in long-term patient outcomes, and we would expect to see this trend continue when further data cuts become available.

A2. Priority question. Please justify why OS data from CA184-029 weren't censored after 1 year of treatment with ipilimumab in the ITC PLD meta-regression analysis whereas censoring after 1 year was done in the analysis of RFS.

The limitations for this OS analysis are similar to those observed for the corresponding RFS analysis, with informative censoring being the most notable issue. It is likely that the censored patients are those with the best prognosis at 1 year which would bias results against ipilimumab. By definition, if a patient was still receiving treatment after 1 year then they are also known to be alive. In addition, given patients are typically treated until disease recurrence, OS patients who are censored are more likely to be in the recurrence-free state, whereas patients who are not censored are more likely to be in the post recurrence state, this is shown in Table 1.

Table 1: Health state of patients 1 year after starting treatment

Health state - 1 year after starting treatment	**Off-treatment 1 year after starting treatment**		**Still on treatment 1 year after starting treatment**	
	Ipilimumab	**Placebo**	**Ipilimumab**	**Placebo**
Pre-recurrence - on treatment	[redacted]	[redacted]	[redacted]	[redacted]
Pre-recurrence - off treatment	[redacted]	[redacted]	[redacted]	[redacted]
Alive - censored RFS	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Censored OS	[redacted]	[redacted]	[redacted]	[redacted]
Died	[redacted]	[redacted]	[redacted]	[redacted]

As stated in the submission (Section 15.6), the ERG in their assessment of this analysis for RFS, recognized its limitations and considered it a "worst case scenario" within their report for the previous submission.

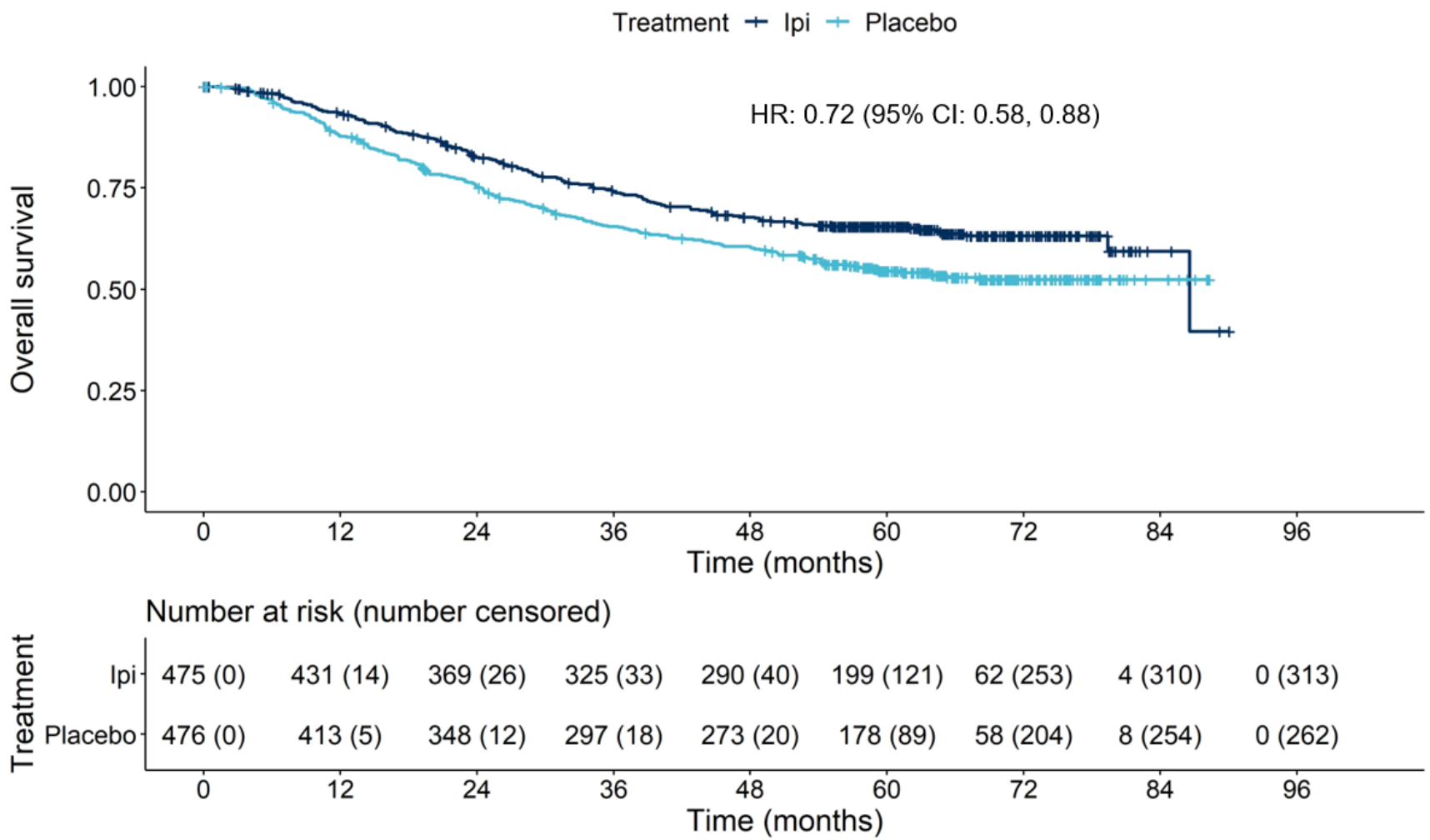
"*Patients from CA184-029 censored at one year are likely to be those that are healthier than patients who stop receiving ipilimumab. The ERG considers that an analysis where these patients are censored is likely to underestimate RFS in the ipilimumab group compared with placebo. The subsequent ITC would, therefore, potentially underestimate the difference in RFS between nivolumab and routine*

surveillance. The ERG considers this analysis to be a 'worst case' scenario based on the current data available"[1]

Figure 1 presents the OS for the observed ITT population in CA184-029 and Figure 2 presents OS for the ITT population where all patients are censored at one year if they were still receiving treatment. To aid comparison these figures have also been presented together in Figure 3. [redacted]

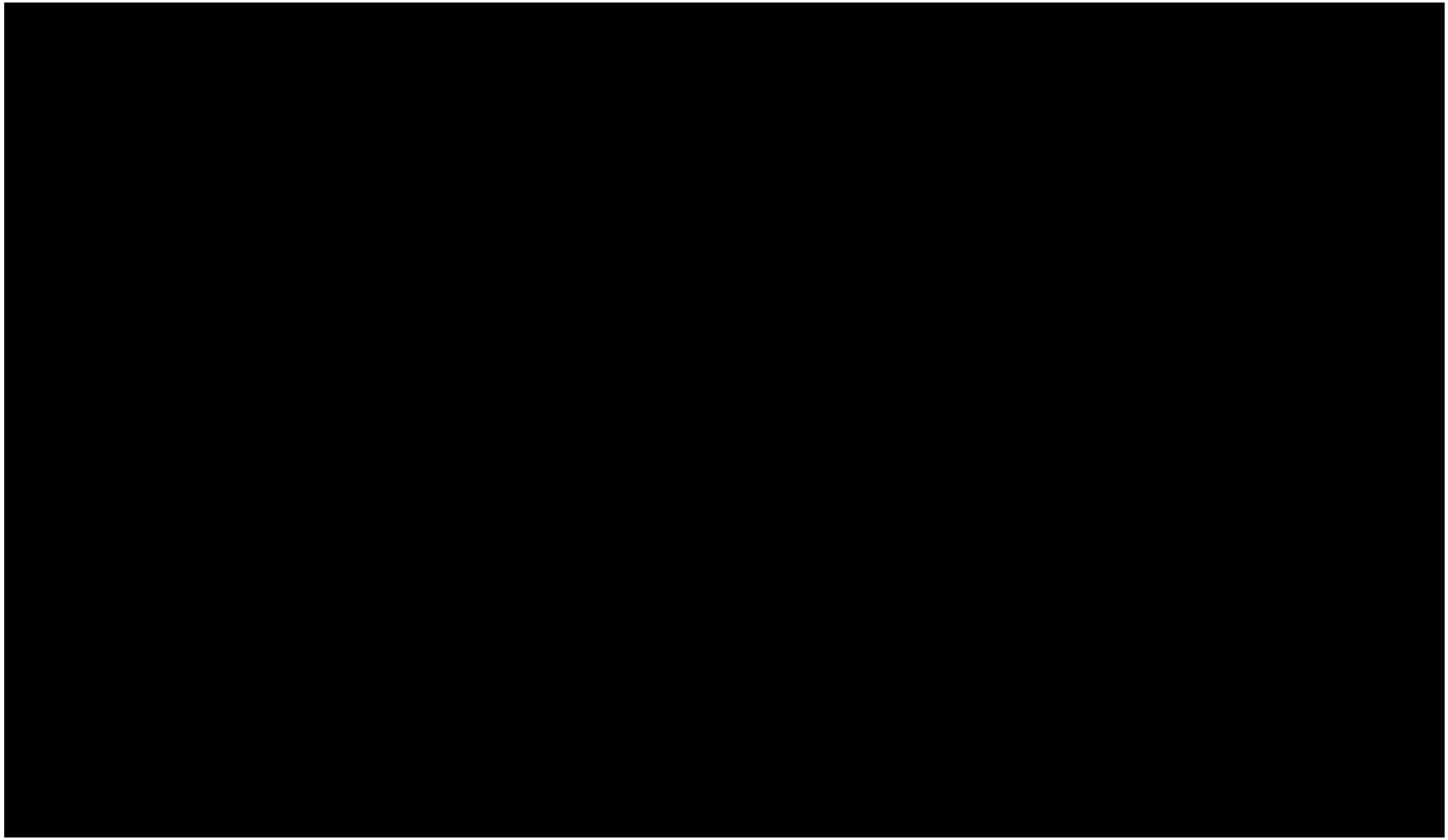
Although censoring the ipilimumab arm after one year of treatments provides the worst case scenario for RFS, the dramatic effect of informative censoring within the OS analysis as shown by the placebo arm (as shown in Figure 3) gives implausible results, and is unsuitable for informing the cost effectiveness of nivolumab.

Figure 1: CA184-029 overall-free survival KM for the observed ITT population



Key: HR, hazard ratio; Ipi, ipilimumab 10 mg; ITT, intention-to-treat KM, Kaplan–Meier; PBO, placebo; TRT, treatment; yr, year
Note: Hazard ratios presented are unstratified. Dashed line indicates 1 year after randomization; patients typically started treatment a few days after randomization.

Figure 2: CA184-029 overall-free survival KM where patients who were still on ipilimumab treatment after 1 year were censored



Key: HR, hazard ratio; Ipi, ipilimumab 10 mg; ITT, intention-to-treat KM, Kaplan–Meier; PBO, placebo; TRT, treatment; yr, year
Note: Hazard ratios presented are unstratified. Dashed line indicates 1 year after randomization; patients typically started treatment a few days after randomization.

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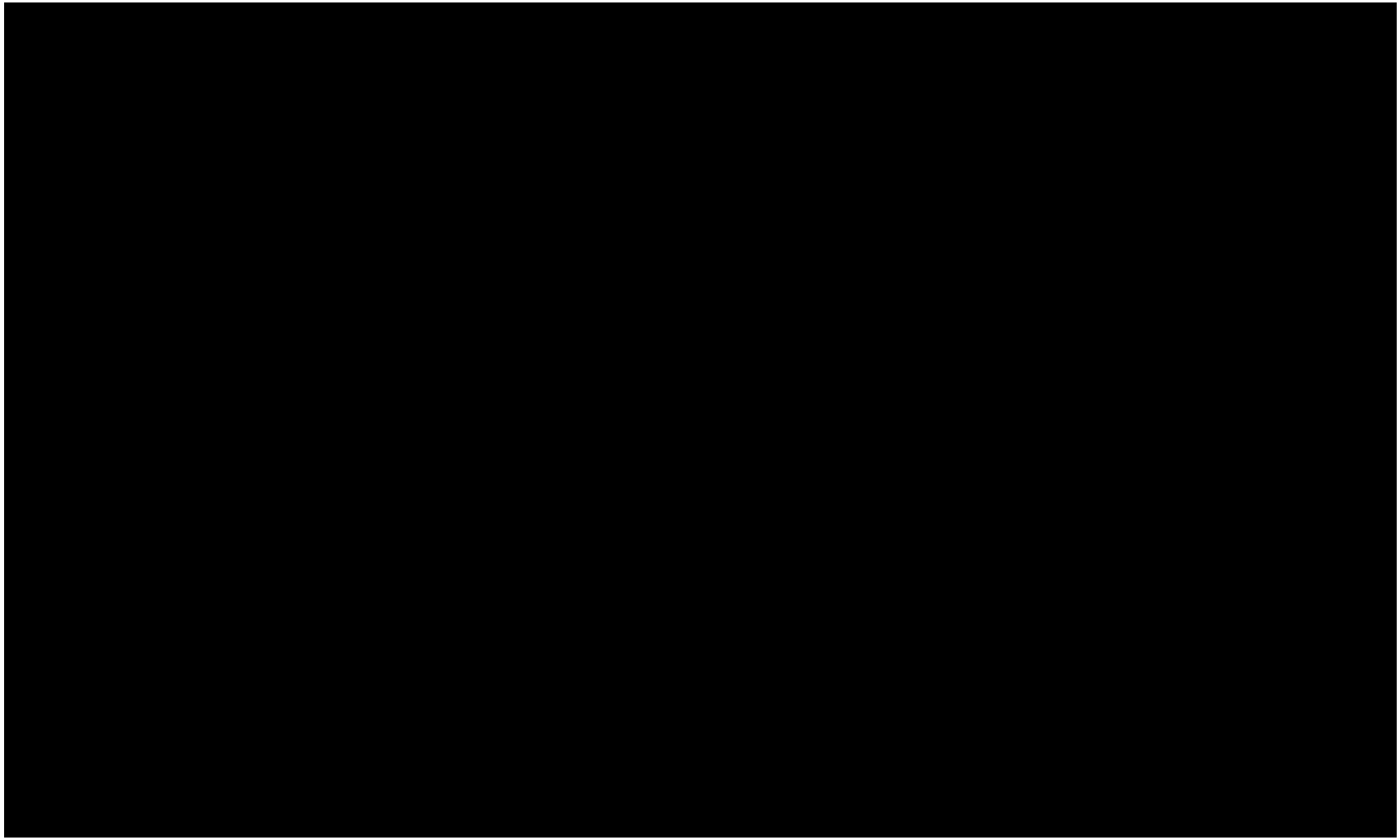
Figure 3: CA184-029 overall-free survival KM for the observed ITT population and for the observed ITT population where ipilimumab patients are censored after 1 year of treatment



Key: HR, hazard ratio; Ipi, ipilimumab 10 mg; ITT, intention-to-treat KM, Kaplan–Meier; PBO, placebo; TRT, treatment; yr, year
Notes: Dashed line indicates 1 year after randomization; patients typically started treatment a few days after randomization.

A3. Priority question. Please conduct an ITC PLD meta-regression analysis using the OS data from CheckMate 238 and CA184-029 with censoring of patients after 1 year of treatment with ipilimumab similar to the analysis of RFS. Please provide the resulting Figures (equivalent to Figures 3 and 4 in the company submission) and model fit statistics (equivalent to Table 10 in the company submission).

The goodness of fit statistics for the OS PLD meta-regression where patients are censored in CA184-029 if still on treatment after 1 year are presented in Table 2, and the fitted generalised gamma curves are presented in Figure 4 and Figure 5 for the nivolumab (CheckMate 238) and placebo (CA184-029) arms respectively. [redacted]. Comparisons of treatments in a matched population are presented in Figure 26 (partitioned survival model) within the response to question B2.

Table 2: Overall survival (ipilimumab patients censored after 1 year of treatment) – ITC PLD meta-regression model fit statistics

Model	AIC	AIC rank	BIC	BIC rank
Exponential	10590.40	6	10640.12	4
Generalised gamma	**10477.00**	**1**	**10548.82**	**1**
Gompertz	10588.45	5	10654.75	6
Log-logistic	10541.55	3	10607.85	3
Log-normal	10502.33	2	10568.63	2
Weibull	10579.11	4	10645.41	5

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITC, indirect treatment comparison; PLD, patient level data.
Note: Bold distribution represents the base case selection.

Figure 4: CheckMate 238 overall survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – generalised gamma survival extrapolations – nivolumab arm

Figure 5: CA184-029 overall survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – generalised gamma survival extrapolations – placebo arm

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A4. Priority question. Please conduct an ITC using the Bucher method for the outcome of OS with data from CheckMate 238 and CA184-029 with censoring of patients after 1 year of treatment with ipilimumab similar to the analysis of RFS. Please provide the resulting hazard ratio and 95%CI.

The results of the Bucher analysis and the corresponding within trial analyses where ipilimumab patients are censored after 1 year of treatment in CA184-029 are presented in Table 3. The results indicate that [redacted] (HR: [redacted]. However, given the reasons detailed in question A2, the analysis is not appropriate and [redacted].

Table 3: Within trial and Bucher analysis results – overall survival (observed results and results where ipilimumab patients are censored after 1 year of treatment in CA184-029)

Comparison	Study	Observed ITT HR (95% CI)	Ipilimumab censored analysis* HR (95% CI)
Nivolumab vs ipilimumab	CheckMate 238	[redacted]	[redacted]
Placebo vs ipilimumab	CA184-029	[redacted]	[redacted]
Nivolumab vs placebo	Bucher	[redacted]	[redacted]

Notes: * ipilimumab patients censored after 1 year of treatment in CA184-029; Presented hazard ratios are unstratified.

A5. Priority question. Please provide the ITC PLD meta-regression plots with data for nivolumab and routine surveillance in the same figure including a shaded area around each plot designating the 95% CI around the estimates for the outcomes of:

a) RFS;
b) OS.

Within the timeframe provided, we have produced a mean of covariates approach to provide graphical estimates of uncertainty around the extrapolations. Within the

mean of covariates analysis the patient population was matched for both treatment arms, and the covariate values used within the analysis is presented in Table 4. The ITC PLD meta-regression extrapolations using the log-logistic distribution for RFS are presented in Figure 6. Note, for RFS, uncertainty is not presented for the first 12 weeks as patients were rebased at 12 weeks within this analysis. The ITC PLD meta-regression extrapolations using the generalised gamma distribution for OS are presented in Figure 7. Note, the mean of covariates produces similar but not identical results to the matched extrapolations presented in Figure 7 and Figure 8 of the submission dossier for RFS and OS respectively.

Table 4: Covariate proportions used in matched meta-regression analysis (mean of covariates)

Covariate group	Covariate	Covariate proportion	
		Nivolumab	Placebo
Treatment	Nivolumab	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
	Ipilimumab	[redacted]	[redacted]
Disease Stage	Stage IIIa	[redacted]	[redacted]
	Stage IIIb	[redacted]	[redacted]
	Stage IIIc	[redacted]	[redacted]
	Stage IV	[redacted]	[redacted]
Sex	Male	[redacted]	[redacted]
	Female	[redacted]	[redacted]
Age group	≥ 65	[redacted]	[redacted]
	< 65	[redacted]	[redacted]
Trial	CA-184-029	[redacted]	[redacted]
	CheckMate 238	[redacted]	[redacted]

Figure 6: RFS PLD meta-regression (log-logistic) extrapolations using matched population

Key: nivo, nivolumab.

Figure 7: OS PLD meta-regression (generalised gamma) extrapolations using matched population

Key: nivo, nivolumab.

A6. Please conduct an ITC PLD meta-regression analysis for CheckMate 238 and CA184-029 for the outcomes of OS and RFS including covariate adjustment for BRAF status at baseline. Please include the censoring of patients after 1 year of treatment with ipilimumab in CA184-029 and present the resulting Figures and model fit statistics (as requested in question A3).

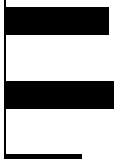
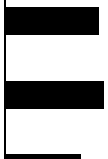
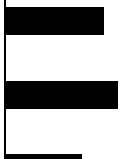
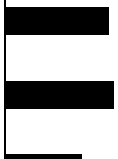
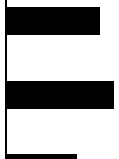
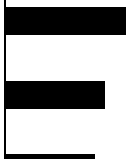
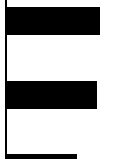
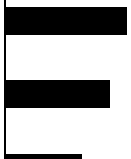
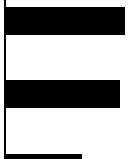
Within the CA184-029 study BRAF status was only collected retrospectively, as such approximately 85% of patients do not have a BRAF status reported. Given this, two alternative analyses have been performed, in which the subgroups of BRAF mutant and BRAF wild type were separately compared to the ITT population of CA184-029 for both RFS (ipilimumab patients censored after one year of treatment) and OS; ipilimumab patients were not censored after one year of treatment within the OS analysis for the reasons detailed in question A2. Approximately 15% patients in the nivolumab arm and 10% of patients in the ipilimumab arm of CheckMate 238 did not have BRAF status reported as such are excluded from this analysis; [redacted]. A limitation of this approach is that by analysing the entire ITT population for CA184-029, it is assumed that the relative treatment effect between ipilimumab is the same in both subgroups, whereas in reality treatment effect modification may exist which may bias results.

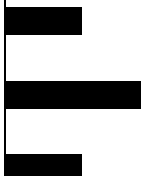
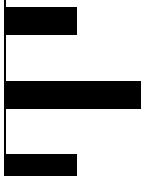
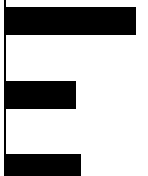
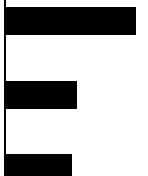
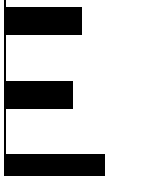
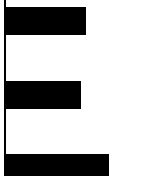
A further limitation is that BRAF status was not a stratification factor for randomisation within CheckMate 238. Therefore randomisation cannot be assumed within subgroups and as such a summary of patient characteristics by BRAF status and treatment arm are presented in Table 5. [redacted]

[redacted]

Table 5: Summary of baseline characteristics by BRAF status and treatment arm

Characteristic	Mutant		Wild type		BRAF not reported	
	Nivo (n = 187)	Ipi (n = 194)	Nivo (n = 197)	Ipi (n = 212)	Nivo (n = 69)	Ipi (n = 47)
Gender Male (%)						
Age Median (range) < 65 years old (%)						
Disease stage (7th edition) IIIA (%) IIIB (%) IIIC (%) IV (%) Other/Not reported (%)						
Disease stage (7th edition) (IIIB/C subgroup) IIIB (%) IIIC (%)						
Stage III lymph node involvement Microscopic (%)						

Characteristic	Mutant		Wild type		BRAF not reported	
	Nivo (n = 187)	Ipi (n = 194)	Nivo (n = 197)	Ipi (n = 212)	Nivo (n = 69)	Ipi (n = 47)
Macroscopic (%) Not reported (%)						
Stage III tumour ulceration Present (%) Absent (%) Not reported (%)						
Melanoma subtype Cutaneous (%) Acral (%) Extracutaneous (%) Mucosal (%) Other (%)						
ECOG PS 0 (%) 1 (%) 2 (%)						

Characteristic	Mutant		Wild type		BRAF not reported	
	Nivo (n = 187)	Ipi (n = 194)	Nivo (n = 197)	Ipi (n = 212)	Nivo (n = 69)	Ipi (n = 47)
BRAF Wild type (%) Mutant (%) Not reported (%)						
PD-L1 status <5% / Indeterminate (%) ≥5%(%)						

Key: ECOG PS, Eastern Cooperative Oncology Group performance status; Ipi, ipilimumab; Nivo, nivolumab; n, number of patients; PBO, placebo; PD-L1, programmed cell death ligand 1.

RFS – BRAF mutant population

The Kaplan Meier curve for RFS within CheckMate 238 for the BRAF mutant population is presented in Figure 8.

Figure 8: Kaplan–Meier curve for recurrence-free survival by treatment arm – CheckMate 238 (48-month minimum follow-up) – BRAF mutant population

Key: Ipi, ipilimumab; Nivo, nivolumab.

The goodness of fit statistics for the RFS BRAF mutant population PLD meta-regression are presented in Table 6, and the fitted log-logistic curves are presented in Figure 9 and Figure 10 for the nivolumab (CheckMate 238) and placebo (CA184-029) arms respectively. Comparisons of treatments in a matched population are presented in Figure 22 (partitioned survival model) and in Figure 23 (state transition model) within the response to question B2.

Table 6: RFS (ipilimumab patients censored after 1 year of treatment in CA184-029) PLD meta-regression, BRAF mutant population – goodness of fit statistics

Model	AIC	AIC rank	BIC	BIC rank
Exponential	9098.61	6	9143.84	6
Generalised gamma	8862.43	2	8927.76	3
Gompertz	8890.13	5	8950.43	5
Log-logistic	**8852.99**	**1**	**8913.30**	**1**
Log-normal	8865.53	3	8925.84	2
Weibull	8880.21	4	8940.52	4

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITC, indirect treatment comparison; PLD, patient level data.
Note: Bold distribution represents the lowest AIC/BIC.

Figure 9: CheckMate 238 recurrence-free survival (ipilimumab patients censored after 1 year of treatment in CA184-029) ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 – nivolumab arm – BRAF mutant population

Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; PLD, patient level data.
Note: KM from baseline is displayed, log-logistic curve is fitted from 12 weeks onwards

Figure 10: CA184-029 recurrence-free survival (ipilimumab patients censored after 1 year of treatment in CA184-029) ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 – placebo arm – BRAF mutant population

Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; PLD, patient level data.
Note: KM from baseline is displayed, log-logistic curve is fitted from 12 weeks onwards

RFS – BRAF wild type population

The Kaplan Meier curve for RFS within CheckMate 238 for the BRAF wild type population is presented in Figure 11.

Figure 11: Kaplan–Meier curve for recurrence-free survival by treatment arm – CheckMate 238 (48-month minimum follow-up) – BRAF wild type population

Key: Ipi, ipilimumab; Nivo, nivolumab.

The goodness of fit statistics for the RFS (ipilimumab patients censored after 1 year of treatment in CA184-029) BRAF wild type population PLD meta-regression analysis are presented in Table 7 , and the fitted log-logistic curves are presented in Figure 12 and Figure 13 for the nivolumab (CheckMate 238) and placebo (CA184-029) arms respectively. Comparisons of treatments in a matched population are presented in Figure 24 (partitioned survival model) and in Figure 25 (state transition model) within the response to question B2.

Table 7: RFS (ipilimumab patients censored after 1 year of treatment in CA184-029) PLD meta-regression, BRAF wild type population – goodness of fit statistics

Model	AIC	AIC rank	BIC	BIC rank
Exponential	9652.64	6	9698.14	6
Generalised gamma	9406.78	2	9472.50	3
Gompertz	9444.68	5	9505.35	5
Log-logistic	**9398.77**	**1**	**9459.44**	**1**
Log-normal	9410.00	3	9470.66	2
Weibull	9425.97	4	9486.64	4

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITC, indirect treatment comparison; PLD, patient level data.
Note: Bold distribution represents the lowest AIC/BIC.

Figure 12: CheckMate 238 recurrence-free survival (ipilimumab patients censored after 1 year of treatment in CA184-029) ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 – nivolumab arm – BRAF wild type population

Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; PBO, placebo; PLD, patient level data.
Note: KM from baseline is displayed, log-logistic curve is fitted from 12 weeks onwards

Figure 13: CA184-029 recurrence-free survival (ipilimumab patients censored after 1 year of treatment in CA184-029) ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 – placebo arm – BRAF wild type population

Key: ITC, indirect treatment comparison; KM, Kaplan–Meier; PBO, placebo; PLD, patient level data.
Note: KM from baseline is displayed, log-logistic curve is fitted from 12 weeks onwards

OS – BRAF mutant population

The Kaplan Meier curve for OS within CheckMate 238 for the BRAF mutant population is presented in Figure 14.

Figure 14: Kaplan–Meier curve for overall survival by treatment arm – CheckMate 238 (48-month minimum follow-up) – BRAF mutant population

Key: Ipi, ipilimumab; Nivo, nivolumab.

The goodness of fit statistics for the OS BRAF mutant population PLD meta-regression are presented in Table 8, and the fitted generalized gamma curves are presented in Figure 15 and Figure 16 for the nivolumab (CheckMate 238) and placebo (CA184-029) arms respectively. Comparisons of treatments in a matched population are presented in Figure 22 (partitioned survival model) and in Figure 23 (state transition model) within the response to question B2.

Table 8: OS PLD meta-regression, BRAF mutant population – goodness of fit statistics

Model	AIC	AIC rank	BIC	BIC rank
Exponential	8459.64	5	8506.38	4
Generalised gamma	**8376.87**	**1**	**8444.38**	**1**
Gompertz	8456.82	4	8519.15	5
Log-logistic	8429.71	3	8492.03	3
Log-normal	8398.68	2	8461.01	2
Weibull	8461.13	6	8523.45	6

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITC, indirect treatment comparison; PLD, patient level data.
Note: Bold distribution represents the lowest AIC/BIC.

Figure 15: CheckMate 238 overall survival ITC PLD meta-regression model – generalised gamma survival extrapolations – nivolumab arm – BRAF mutant population

Key: ITC, indirect treatment comparison; PLD, patient level data.

Figure 16: CA184-029 overall survival ITC PLD meta-regression model – generalised gamma survival extrapolations – placebo arm – BRAF mutant population

Key: ITC, indirect treatment comparison; PLD, patient level data.

OS – BRAF wild type population

The Kaplan Meier curve for OS within CheckMate 238 for the BRAF wild type population is presented in Figure 17.

Figure 17: Kaplan–Meier curve for overall survival by treatment arm – CheckMate 238 (48-month minimum follow-up) – BRAF wild type population

Key: Ipi, ipilimumab; Nivo, nivolumab.

The goodness of fit statistics for the OS BRAF wild type population PLD meta-regression analysis are presented in Table 9, and the fitted generalized gamma curves are presented in Figure 18 and Figure 19 for the nivolumab (CheckMate 238) and placebo (CA184-029) arms for the BRAF wild type population, respectively. Comparisons of treatments in a matched population are presented in Figure 24 (partitioned survival model) and in Figure 25 (state transition model) within the response to question B2.

Table 9: OS PLD meta-regression, BRAF wild type population – goodness of fit statistics

Model	AIC	AIC rank	BIC	BIC rank
Exponential	8855.68	5	8902.61	4
Generalised gamma	**8764.33**	**1**	**8832.12**	**1**
Gompertz	8853.71	4	8916.28	5
Log-logistic	8825.07	3	8887.65	3
Log-normal	8790.75	2	8853.33	2
Weibull	8857.33	6	8919.90	6

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITC, indirect treatment comparison; PLD, patient level data.
Note: Bold distribution represents the lowest AIC/BIC.

Figure 18: CheckMate 238 overall survival ITC PLD meta-regression model – generalised gamma survival extrapolations – nivolumab arm – BRAF wild type population

Key: ITC, indirect treatment comparison; PLD, patient level data.

Figure 19: CA184-029 overall survival ITC PLD meta-regression model – generalised gamma survival extrapolations – placebo arm – BRAF wild type population

Key: ITC, indirect treatment comparison; PLD, patient level data.

A7. Please provide subgroup results including forest plots, number of events, number of patients, hazard ratios and 95% confidence intervals for the following subgroups in CheckMate 238 for the outcomes of RFS and OS:

a) Age;
b) Sex;
c) VRAF status;
d) PD-L1 status;
e) Disease stage;
f) ECOG status; and
g) Geographical region**.**

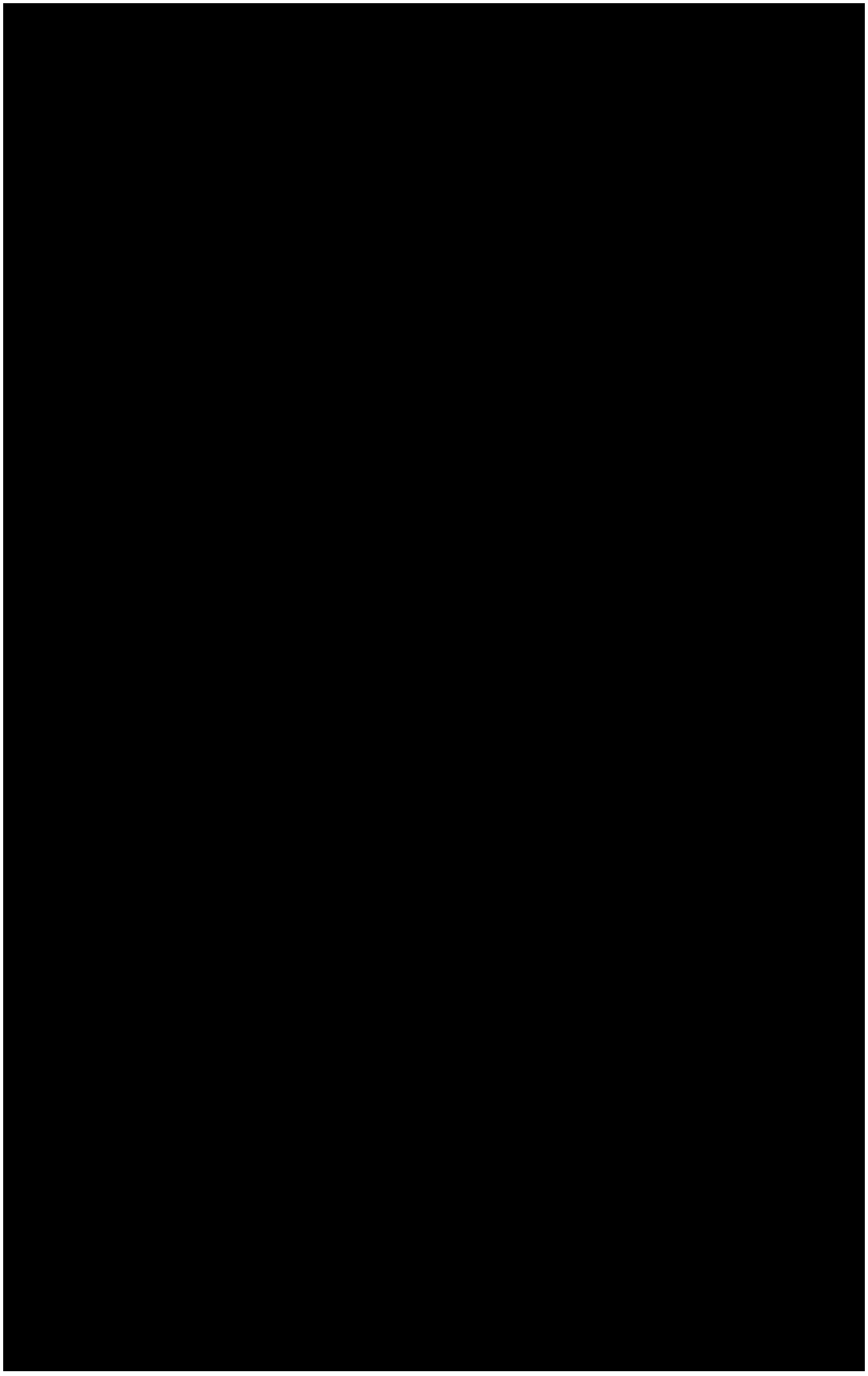
Forest plots comparing nivolumab and ipilimumab for subgroups in CheckMate 238 are presented in Figure 20 and Figure 21 below for the outcomes of RFS and OS respectively. It should be noted that randomisation within CheckMate 238 was stratified according to disease stage (Stage IIIB or IIIC vs Stage IV M1a or M1b vs

Stage IV M1c) and PDL1 status (<5% / Indeterminate vs ≥5%), as such randomisation cannot be assumed for other subgroups.

For RFS, [redacted]

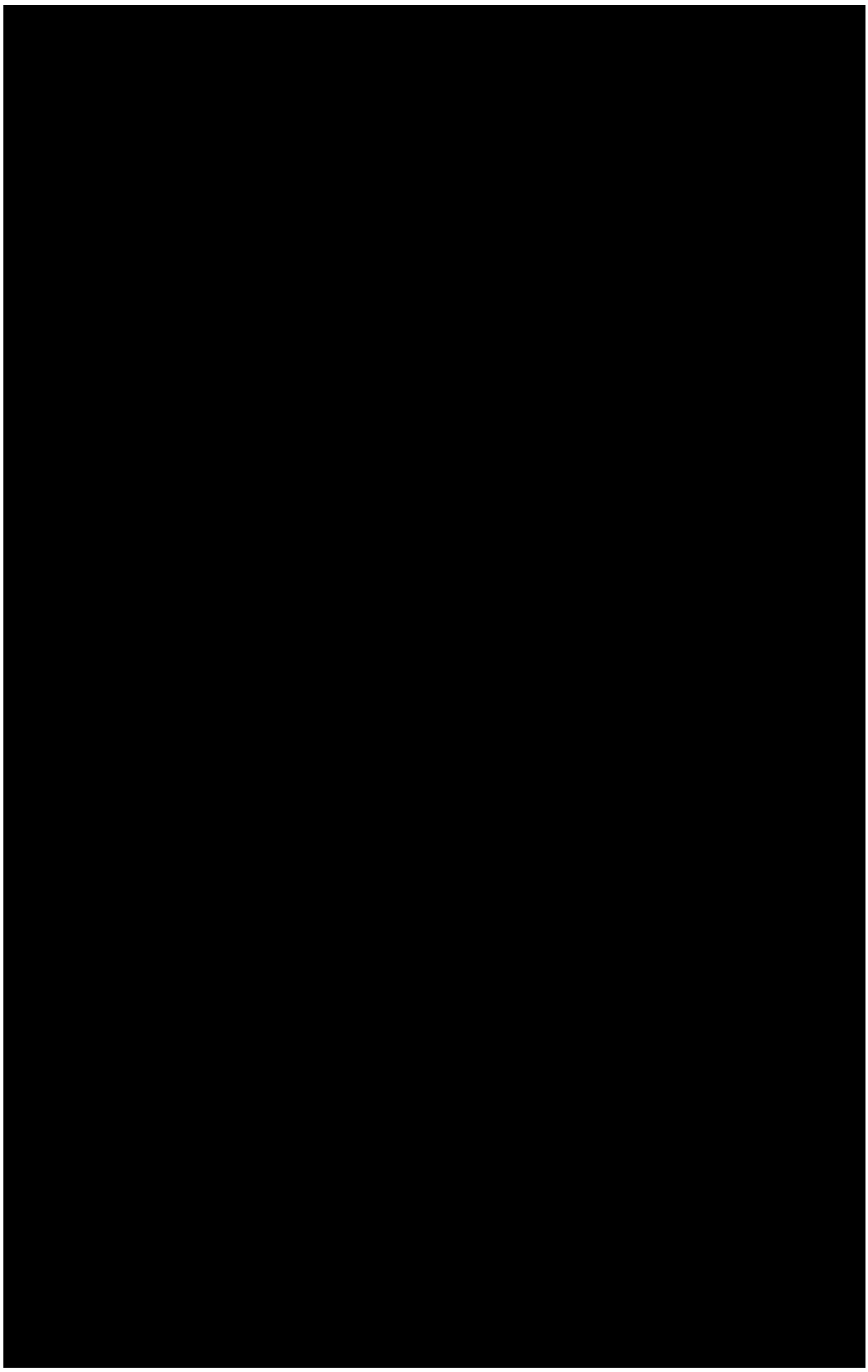
[redacted]

Figure 20: Forest plot of recurrence-free survival in subgroups: CheckMate 238 (48-month minimum follow-up)



Key: CI, confidence interval; F, female; HR, hazard ratio; Ipi, ipilimumab; M, male; NA, not available; Nivo, nivolumab; ROW, rest of the world.

Figure 21: Forest plot of overall survival in subgroups: CheckMate 238 (48-month minimum follow-up)



Key: CI, confidence interval; F, female; HR, hazard ratio; Ipi, ipilimumab; M, male; NA, not available; Nivo, nivolumab; ROW, rest of the world.

A8. Please provide the median (and interquartile range) and mean (with standard deviation) duration of treatment for each arm in CheckMate 238 for the 48-month minimum follow-up data cut reported in the company submission.

Information on duration of treatment for each arm in CheckMate 238 for the 48-month minimum follow-up data cut is included in Table 10 below. Duration of treatment was calculated from first to last exposure to treatment.

[redacted]

Table 10: Duration of treatment in CheckMate 238 for the 48-month minimum follow-up data cut

Treatment	N	Median	IQR (25th, 75th percentile)	Mean (SD)
Ipilimumab	453	[redacted]	[redacted]	[redacted]
Nivolumab	452	[redacted]	[redacted]	[redacted]

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model. Furthermore, if the company chooses to update its base case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response.

Survival analysis

B1. **Priority question**: The terms of engagement for the CDF review document stated that "The survival data from the clinical trial CheckMate 238 were considered very immature. The committee was therefore unable to identify a range of plausible ICERs". [redacted]

[redacted]

During the consultation period for the original submission (TA558) BMS provided overall-survival data from an unplanned analysis of CheckMate 238 with a minimum follow up of 24 months. Consequently, whilst the ICER ranges presented showed that nivolumab had the plausible potential to be cost-effective, we understand the recommendations detailed in the FAD that state 'more mature overall-survival data are needed to determine whether the company's updated ICER is robust'. The updated ICERs associated with the CDF review submission makes use of overall-survival data from the CheckMate 238 study with a minimum follow-up of 48 months. The observed trend in event rates with 2 years of additional data show that the hazard of death is lower for patients treated with nivolumab compared with those treated with ipilimumab (hazard ratio [HR]: 0.87 [95% confidence interval [CI]: 0.66, 1.14]). This is an improvement in what was observed in the 24-month data cut (hazard ratio [HR]: 0.96 [95% confidence interval [CI]: 0.66, 1.39]). When compared with placebo via the indirect treatment comparison, nivolumab continues to show a clear and robust improvement in overall survival. Results of the Bucher comparison using the 48-month data show that treatment with nivolumab is associated with a significantly reduced hazard of death compared with treatment with routine surveillance ([redacted] This is an improvement on similar analyses using 24-month data ([redacted]].

The FAD for the original submission TA558 concluded that both of the model structures are potentially acceptable for decision making, and as such limited changes were made for the CDF submission. New data from CheckMate 238 incorporated into the cost-effectiveness model reduced the ICERs for both the partitioned survival and state-transition models. The new data from CheckMate 238 also included the ITC meta-regression for OS, whereas the previous submission was based on assumptions using the CA184-029 trial. The results of both models validate the conclusions of the original submission in that nivolumab is cost effective compared with routine surveillance at the £30,000 willingness to pay threshold. We acknowledge that further data will always be informative but believe the clinically

supported expectation that with even longer follow-up nivolumab would continue to maintain its overall survival benefit over placebo and would maintain ICERs below NICE's willingness to pay threshold. Sensitivity analysis confirm that using parameter extremes the ICER remains below £30,000 threshold and probabilistic analysis gives a greater than 90% chance of being cost-effective. In addition, the submission includes two different model structures such that structural uncertainty and scenarios around subsequent treatments (not relying on OS data) is used which all show ICERs below the threshold. The trend in model results from the use of the 24-month data and 48-month data should give NICE confidence that nivolumab is a cost-effective use of NHS resources.

B2. Priority question: If, based on the responses to questions in section A, the ITC analyses are updated, please ensure these are updated in the economic model and provide revised cost-effectiveness results.

BRAF subgroups

As discussed in response to clarification question A6, the ITC meta-regression has been conducted subgrouping patients with BRAF mutant status and BRAF wild type status separately. These meta-regressions have been incorporated into the economic model along with updated subsequent treatment data (from CheckMate 238) and patient characteristics informing age and weight distributions. All other inputs and model settings remain consistent with the base case.

As discussed in response to A6, there are many limitations with this subgroup analysis. Firstly, the key efficacy data for routine surveillance informed by the CA184-029 trial only collected BRAF status retrospectively (only 15% available) and therefore was not well reported and these patients could not be subgrouped for this analysis. The impact of this is unknown given that this subgroup was never assessed in CA184-029. Secondly, patients within CheckMate 238 were not randomised by BRAF status resulting in an unbalanced population per subgroup. Though the comparison of patient characteristics appears to be balanced, there are small differences between treatment arms. Lastly, the subgroup analysis presented in response to A7 shows numerical differences between BRAF status, in particular for OS in the BRAF mutant subgroup, however these remain not statistically significant and show no evidence of a difference in OS or RFS between treatment arms per

subgroup, moreover, retrospective analyses have confirmed that nivolumab has similar efficacy and safety outcomes regardless of BRAF mutation status.[2]

As requested by the ERG, cost-effectiveness results for the BRAF subgroups are presented below however BMS would like to stress the limitations of the analyses and would not consider these subgroups to be appropriate or conclusive. In addition, BMS would like to highlight that BRAF status is not relevant for this submission given that both routine surveillance and nivolumab apply to all patients regardless of BRAF status.

BRAF mutant

Table 11 presents the subsequent treatment data from CheckMate 238 for the BRAF mutant population only. As expected, a high majority of patients receiving subsequent systemic therapy received dabrafenib + trametinib which is specifically targets BRAF mutant genes.

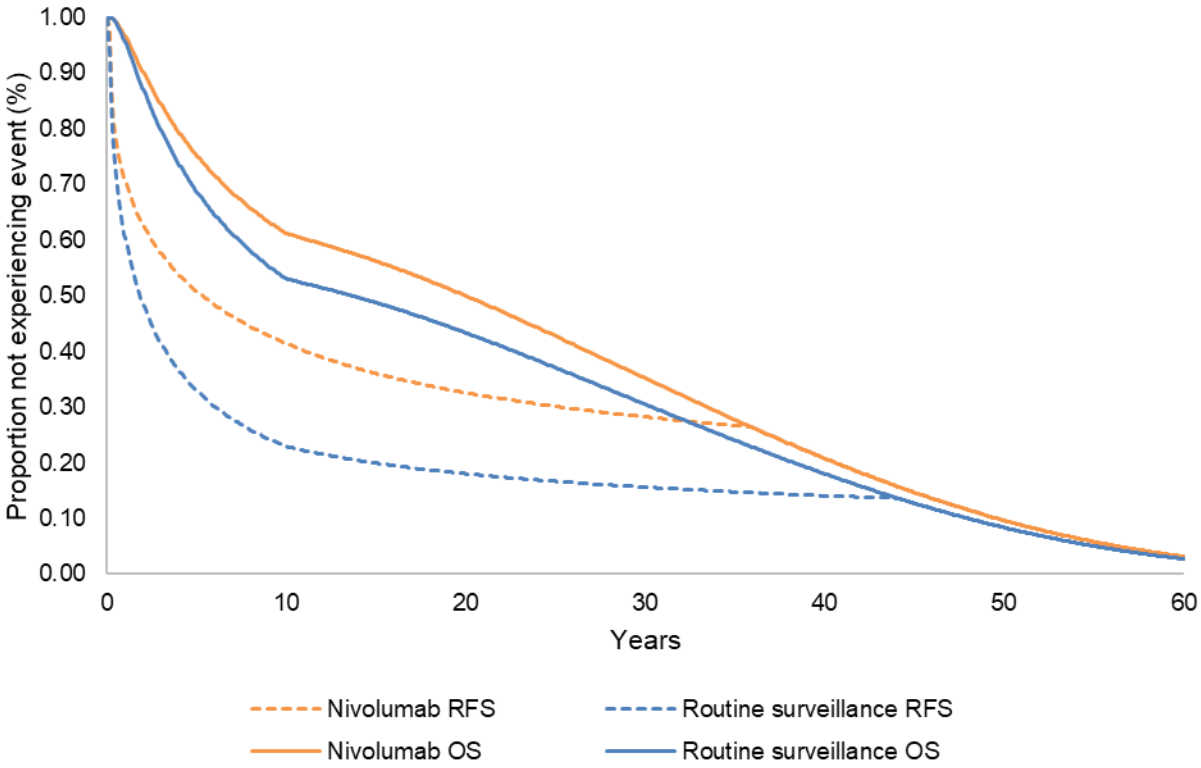
Table 11: Subsequent treatment data – BRAF mutant population

Subsequent treatment	Local/regional		Distant	
	Nivolumab	Ipilimumab	Nivolumab	Ipilimumab
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib*	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]

Subsequent treatment	Local/regional		Distant	
	Nivolumab	Ipilimumab	Nivolumab	Ipilimumab
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent surgery	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]

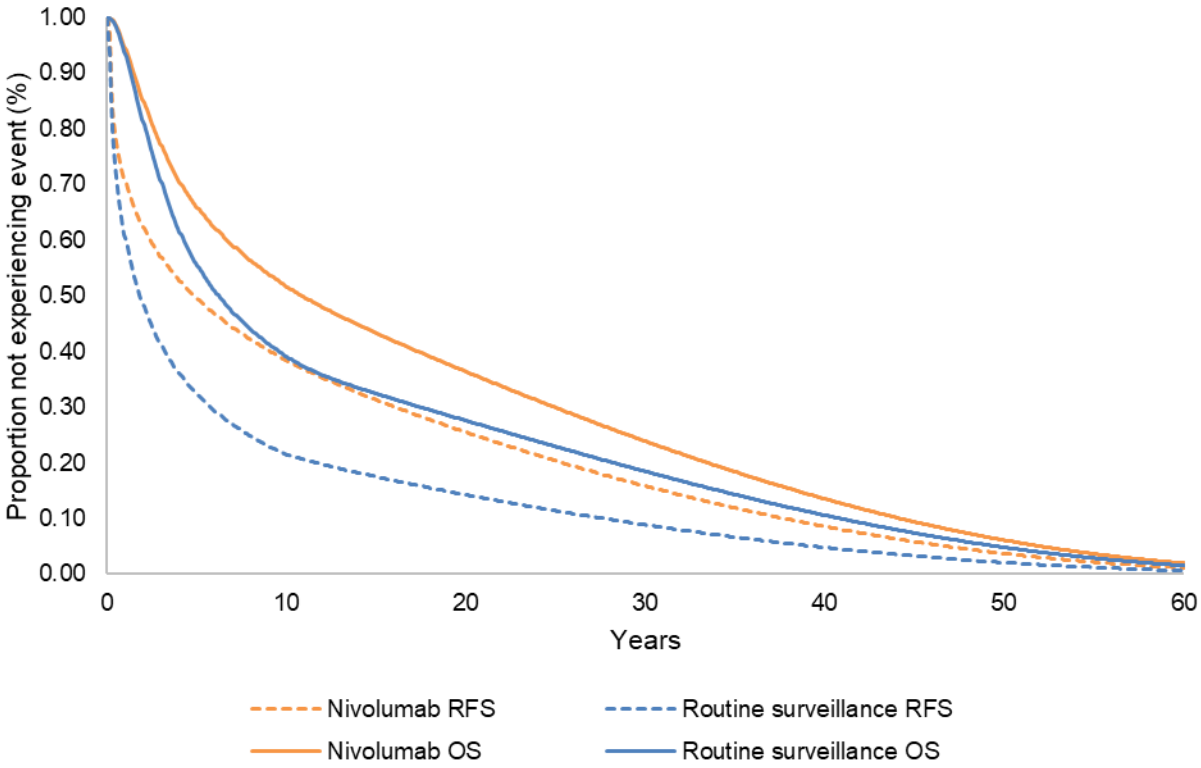
The ITC meta-regression was updated for both RFS and OS using the BRAF subgroups. As discussed in response to clarification question A6, log-logistic is the best fitting curve for RFS and generalised gamma for OS, this is consistent with the base case population selected curves and therefore was also chosen to represent the base case curves for the BRAF mutant population. The resulting RFS and OS model curves are presented in Figure 22 for the partitioned survival model and Figure 23 for the state-transition model.

Figure 22: Model OS and RFS – BRAF mutant – partitioned survival model



Key: OS, overall survival; RFS, recurrence-free survival

Figure 23: Model OS and RFS – BRAF mutant – state-transition model



Key: OS, overall survival; RFS, recurrence-free survival

The cost-effectiveness results for the BRAF mutant subgroup for both model structures are presented in Table 12.

Table 12: Cost-effectiveness results – BRAF mutant subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							
Routine surveillance	[redacted]	20.00	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,039
State-transition model							
Routine surveillance	[redacted]	14.22	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,960
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

BRAF wild type

Table 13 presents the subsequent treatment data from CheckMate 238 for the BRAF wild type population only. The majority of patients receiving subsequent systemic therapy received anti-PDL1s after recurrence and as expected hardly any patients received BRAF targeted therapies.

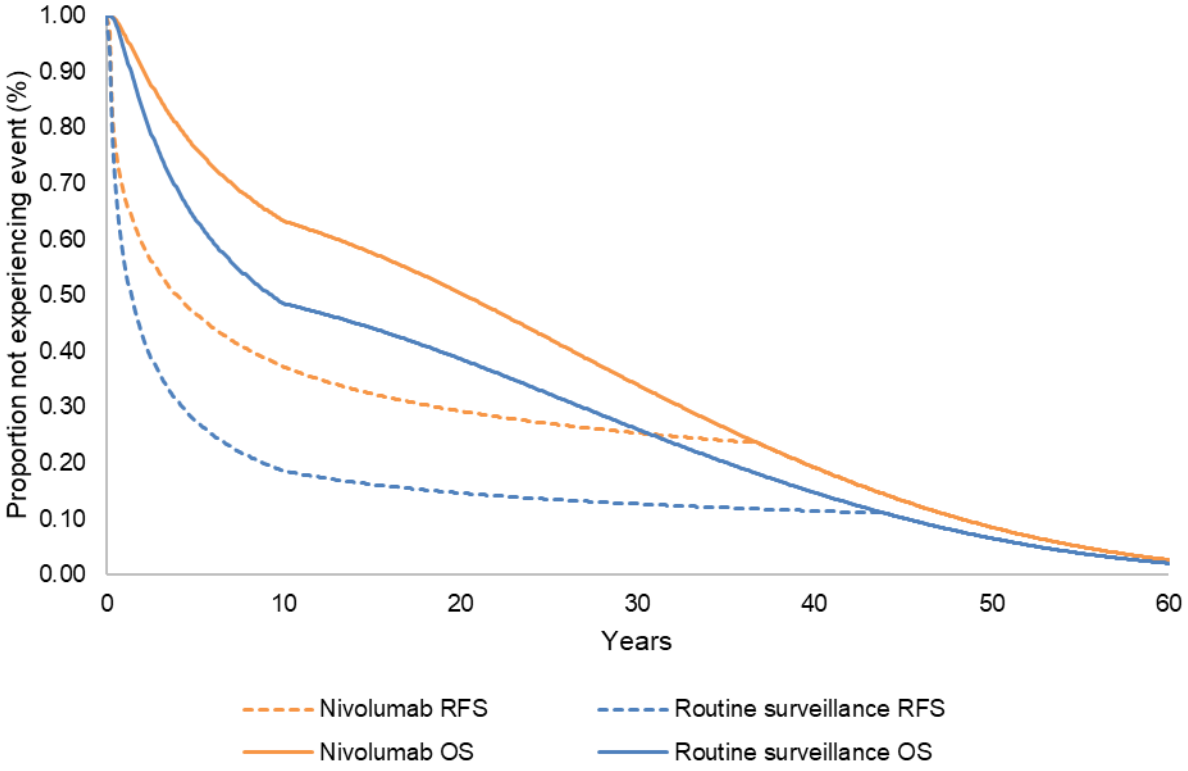
Table 13: Subsequent treatment data – BRAF wild type

Subsequent treatment	Local/regional		Distant	
	Nivolumab	Ipilimumab	Nivolumab	Ipilimumab
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]

Subsequent treatment	Local/regional		Distant	
	Nivolumab	Ipilimumab	Nivolumab	Ipilimumab
Dabrafenib + trametinib*	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent surgery	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]

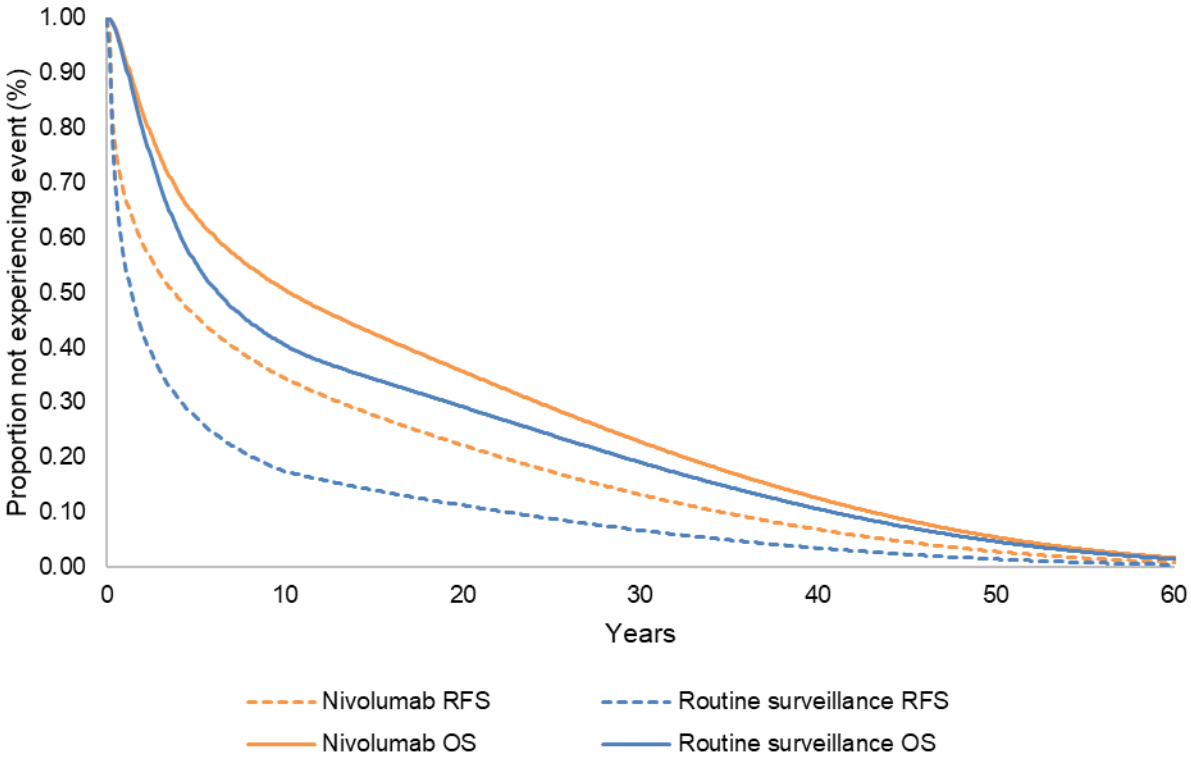
As per the BRAF mutant subpopulation, the log-logistic appeared to be the best fitting curve for RFS and generalised gamma for OS, and was therefore chosen to represent the base case curves for the BRAF wild type population. The resulting RFS and OS model curves are presented in Figure 24 for the partitioned survival model and Figure 25 for the state-transition model.

Figure 24: Model OS and RFS – BRAF wild type – partitioned survival model



Key: OS, overall survival; RFS, recurrence-free survival

Figure 25: Model OS and RFS – BRAF wild type – state-transition model



Key: OS, overall survival; RFS, recurrence-free survival

The cost-effectiveness results for the BRAF wild type subgroup for both model structures are presented in Table 14.

Table 14: Cost-effectiveness results – BRAF wild type subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							
Routine surveillance	[redacted]	17.86	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,909
State-transition model							
Routine surveillance	[redacted]	14.47	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,306
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

OS data from CheckMate 238 and CA184-029 with censoring of patients after 1 year of treatment with ipilimumab

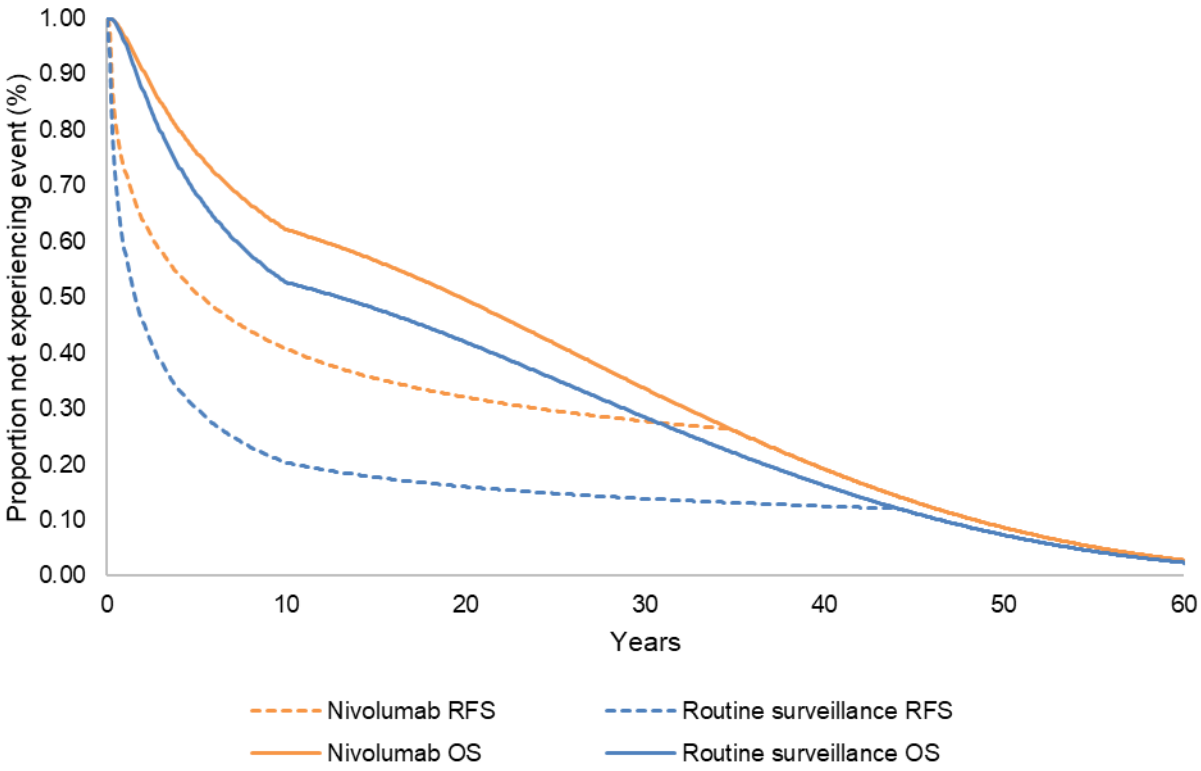
As discussed in response to clarification question A3, the ITC meta-regression has been conducted also including an option to look at OS where ipilimumab patients are censored after 1 year of treatment with ipilimumab. These meta-regressions have been incorporated into the economic model. All other inputs and model settings remain consistent with the base case. As discussed in response to A2, there are many limitations with this analysis based on the informative censoring of ipilimumab patients who are doing well on treatment.

As requested by the ERG, cost-effectiveness results for the OS where patients are censored after 1 year of treatment with ipilimumab are presented below however BMS would like to stress the limitations of the analyses as highlighted in response to A2.

The ITC meta-regression was updated for OS using the ipilimumab censored data. As discussed in response to clarification question A3, generalised-gamma is the best fitting curve for OS, this is consistent with the base case population selected curves and therefore was also chosen to represent the base case curves for the ipilimumab censored population, RFS has not been updated and this remains the same as the

base case using the ipilimumab censored meta-regression. The resulting RFS and OS model curves are presented in Figure 26 for the partitioned survival model.

Figure 26: Model OS and RFS – Ipilimumab censored – partitioned survival model



Key: OS, overall survival; RFS, recurrence-free survival

The cost-effectiveness results for the ipilimumab censored population for partitioned survival model is presented in Table 15.

Table 15: Cost-effectiveness results – Ipilimumab censored OS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	19.29	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,404
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

B3. Priority question: Given the immaturity of overall survival from Checkmate 238, the ERG considers that it would be useful to explore several scenarios around overall survival to provide a range of potentially plausible ICERs for the committee to

consider. The ERG acknowledges the strong assumptions in each of the following requested scenarios and will explore these in its report. Please provide the following scenarios using the partitioned survival model:

a) Implement the OS ITC (CGP adjusted) survival curves for both nivolumab and routine surveillance for the first two years of the model. After two years, assume the risk/hazard of death for both nivolumab and routine surveillance patients is the same as risk/hazards of death estimated in the OS ITC survival curves (CGP adjusted) for nivolumab. The scenario implicitly assumes that for nivolumab patients, rechallenge can happen one year after treatment.
b) Implement the OS ITC for both nivolumab and routine surveillance for the first three years of the model. After three years, assume the risk/hazard of death for both nivolumab and routine surveillance patients is the same as risk/hazards of death estimated in the OS ITC survival curves (CGP adjusted) for nivolumab. The scenario implicitly assumes that for nivolumab patients, rechallenge can happen two years after treatment.
c) Assume overall survival for nivolumab and routine surveillance is equal to the OS ITC (CGP adjusted) survival curve for nivolumab.

In all scenarios:

- The modelling of RFS for both nivolumab and routine surveillance should remain unchanged to the company's base case.

- Please ensure that costs of subsequent therapies are aligned to the assumptions of overall survival in each scenario. For instance, in scenarios a and b, after the threshold (two or three years) and for scenario c for the entire time horizon, cost

of subsequent therapy should reflect subsequent therapy received in the nivolumab arm of Checkmate 238.

- If the OS ITC is updated based on responses to questions in Section A (for instance, OS for ipilimumab from CA184-029 is restricted to one year), please ensure that this is also explored in the requested scenarios.

- To check the internal validity of each of the scenarios, please provide overall survival plots comparing nivolumab and routine surveillance, based on estimates in the model.

Firstly, we thank the ERG for acknowledging that these are strong assumptions. BMS do not agree that these scenarios implicitly assume that re-challenge can happen after 2 or 3 years as the adjustment is also made to the routine surveillance arm. The nivolumab curve uses the OS hazard derived from the ITC meta-regression from baseline and subsequent treatment costs from CheckMate 238 throughout, which as presented in Section A.6.1 in the CDF submission, demonstrates that patients are re-challenged with nivolumab within the first 2 years (including some patients within the first 6 months).

The scenarios requested by the ERG assume that patients who only receive routine surveillance have the same hazard of death as those patients treated with adjuvant nivolumab at 2 years, 3 years or the whole time horizon implying these are a result of the subsequent treatments. More appropriate ways of modelling scenarios around these assumptions have been provided using the state-transition model which implicitly models assumptions around post-recurrence survival based on subsequent treatment usage and have provided scenarios on re-challenge and subsequent treatment distributions which impact both efficacy (post-recurrence survival and resulting OS) and subsequent costs.

The request to assume the same OS for the entire time horizon is clinically implausible, assuming no benefit of nivolumab in terms of survival compared to patients who receive no adjuvant treatment. This contradicts the available evidence which shows nivolumab having a greater mean survival compared to ipilimumab which in turn demonstrates a statistically significant improvement in survival compared to placebo. This was also the view of the previous committee and

clinicians who felt that: *"although the overall-survival data were very immature, there was general agreement between consultees and invited clinical experts that, based on their wider experience with immunotherapy treatments in other cancers, it was reasonable to expect that the recurrence-free survival benefit seen in CheckMate 238 would be translated to some extent into an overall-survival benefit. The committee therefore concluded that adjuvant nivolumab may improve overall survival compared with routine surveillance."* BMS would like it to be acknowledged that this is not only a strong assumption but goes against the available evidence seen from the clinical trials and also the perception of clinical experts.

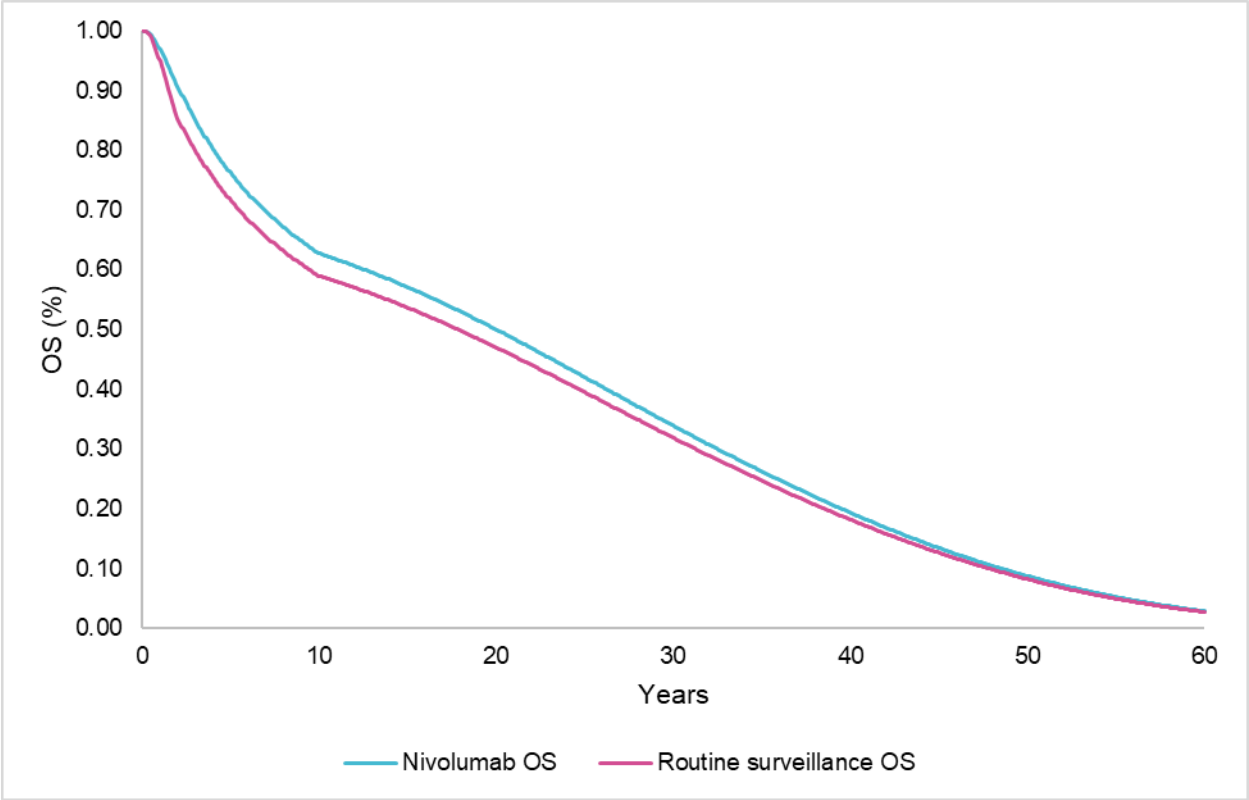
OS meta-regression

Results for each analysis are presented in Table 16 - Table 18 respectively. Please note that results below reflect also updating the base case to use 480mg Q4 dosing (as requested in B9). For these scenarios, the subsequent treatment costs are also applied as requested by the ERG and all other base case inputs remain the same.

Table 16: B3.A - Assume that hazard of death for routine surveillance is the same as nivolumab at 2 years.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	21.00	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,809
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 27: B3.A – Overall survival assuming hazard of death for routine surveillance is the same as nivolumab at 2 years

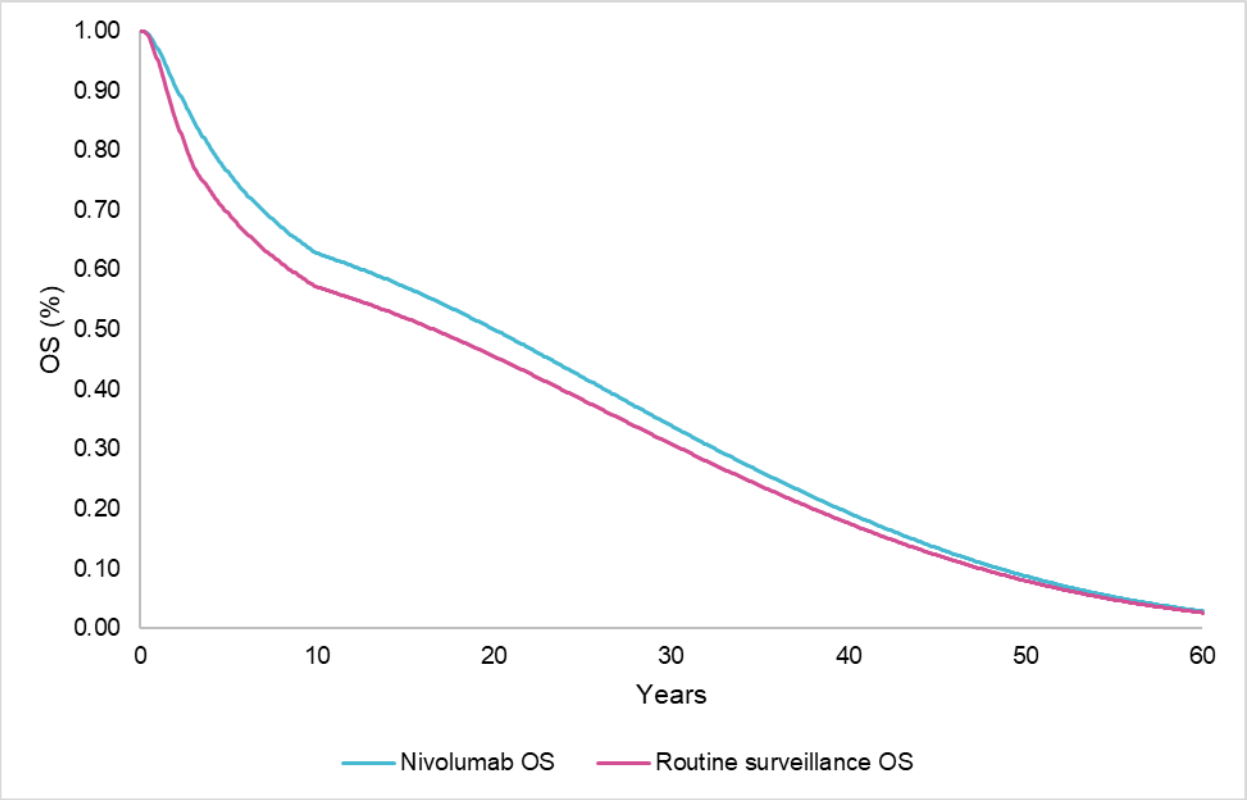


Key: OS, overall survival

Table 17: B3.B - Assume that hazard of death for routine surveillance is the same as nivolumab at 3 years.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	20.39	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,487
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 28: B3.B – Overall survival assuming hazard of death for routine surveillance is the same as nivolumab at 3 years

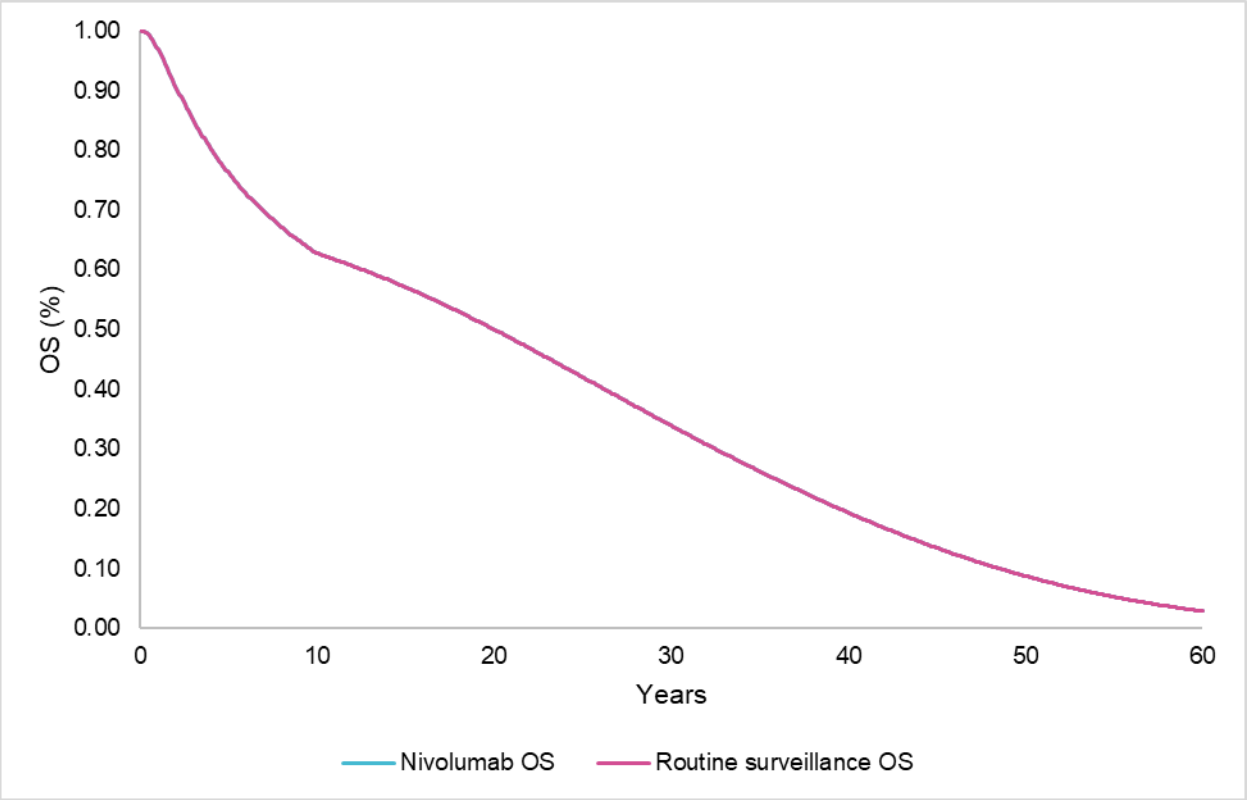


Key: OS, overall survival

Table 18: B3.C - Assume that for nivolumab hazard of death for routine surveillance is the same as nivolumab from baseline

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	22.26	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£75,489
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 29: B3.C – Overall survival assuming hazard of death for routine surveillance is the same as nivolumab from baseline



Key: OS, overall survival

OS meta-regression ipilimumab censored

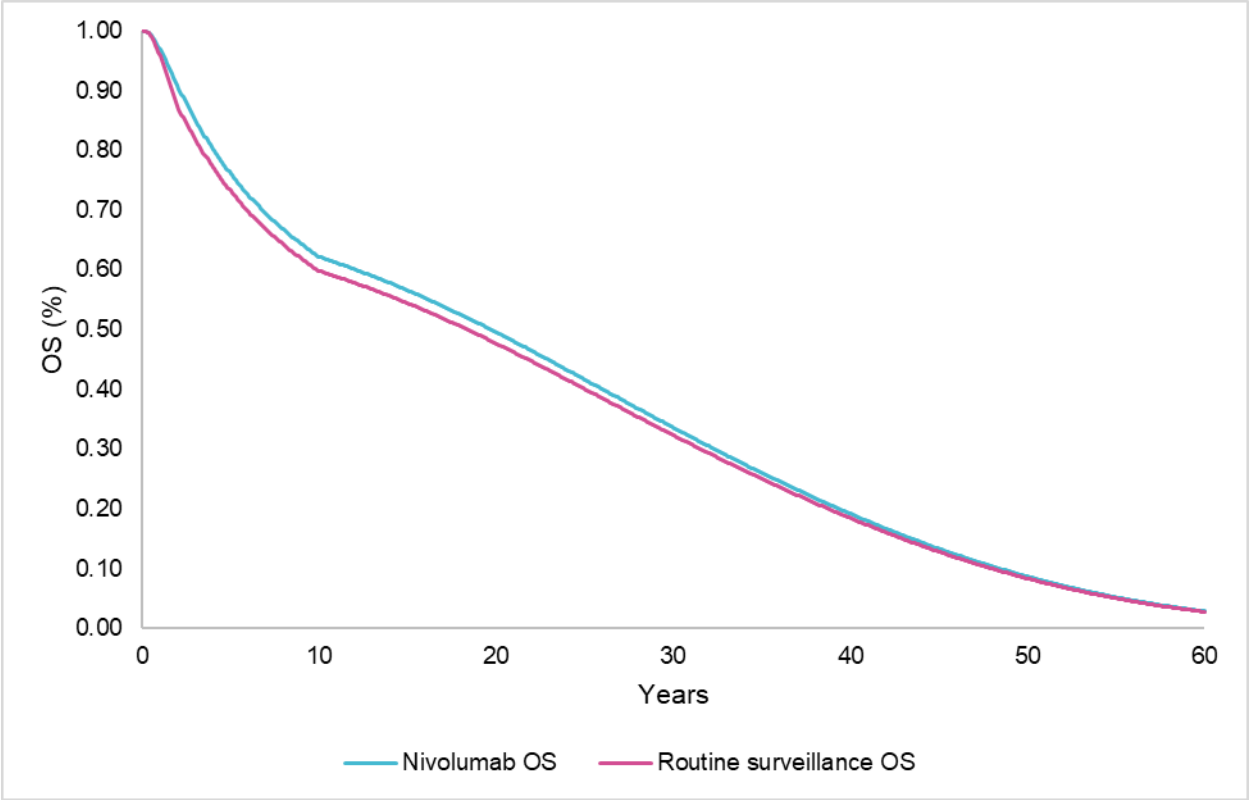
The above scenarios have also been conducted using the OS meta-regression where ipilimumab patients have been censored at 12 months as per requested in B3.

Results for each analysis are presented in Table 19 - Table 21 respectively.

Table 19: B3.A - Assume that hazard of death for routine surveillance is the same as nivolumab at 2 years.(OS ipi cesnored)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	21.32	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,371
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 30: B3.A – Overall survival assuming hazard of death for routine surveillance is the same as nivolumab at 2 years (OS ipi censored)

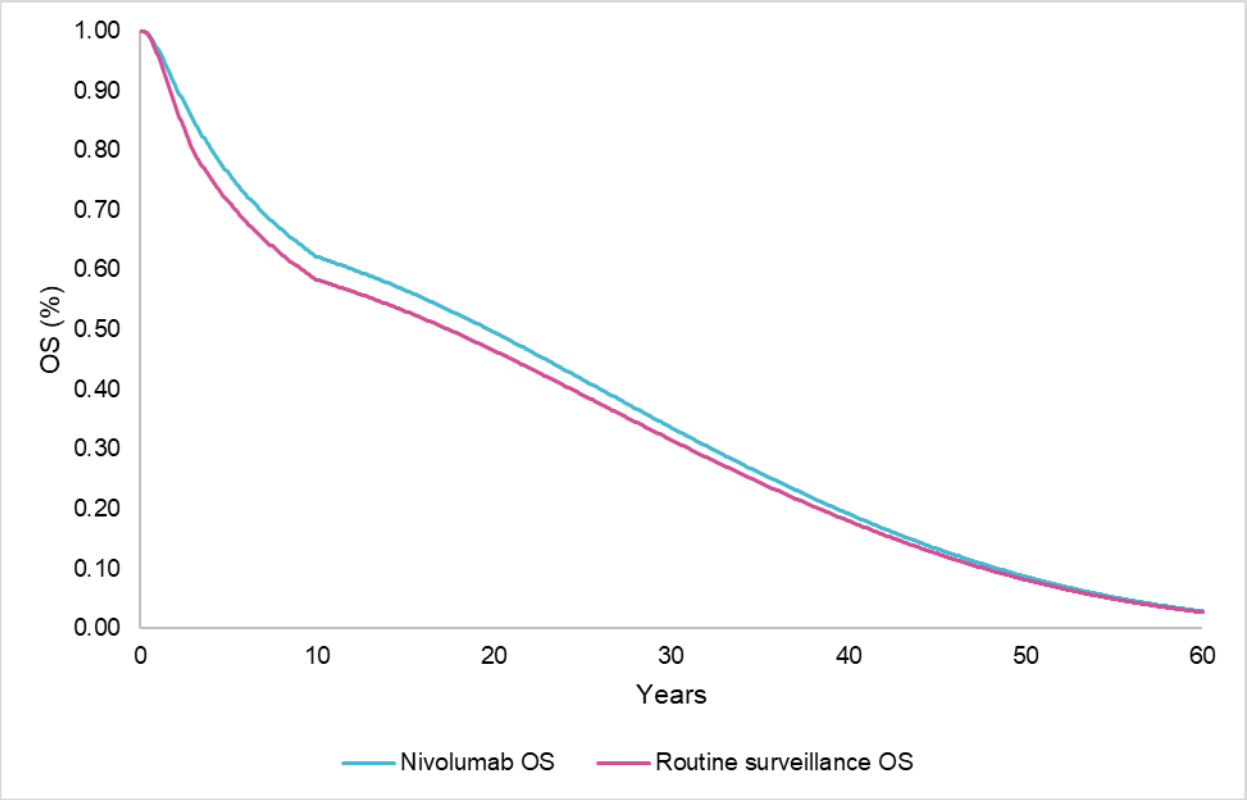


Key: OS, overall survival

Table 20: B3.B - Assume that hazard of death for routine surveillance is the same as nivolumab at 3 years (OS ipi censored).

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	20.85	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,011
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 31: B3.B – Overall survival assuming hazard of death for routine surveillance is the same as nivolumab at 3 years (OS ipi censored)

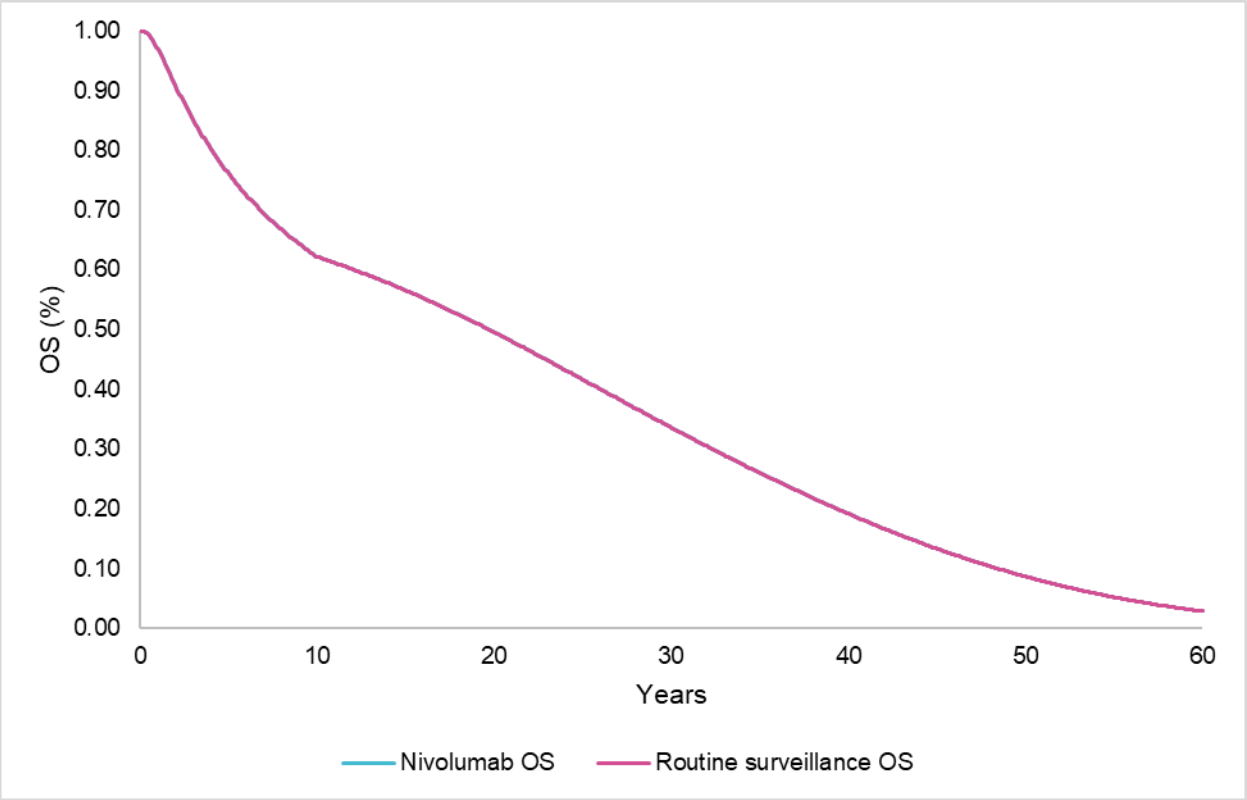


Key: OS, overall survival

Table 21: B3.C - Assume that for nivolumab hazard of death for routine surveillance is the same as nivolumab from baseline (OS ipi censored)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	22.11	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£75,562
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 32: B3.C – Overall survival assuming hazard of death for routine surveillance is the same as nivolumab from baseline (OS ipi censored)



Key: OS, overall survival

B4. Priority question: Please explain why the RFS ITC based on more mature data from Checkmate 238 could not be used after 12 weeks for the remainder of the model time horizon for both the PSM and state transition model?

a) Please provide a scenario for both the PSM and state-transition model where the RFS ITC is used for the entire time horizon after 12 weeks.

In the original TA558 submission, given the uncertainty associated with long-term recurrence-free survival and overall survival in adjuvant melanoma, BMS applied the functionality to make use of long-term melanoma registry data[3] assuming the same hazard of death and recurrence at 10 years for both treatment arms (10 years was used based on long term data showing a plateau at this time).

Despite having additional follow-up for RFS and more mature data, the clinical trial data only goes up to 54-months and is therefore still associated with some uncertainty in the long-term should it be extrapolated for the whole time horizon of 60 years. Therefore, BMS made the decision to stick with the most conservative option and use long-term data available in the literature at 10 years. BMS acknowledged

that adjusting the RFS curves was more complex due to the lack of available direct registry data for RFS and therefore provided a scenario where the adjustment to RFS curves is not applied and the ITC is used after 12 weeks for the remainder of the time horizon (see Section A.15.17).

Table 22 demonstrates the results of not including capping the RFS extrapolations at 10 years, but instead using this for the entire time horizon. Please note that results below reflect also updating the base case to use 480mg Q4 dosing (as requested in B9). In doing so the ICER for nivolumab is reduced.

Table 22: RFS extrapolations used for entire time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							
Routine surveillance	[redacted]	18.65	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,515
State-transition model							
Routine surveillance	[redacted]	13.91	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,004
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

B5. Priority question: Please explain why the OS ITC survival curves for adjuvant nivolumab and routine surveillance are not used for the entire duration of the PSM model

As per the response to B4, BMS sought to be conservative in their approach, given the possible uncertainty of applying the extrapolation to the entire time horizon. Table 23 demonstrates the results of not including capping to the RFS and OS extrapolations at 10 years, but instead using these for the entire time horizon. In doing so the ICER for nivolumab is reduced.

Table 23: OS and RFS extrapolations used for entire time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	17.77	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,790
State-transition model							
Routine surveillance	[redacted]	13.67	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,017
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Subsequent therapy

B6. Priority question: Please provide a scenario using the revised state-transition model that reflects the ERG's preferred assumptions outlined in the ERG's response to ACD comments, Table 3. That is, using the Wilmington Health Care subsequent treatment data and assuming rechallenge with nivolumab never becomes beneficial.

Table 24 presents results using the previous ERG preferred base case, that is, using the Wilmington Health Care subsequent treatment data and assuming rechallenge with nivolumab never becomes beneficial, additionally, the dosing regimen has been updated to 480mg Q4 as requested in B9.

Table 24: ERG preferred base case, including dosing update to 480mg Q4

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	14.45	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,823
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

B7. Priority question: Please clarify why the Wilmington and SACT data for subsequent therapies are only applicable to distant recurrences (cells J65 and J67 in the "Controls" tab of the model).

Subsequent therapies described in the Wilmington source represent only metastatic melanoma disease, and as such have only been applied as potential options for distant recurrences in the model. The SACT data collected information on patients who received subsequent treatment after nivolumab adjuvant therapy however it did not distinguish between type of recurrence. Most of the subsequent treatments within the data set are not available to patients with a local-regional recurrence where it is assumed they would receive adjuvant therapy. Although pembrolizumab and dabrafenib + trametinib are within the list of treatments and are available for patients as an adjuvant treatment in the UK, the numbers were too small to make any assumptions (n=1 and n=3 respectively). Therefore, it was assumed to only represent metastatic subsequent treatments in the model. Local-regional subsequent treatment costs are not a big driver of model results and do not affect the efficacy of the post-recurrence survival for the state-transition model therefore, the impact of these unknowns are still likely to be minimal. In addition, the base case for the state-transition model removes costs of local-regional costs as they did not represent the previous UK standard of care at the time of the previous TA558 submission and this has been carried forward for the recent CDF submission due to lack of data to inform otherwise.

B8. Priority question: For the estimation of subsequent therapy proportions for the nivolumab arm of the state transition model, the company has assumed that post-rechallenge, proportions reflect the routine surveillance arm (based on ipilimumab data from Checkmate 238). Pre-rechallenge, any patients on PD1 inhibitors are assumed to have the costs and survival benefit associated with ipilimumab. Thus, in the state-transition model, the ERG expects to see the proportions on nivolumab, nivo+ipi and pembrolizumab to be 0%, but they are 4%, 4% and 7.6%, respectively. Please investigate whether the costs of subsequent therapy for nivolumab in the pre-rechallenge period include double counting for PD1 inhibitors. If a correction is needed, please provide updated base case results.

The rechallenge scenarios are only applied to first line subsequent treatments. The model splits data by first line and second line therefore the costs for anti-PD1s

received in second line are still included. Therefore, the percentages applied represent the treatments applied at 2nd line as a proportion of total treatments applied (1L and 2L), this can be seen in Table 25.

Table 25: Subsequent treatment %'s for the nivolumab rechallenge scenario

Subsequent treatment	1L (pre re-challenge)	1L (post re-challenge)	2L+	Total (pre-rechallenge)	Total (post-rechallenge)
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

If we also assume that the second line-treatments are included in the re-challenge scenario then the base case ICER reduces to £15,889 (see Table 26). Please note, the dosing regimen has also been updated to 480mg Q4 as requested in B9.

Table 26: Including both first- and second-line subsequent treatments in rechallenge

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine surveillance	[redacted]	14.27	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,889
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Resource use and costs

B9. Priority question: The ERG's clinical experts have indicated that adjuvant nivolumab will be given as a flat dose of 480mg once every four weeks in UK clinical practice. Please revise the base case results to reflect this regimen**.**

We acknowledge the clinical experts decision, and have updated the base case to reflect 480mg Q4 dosing throughout, the updated base case for each model are presented in Table 27.

Table 27: Updated base case (dosing changed to 480mg Q4)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							
Routine surveillance	[redacted]	17.83	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,301
State-transition model							
Routine surveillance	[redacted]	14.27	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,171
Key: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

B10. Priority question: For the first appraisal committee meeting of this topic, NHS England made a submission to NICE that stated, "*the NHS England chemotherapy delivery tariff in 2017/18 for nivolumab is coded as SB13Z"*. No mention was made for the chosen tariff by NHS England related to weight-based dosing, but specifically for nivolumab as an adjuvant treatment. In the CDF submission, the cost code has

been changed back to SB12Z. Please revise the base case to align with NHS England's guidance for the administration cost code to reflect SB13Z for nivolumab.

The cost code for administration, SB12Z, reflects that of the flat dose applied and should therefore remain as the base case. This is in line with the HRG cost applied in the NHS OPCS-4 coding standards for chemotherapy 2017-2018.[4]

Section C: Textual clarification and additional points

C1. Priority question: In Table 2 of the submission, the dose of nivolumab is stated to be 240 mg every 2 weeks or 480 mg every 4 weeks. However, on page 41 the dose is stated to be 240mg twice per week or a flat dose of 480mg four times per week. Please clarify what is the updated dose and regimen for nivolumab.

Nivolumab is administered as an intravenous infusion with a recommended dose of 240 mg every 2 weeks or 480 mg every 4 weeks for the treatment of adjuvant melanoma. The cost-effectiveness model costs nivolumab in this way. The text described on page 41 is an error.

References

1. National Institute for Health and Care Excellence (NICE). TA558: Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease. 2018. Available at: https://www.nice.org.uk/guidance/TA558. Accessed: 03 July 2020.
2. Gangadhar TC and Schuchter LM. Broad Applicability of Nivolumab in Melanoma Regardless of BRAF Mutation Status. *JAMA Oncol*. 2015; 1(4):427-8.
3. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017; 67(6):472-92.
4. NHS Digital. National Tariff Chemotherapy Regimens List 2017 - 18 (Excel document). 2018. Available at: https://hscic.kahootz.com/connect.ti/t_c_home/view?objectId=16878800. Accessed: 28 July 2020.

Appendix: New base case sensitivity analysis

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed for 1,000 iterations for the new company base case.

The average (mean) incremental QALYs gained from nivolumab with the PAS applied across the 1,000 iterations are displayed in Table 28. The visual results of the probabilistic sensitivity analysis runs are presented in Figure 33 for the partitioned survival model and Figure 34 for the state-transition model. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability of nivolumab being the most cost-effective treatment option was [redacted] in the partitioned survival model and [redacted] with the state-transition model (with the PAS applied). The results of the probabilistic analysis were similar to those of the deterministic analysis.

Table 28: Updated base-case results (probabilistic) – B.3.8 (Page 169)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Partitioned survival model							
Routine surveillance	[redacted]	19.28	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,566
State-transition model							
Routine surveillance	[redacted]	14.46	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,954
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 33: Cost-effectiveness plane: partitioned survival model

Key: QALY, quality-adjusted life year; WTP, willingness to pay.

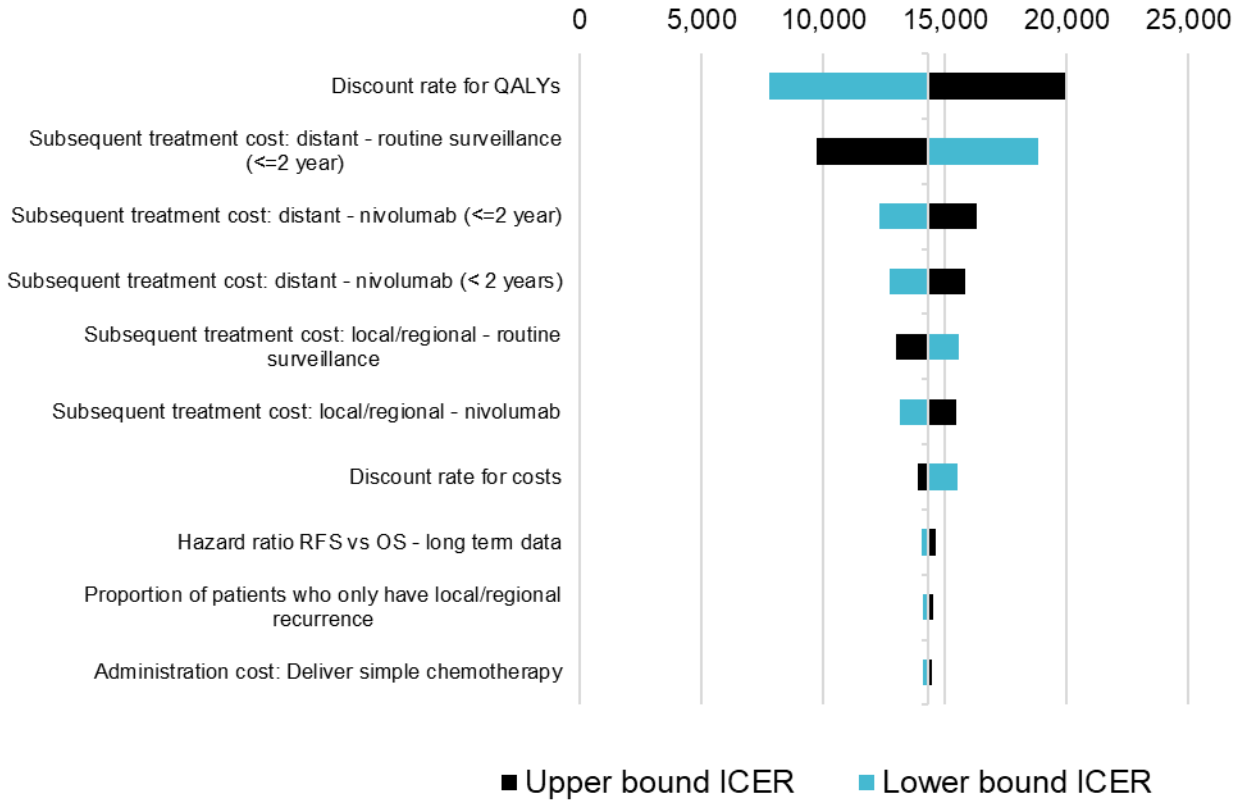
Figure 34: Cost-effectiveness plane: state-transition model

Key: QALY, quality-adjusted life year; WTP, willingness to pay.

Deterministic sensitivity and scenario analyses

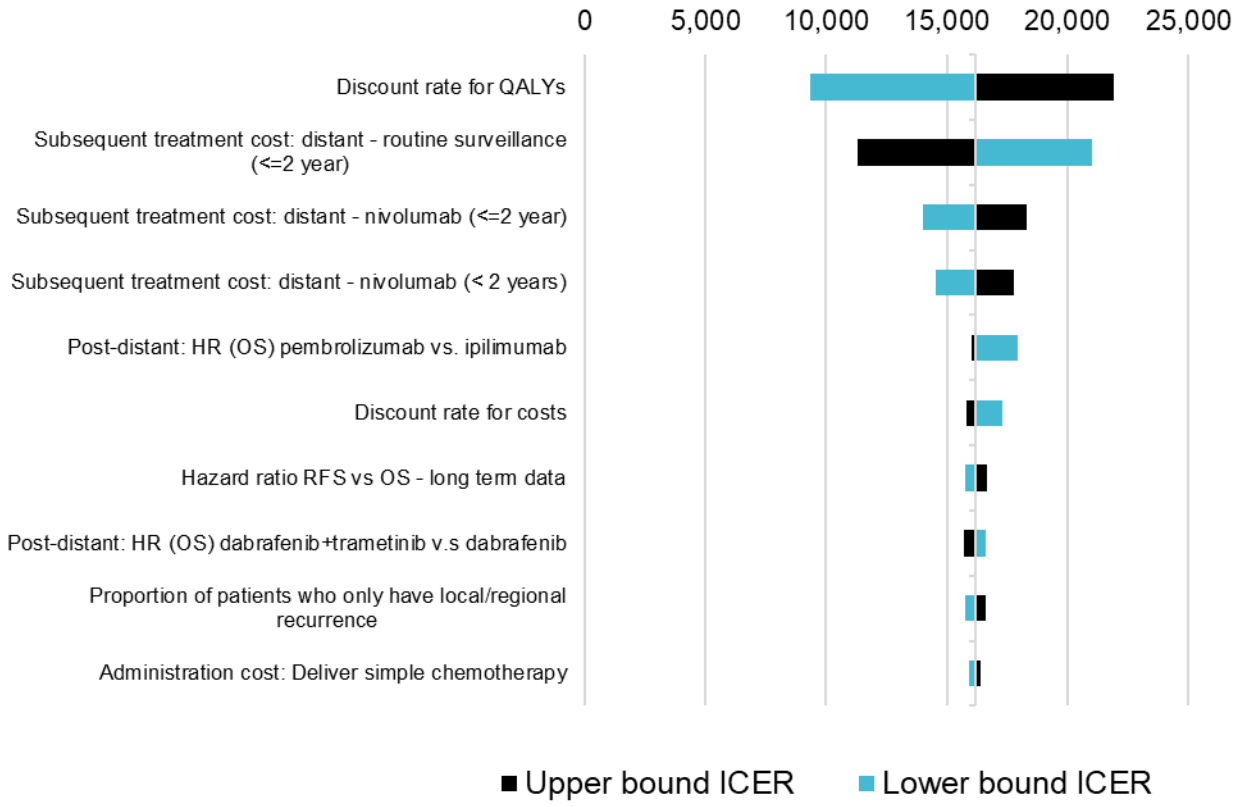
Figure 35 and Figure 36 present tornado diagrams showing the top 10 drivers of cost effectiveness with descending sensitivity from the one-way sensitivity analysis when nivolumab is provided with the PAS discount. The ICERs for both models were most sensitive to the discount rate applied to QALYs and subsequent treatment costs. All ICERs remained below the £30,000 willingness-to-pay threshold for each parameter tested.

Figure 35: Tornado diagram – partitioned survival model



Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life-year; RFS, recurrence-free survival.

Figure 36: Tornado diagram – state-transition model



Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life-year; RFS, recurrence-free survival.

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis. The full scenario analyses are presented in Table 29 and Table 30 for the partitioned survival and state-transition models, respectively (where nivolumab is provided with the PAS discount).

Table 29: Partitioned survival model (scenario analysis results)

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs routine surveillance
			Costs (£)	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	14,301
Population	Patient characteristics: (CA184-029 and CheckMate 238) Stage proportions: CA184-029 & CheckMate 238 adjusted RFS for nivolumab and routine surveillance:	CheckMate 238 CheckMate 238 Nivo: CheckMate 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	12,504

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs routine surveillance
			Costs (£)	LYs	QALYs	
	ITC (CA184-029 and CheckMate 238)					
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	13,648
Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	14,827
		50 years	[redacted]	[redacted]	[redacted]	14,403
Nivolumab dosing	240 Q2W	3mg/kg Q2W	[redacted]	[redacted]	[redacted]	14,935
		240mg Q2W	[redacted]	[redacted]	[redacted]	14,195
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	14,195
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	14,199
Nivolumab administration cost reference	SB12Z	SB13Z	[redacted]	[redacted]	[redacted]	14,301
Subsequent treatment (local/regional)	CheckMate 238	CA184-029	[redacted]	[redacted]	[redacted]	14,304
Nivolumab subsequent treatment (distant)	CheckMate 238	SACT data	[redacted]	[redacted]	[redacted]	11,520
RFS ITC method	ITC 48-month DBL (subgroup 1-year ipi treatment in 029)	ITC 48-month DBL	[redacted]	[redacted]	[redacted]	7,726
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	18,545
		Gompertz	[redacted]	[redacted]	[redacted]	14,426
		Log-normal	[redacted]	[redacted]	[redacted]	13,545
		Generalised gamma	[redacted]	[redacted]	[redacted]	13,933
		Weibull	[redacted]	[redacted]	[redacted]	14,938
Long-term survival adjustment	Gershenwald, applied after10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	12,790
		No long-term adjustment to RFS	[redacted]	[redacted]	[redacted]	13,515
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	18,458
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	12,958
		Balch, 5 years	[redacted]	[redacted]	[redacted]	26,282

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs routine surveillance
			Costs (£)	LYs	QALYs	
		Balch, 10 years	[redacted]	[redacted]	[redacted]	17,331
		Balch, 20 years	[redacted]	[redacted]	[redacted]	13,848
		OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	14,655
		Balch, OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	17,932
OS distribution (all)	Generalised gamma	Exponential*	[redacted]	[redacted]	[redacted]	12,706
		Gompertz*	[redacted]	[redacted]	[redacted]	29,962
		Log-normal	[redacted]	[redacted]	[redacted]	14,646
		Log-logistic	[redacted]	[redacted]	[redacted]	15,007
		Weibull	[redacted]	[redacted]	[redacted]	15,172
Long-term-data curve selection	Gershenwald, Generalised gamma	Balch, Exponential*	[redacted]	[redacted]	[redacted]	24,581
		Balch, Generalised gamma	[redacted]	[redacted]	[redacted]	17,331
		Balch, Gompertz	[redacted]	[redacted]	[redacted]	14,104
		Balch, log-normal	[redacted]	[redacted]	[redacted]	19,971
		Balch, log-logistic	[redacted]	[redacted]	[redacted]	19,933
		Balch, Weibull*	[redacted]	[redacted]	[redacted]	21,361
		Exponential*	[redacted]	[redacted]	[redacted]	18,142
		Gompertz	[redacted]	[redacted]	[redacted]	13,723
		Log-normal	[redacted]	[redacted]	[redacted]	15,903
		Log-logistic	[redacted]	[redacted]	[redacted]	16,315
		Weibull*	[redacted]	[redacted]	[redacted]	17,104
End-of-life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	14,186
Utilities source	Observed EQ-5D Apply same utility to across treatments Separate stage covariate	Include AE disutilities: No	[redacted]	[redacted]	[redacted]	14,276
		Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	14,439

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs routine surveillance
			Costs (£)	LYs	QALYs	
	Include AE disutilities: yes	Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	14,464
		Middleton et al.	[redacted]	[redacted]	[redacted]	11,747
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	14,517
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	14,685
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	14,301
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	14,464
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	14,448

Key: AE, adverse event; HR, hazard ratio; DBL, database lock; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; ipi, ipilimumab; ITC, indirect treatment comparison; LY, life year; nivo, nivolumab; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival; SACT, Systemic Anti-Cancer Therapy.
Note: The curve fits that are indicated (*) are those that fit the data poorly.

Table 30: State-transition model (scenario analysis results)

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	16,171
Population	Patient characteristics: (CA184-029 and CheckMate 238) Stage proportions: CA184-029 & CheckMate 238 adjusted RFS for nivolumab and routine surveillance: ITC (CA184-029 and CheckMate 238)	CheckMate 238 CheckMate 238 Nivo: CheckMate 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	13,421
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	15,608
Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	16,572
		50 years	[redacted]	[redacted]	[redacted]	16,254
Nivolumab dosing	240 Q2W	3mg/kg Q2W	[redacted]	[redacted]	[redacted]	17,919

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
		240mg Q"W	[redacted]	[redacted]	[redacted]	17,120
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	17,120
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	16,171
Nivolumab administration cost reference	SB12Z	SB13Z	[redacted]	[redacted]	[redacted]	16,173
Subsequent treatment (local/regional)	CheckMate 238	CA184-029	[redacted]	[redacted]	[redacted]	16,160
Nivolumab subsequent treatment (distant)	CheckMate 238	SACT data	[redacted]	[redacted]	[redacted]	9,394
		Wilmington	[redacted]	[redacted]	[redacted]	10,772
		IPSOS	[redacted]	[redacted]	[redacted]	11,837
RFS ITC method	ITC 48-month DBL (subgroup 1-year ipi treatment in CA184-029)	ITC 48-month DBL	[redacted]	[redacted]	[redacted]	14,826
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	30,887
		Gompertz	[redacted]	[redacted]	[redacted]	16,889
		Log-normal	[redacted]	[redacted]	[redacted]	14,576
		Generalised gamma	[redacted]	[redacted]	[redacted]	15,419
		Weibull	[redacted]	[redacted]	[redacted]	17,868
Long-term survival adjustment	Gershenwald, applied after 10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	15,017
		No long-term adjustment to RFS	[redacted]	[redacted]	[redacted]	15,004
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	20,037
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	15,105
		Balch, 5 years	[redacted]	[redacted]	[redacted]	28,202
		Balch, 10 years	[redacted]	[redacted]	[redacted]	19,484
		Balch, 20 years	[redacted]	[redacted]	[redacted]	16,019
		OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	16,725
		Balch, OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	20,683
Long-term-data curve selection	Gershenwald, Generalised gamma	Balch, exponential*	[redacted]	[redacted]	[redacted]	23,573

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
		Balch, Generalised gamma	[redacted]	[redacted]	[redacted]	19,484
		Balch, Gompertz	[redacted]	[redacted]	[redacted]	15,701
		Balch, log-normal	[redacted]	[redacted]	[redacted]	21,504
		Balch, log-logistic	[redacted]	[redacted]	[redacted]	21,495
		Balch, Weibull*	[redacted]	[redacted]	[redacted]	22,185
		Exponential*	[redacted]	[redacted]	[redacted]	20,221
		Gompertz	[redacted]	[redacted]	[redacted]	15,140
		Log-normal	[redacted]	[redacted]	[redacted]	18,152
		Log-logistic	[redacted]	[redacted]	[redacted]	18,583
		Weibull*	[redacted]	[redacted]	[redacted]	19,330
End-of-life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	16,008
Utilities source	Observed EQ-5D Apply same utility to across treatments Separate stage covariate Include AE disutilities: Yes	Include AE disutilities: No	[redacted]	[redacted]	[redacted]	16,141
		Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	16,306
		Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	16,337
		Middleton et al.	[redacted]	[redacted]	[redacted]	13,819
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	16,334
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	16,503
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	16,170
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	16,337
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	16,332
Data used for Markov model curves	CheckMate 067 and other sources	Metastatic NMA	[redacted]	[redacted]	[redacted]	13,247
Post-distant long-term dataset	Balch 2009	Balch 2001	[redacted]	[redacted]	[redacted]	15,638

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Dacarbazine hazard ratio applied	HR (OS) vemurafenib vs dacarbazine	HR (OS) ipi vs gp100	[redacted]	[redacted]	[redacted]	16,550
OS HR pembrolizumab vs ipilimumab source	Bucher comparison	KEYNOTE 006	[redacted]	[redacted]	[redacted]	16,746
Re-challenge scenario	Yes	No	[redacted]	[redacted]	[redacted]	14,979
Re-challenge scenario time-point	2.00	0.50	[redacted]	[redacted]	[redacted]	15,561
		1.00	[redacted]	[redacted]	[redacted]	15,861
		60.00	[redacted]	[redacted]	[redacted]	17,125

Key: AE, adverse event; DBL, database lock; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; ipi, ipilimumab; LY, life year; nivo, nivolumab; NMA, network meta-analysis; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival; SACT, Systemic Anti-Cancer Therapy.
Note: The curve fits that are indicated (*) are those that fit the data poorly.

Public Health England

Protecting and improving the nation's health

Nivolumab for adjuvant treatment of resected stage III and IV melanoma

Data review

Commissioned by NHS England and NHS Improvement

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing and reduce health inequalities. We do this through world-leading science, research, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

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Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of nivolumab for the treatment of patients diagnosed with advanced melanoma. The appraisal committee highlighted clinical uncertainty around the long-term benefit in overall survival (OS) and subsequent treatments used in patients relapsing following adjuvant treatment with nivolumab in the evidence submission. As a result, they recommended commissioning of nivolumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of nivolumab in the CDF population during the managed access period. This report presents the results of the use of nivolumab, in clinical practice, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis of data for the full patient population, with 100% of patients and 100% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement’s Blueteq® system was used to provide a reference list of all patients with an application for nivolumab for melanoma in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE’s routinely collected SACT data to provide SACT treatment history.

Between 30 November 2018 and 29 October 2019, 375 applications for nivolumab were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 284 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

All 284 (100%) unique patients with CDF applications were reported in the SACT dataset.

At the end of the data collection period, 28% (N=79) of patients were identified as no longer being on treatment; 46% (N=36) of these patients stopped treatment due to progression, 39% (N=31) stopped treatment due to acute toxicity, 8% (N=6) chose to end their treatment, 6% (N=5) died on treatment and 1% (N=1) stopped due to developing a second primary.

Conclusion

This report analyses SACT real world data for patients treated with nivolumab for resected stage III and IV melanoma in the CDF. It evaluates treatment outcomes for all patients treated with nivolumab for this indication.

Introduction

Malignant melanoma accounts for 4% of all cancer diagnosed in England. In 2017, 13,740 patients were diagnosed with malignant melanoma (6,971 males, 6,769) females)[2].

Nivolumab is recommended for use within the Cancer Drugs Fund as an option for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease. It is recommended only if the conditions in the managed access agreement are followed[3].

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From the 29th July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical and cost effectiveness. During this period of managed access, ongoing data collection is used to answer the uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE will analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee appraisal of nivolumab for adjuvant treatment of resected stage III and IV melanoma [TA558]

The NICE Appraisal Committee reviewed the evidence for the clinical and cost effectiveness of nivolumab in treating resected stage III and IV melanoma [TA558] and published guidance for this indication in January 2019[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of nivolumab through the CDF for a period of 14 months, November 2018 to January 2020.

During the CDF funding period, results from an ongoing clinical trial evaluating nivolumab in the licensed indication are likely to answer the main clinical uncertainties

raised by the NICE committee. The ongoing trial to support the evaluation of nivolumab is CheckMate 238[7]. Data collected from the CheckMate 238 clinical trial would be the primary source of data collection.

Analysis of the SACT dataset would provide information on real-world treatment patterns and outcomes for nivolumab for resected stage III and IV melanoma in England, during the CDF funding period. This would act as a secondary source of information alongside the results of the CheckMate 238 clinical trial[7].

The committee identified the key areas of uncertainty for re-appraisal at the end of the CDF data collection which were:

- subsequent treatment use in patients relapsing following adjuvant treatment with nivolumab
- overall survival long-term benefit in OS

OS will be reported in the CheckMate 238 trial.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (BMS) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of nivolumab. It also detailed the eligibility criteria for patient access to nivolumab through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for nivolumab, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the EU General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of EU GDPR (processing is necessary for the purposes of preventive or occupational medicine).

As NHS E & I do not have an exemption to the Common Law Duty of Confidentiality, NHS E & I cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Nivolumab clinical treatment criteria

The criteria for patient access to nivolumab are that:

- patient has newly diagnosed melanoma that has been staged according to the AJCC 8th edition as having stage III disease or completely resected stage IV disease

- the stage III or stage IV disease has been completely resected either via sentinel lymph node biopsy (‘sentinel lymphadenectomy’) or when indicated via completion lymph node dissection or by resection of distant metastatic disease
- patient is treatment naïve to systemic therapy for malignant melanoma and in particular has not previously received any BRAF V600 inhibitors or MEK inhibitors or immunotherapy with any check point inhibitors
- clinician has discussed with the patient the benefits and toxicities of adjuvant nivolumab in stage III or completely resected stage IV disease and if stage III disease, provided figures (included in Blueteq) related to the risk of disease relapse if a routine surveillance policy is followed
- patient has an ECOG performance status of either 0 or 1
- treatment with nivolumab will be continued for a maximum of 12 months (or a maximum of 26 cycles if given 2-weekly) from the start of treatment in the absence of disease recurrence, unacceptable toxicity or withdrawal of patient consent
- a formal medical review as to whether treatment with nivolumab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
- treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any immune toxicities to settle

CDF applications – de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The de-duplication rules that are applied are:

- if two trusts apply for nivolumab for the treatment of resected stage III and IV melanoma for the same patient (identified using the patient’s NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected
- if two trusts apply for nivolumab for the treatment of resected stage III and IV melanoma for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust
- if two applications are submitted for nivolumab for the treatment of resected stage III and IV melanoma and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected

Initial CDF cohorts

The analysis cohort is limited to the date nivolumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the pharmaceutical company.

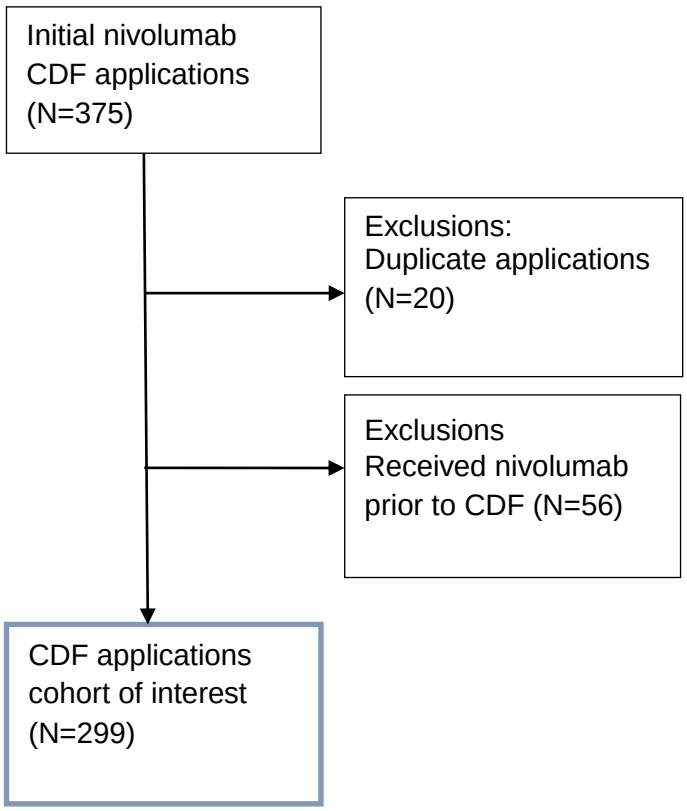
These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 30 November 2018 to 29 October 2019. A snapshot of SACT data was taken on 1 February 2020 and made available for analysis on 7 February 2020. The snapshot includes SACT activity up to the 31 October 2019. Tracing the patients' vital status was carried out on 3 April 2020 using the personal demographics service (PDS)[1].

There were 375 applications for CDF funding for nivolumab to treat resected stage III and IV melanoma between 30 November 2018 to 29 October 2019 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 355 unique patients.

Fifty-six patients were excluded from these analyses as they appeared to have received nivolumab prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from the initial CDF applications made for nivolumab for resected stage III and IV melanoma between 30 November 2018 and 29 October 2019



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for nivolumab in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Subsequent treatments in SACT

Regimens in SACT that were delivered after a patient's last nivolumab treatment in SACT.

Time to next treatment

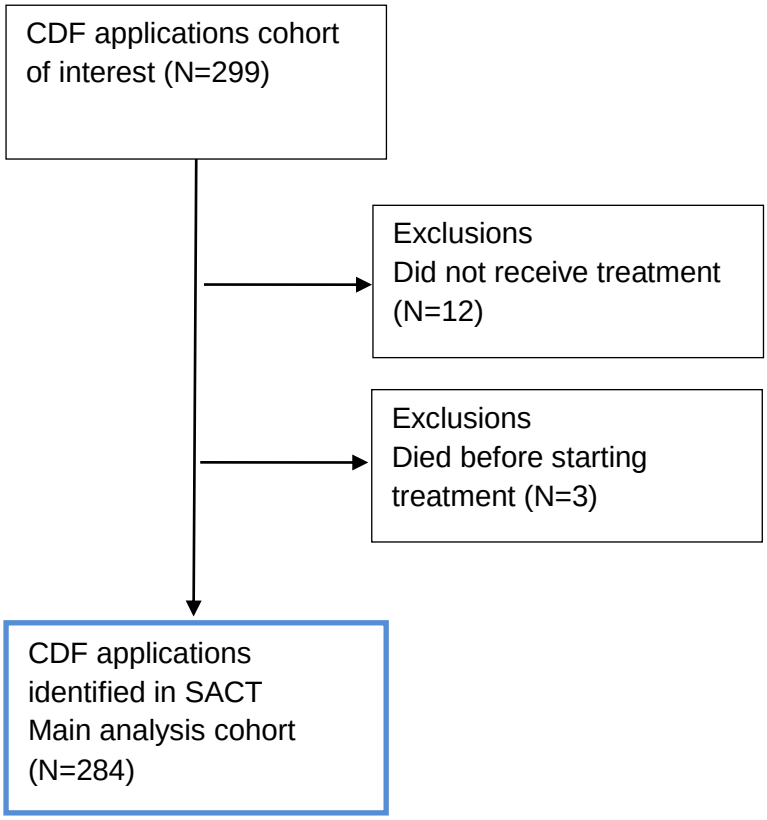
The median time from a patient's last nivolumab treatment in SACT to the start of their next regimen.

Results

Cohort of interest

Of the 299 new applications for CDF funding for nivolumab for resected stage III and IV melanoma, 12 patients did not receive treatment and three patients died before treatment[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for nivolumab for resected stage III and IV melanoma between 30 November 2018 and 29 October 2019



A maximum of 284 nivolumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 100% (284/284) of these applicants for CDF funding have a treatment record in SACT.

[a] The 12 patients that did not receive treatment and 3 that died before treatment were confirmed with the relevant trusts by the PHE data liaison team.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Completeness for performance status at the start of regimen is 93%.

Table 1: Completeness of key SACT data items for the nivolumab cohort (N=284)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	93%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with nivolumab in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 79 patients. Of these, 79 (100%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=79)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	100%

Completeness of Blueteq key variables

Clinicians were asked to submit BRAF mutation status and stage to the NHS England and NHS Improvement Blueteq system. Table 3 presents the completeness of these key data items required from Blueteq. Completeness of melanoma BRAF mutation status and stage was 100%.

Table 3: Completeness of BRAF mutation status and stage in Blueteq (N=284)

Variable	Completeness (%)
Nivolumab BRAF mutation status	100%
Nivolumab Melanoma Stage	100%

Patient characteristics

The median age of the 284 patients receiving nivolumab for resected stage III and IV melanoma was 63 years. The median age in males and females was 61 and 63 years respectively.

Table 4: Patient characteristics (N=284)

Patient characteristics[b]		Frequency (N)	Percentage (%)
Sex	Male	157	55%
	Female	127	45%
Age	<40	25	9%
	40-49	32	11%
	50-59	63	22%
	60-69	81	29%
	70-79	69	24%
	80+	14	5%
Performance status	0	199	70%
	1	62	22%
	2	2	1%
	3	0	0%
	4	0	0%
	Missing/unknown	21	7%

[b] Figures may not sum to 100% due to rounding

Melanoma BRAF mutation status distribution

The distribution of BRAF mutation status in table 5 shows that 78% (N=222) of patients were BRAF V600 mutation negative and 22% (N=62) of patients were BRAF V600 mutation positive.

Table 5: Distribution of BRAF mutation status in Blueteq (N=284)

Melanoma BRAF mutation status	N	%
BRAF V600 mutation negative	222	78%
BRAF V600 mutation positive	62	22%
Total	**284**	**100%**

Melanoma Stage distribution

The distribution of stage of disease in table 6 shows that 9% (N=25) of patients were stage IIIA, 26% (N=73) of patients were stage IIIB, 29% (N=83) of patients were stage IIIC, 2% (N=5) of patients were stage IIID and 35% (N=98) of patients were stage IV.

Table 6: Distribution of stage of the disease in Blueteq (N=284)

Melanoma stage	N	%
Stage IIIA disease	25	9%
Stage IIIB disease	73	26%
Stage IIIC disease	83	29%
Stage IIID disease	5	2%
Stage IV disease that has been completely resected	98	35%
Total	**284**	**100%**

Table 7: Treatment outcomes for patients that have ended treatment (N=79)[c]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	36	46%
Stopped treatment – acute chemotherapy toxicity	31	39%
Stopped treatment – patient choice	6	8%
Stopped treatment – died	5	6%
Stopped Treatment – treatment ended as patient developed a second primary[d]	1	1%
Total	**79**	**100%**

[c] Figures may not sum to 100% due to rounding.

[d] Patient with an outcome 'ended treatment due to a second primary' was captured by the data liaison team as a result of following up with the trust.

Subsequent treatments in SACT

Twenty-five out of 284 (9%) unique patients who received nivolumab went on to receive subsequent therapies after their last nivolumab cycle in SACT. Table 8 reports regimens prescribed after a patients' last nivolumab cycle in SACT. Of the 25 unique patients who received a subsequent therapy, three patients were identified as still receiving nivolumab monotherapy, this may be as a result of the follow-up time in SACT where we currently have no confirmation if patients have ended monotherapy treatment. All three patients that were identified as still receiving monotherapy went on to receive ipilimumab + nivolumab.

As a result of the short follow-up time in SACT, the 205 patients identified as still receiving treatment are not expected to have received a subsequent treatment at the time this report was produced. Therefore, the number of patients reported as receiving a subsequent treatment may be low.

Of the 25 unique patients who went on to receive a subsequent treatment, 22 patients have been confirmed as completing treatment with nivolumab monotherapy. The percentage of patients who have ended treatment, who then go on to receive a subsequent treatment is 28% (22/79).

Table 8: Distribution of subsequent treatments in SACT (N=25)[e]

Regimen	Count
Ipilimumab + nivolumab	13
Ipilimumab	4
Dabrafenib + trametinib	3
Binimetinib + encorafenib	2
Bleomycin	1
Capecitabine	1
Cisplatin + dacarbazine + vinblastine	1
Pembrolizumab	1
Talimogene laherparepvec	1
Total	**27**

[e] Some patients have received more than one subsequent treatment. Table 8 lists all subsequent therapies including those prescribed immediately after nivolumab monotherapy and in a subsequent treatment line.

Time to next treatment in SACT

The median time from a patient's last nivolumab cycle date in SACT to receiving their next regimen was 35 days (range: 13 days to 197 days).

The snapshot includes SACT activity up to the 31 October 2019, the median follow-up time from a patient last nivolumab cycle in SACT was 154 days (range: 28 days to 262 days).

Conclusions

Two hundred and eight-four patients received nivolumab for resected stage III and IV melanoma [TA558] through the CDF in the reporting period (30 November 2018 and 29 October 2019). All 284 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 100%. An additional 15 patients with a CDF application did not receive treatment or died before treatment. This was confirmed with the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that proportionally more males received nivolumab treatment compared to females (55% (N=157) male, 45% (N=127) female). Most of the cohort was aged between 50 and 79 years (75%, N=213) and 92% (N=261) of patients had a performance status between 0 and 1 at the start of their regimen.

At the end of the data collection period, 28% (N=79) of patients were identified as no longer being on treatment; 46% (N=36) of these patients stopped treatment due to progression, 39% (N=31) stopped treatment due to acute toxicity, 8% (N=6) chose to end their treatment, 6% (N=5) died on treatment and 1% (N=1) stopped due to developing a second primary.

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Public Health England

Protecting and improving the nation's health

Nivolumab for adjuvant treatment of resected stage III and IV melanoma (TA558)

Subsequent treatments in SACT (updated data snapshot)

Commissioned by NHS England and NHS Improvement

A snapshot of SACT data was taken on 1 August 2020 and made available for analysis on 7 August 2020. The snapshot includes SACT activity up to 30 April 2020.

284 applications to the CDF were identified in the NHS England and NHS Improvement Blueteq system as receiving nivolumab monotherapy for the treatment of resected stage III and IV melanoma (TA558) in England between 30 November 2018 and 29 October 2019. Patients were followed up in SACT until 30 April 2020 to establish which SACT regimens were prescribed following a patient's last nivolumab cycle.

41/284 (14%) unique patients who received nivolumab went on to receive a subsequent therapy after their last nivolumab cycle in SACT. Table 1 reports regimens prescribed after a patients' last nivolumab cycle in SACT.

Table 1: Distribution of subsequent treatments in SACT (N=41)[a]

Regimen	Count
Ipilimumab + nivolumab	14
Ipilimumab	12
Dabrafenib + trametinib	9
Binimetinib + encorafenib	6
Bleomycin	1
Capecitabine	1
Cisplatin + dacarbazine + vinblastine	1
Dabrafenib	1
Dacarbazine	1
Hydroxycarbamide	1
Imatinib	1
Pembrolizumab	1
Talimogene laherparepvec	1
Trametinib	1
Total	**51**

Time to next treatment in SACT

The median time from a patient's last nivolumab cycle date in SACT to receiving their next regimen was 47 days (range: 13 day to 311 days).

The snapshot includes SACT activity up to the 30 April 2020, the median follow-up time from a patient last nivolumab cycle in SACT was 276 days (range: 49 days to 444 days).

[a] Some patients have received more than one subsequent treatment. Table 1 lists all subsequent therapies including those prescribed immediately after nivolumab monotherapy and in a subsequent treatment line.

NICE National Institute for Health and Care Excellence

Clinical expert statement

ID1681 Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CDF review of TA558)

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Ruth Plummer**
2. Name of organisation	**Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne**

3. Job title or position	
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of nivolumab in this clinical setting is to reduce the risk of recurrence of melanoma in patients who have had a potentially curative resection but remain at risk of recurrence of disease.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The published randomised trial data for nivolumab is that this treatment reduced the chance of release by 34% compared to the other arm of the study where patients were treated with an alternative immunotherapy, ipilimumab. It had already been shown that ipilimumab improved overall survival in this setting (with a hazard ratio of 0.72 compared to placebo) so it is reasonable to assume that nivolumab will also be shown to improve survival in this setting when the trial data is sufficiently mature. This is, therefore, a clinical significant predicted treatment response in this group of patients, with melanoma being the leading cause of cancer death in young adults, the impact of reducing recurrence and therefore mortality will have a big impact on patients and their families.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Prior to the NICE approval and availability of either adjuvant nivolumab or pembrolizumab the standard of care for this group of patients was observation with regular surveillance scans. Therefore if this treatment were no longer available there would be a significant unmet clinical need as more of this group of patients will relapse from and die of their disease.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Nivolumab and pembrolizumab are currently both available for treatment of this condition, and are standard of care across the NHS in England for stage 3 melanoma, in particular those patients with BRAF wild type disease. Approximately 45% of cutaneous melanomas harbour a BRAF mutation, and for these patients there is the option of treatment either with the above agents or with targeted therapy with dabrafenib and trametinib.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE TA558, NICE Pathways:Treating stage 3 melanoma, ESMO clinical practice guidelines, Cutaneous melanoma (2019),
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care is well defined, in particularly in England as it is based on the three NICE assessments TA558, TA553, TA544.
• What impact would the technology have on the current pathway of care?	Not applicable as already established standard of care
11. Will the technology be used (or is it already used) in	Already used in routine clinical practice as described above

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	No difference as already used
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist outpatient clinics and chemotherapy units in cancer centres in the majority of cases
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No investment needed as this is currently standard of care
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, see details above on predicted benefit based on randomised trial data
• Do you expect the technology to increase	N/A as current standard of care. This is a treatment which is expected to increase life expectancy and has already been shown to improve recurrence free survival in patients.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	N/A as current standard of care. The treatment does have some potential side effects, and patients need to be carefully counselled on these risks, as some toxicities, such as the endocrine side effects of immunotherapy can be life ling
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Stage 3 melanoma can be sub-categorised into higher and lower risk groups for recurrence. At consent to treatment these relative risks are discussed to put the burden of treatment and side effects in context. There is a similar relative benefit in all groups, however the risk of recurrence and therefore absolute risk reduction is less for Stage 3a melanoma compared to stage 3c or d. Specific to TA558 and the use of nivolumab in this setting is that it is the only approved adjuvant treatment for resected stage 4 melanoma, as the only agent with randomised trial data showing a benefit in this population. It is, therefore, the only treatment offered for this group of patients.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	N/A as currently standard of care

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This treatment is recommended for 1 year and is stopped at this point. Patient have regular surveillance scans during this period and treatment would be stopped if they had developed recurrence. In addition, treatment would be stopped if the patient had significant problems with toxicity.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, this group of patients otherwise would have observation only, and the clinical trial data shows that the treatment reduces recurrence risk.
• Is the technology a 'step-change' in the management of the condition?	Yes, see above
• Does the use of the technology address any particular unmet need of the patient population?	N/A as currently in use. If withdrawn from availability the loss of adjuvant therapy to melanoma patients would leave an unmet need in a high-risk population
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of nivolumab in this setting need to be carefully explained to patients before consent to treatment, as this is a major part of the decision process to go ahead. When treated with adjuvant therapy patients are theoretically disease free, without a visible tumour burden, and are therefore feeling well. During the treatment phase, therefore, any side effects do adversely affect quality of like. Approximately 5% of patients will have serious side effects from this treatment although these can usually be managed

	promptly and patients recover. The endocrine side effects of immunotherapy can mean patients need lifelong replacement therapy. However, as this treatment is predicted to roughly half the risk of recurrence, the overall health gain in QOL remains positive.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, and UK centres and patients contributed to the pivotal trials which showed the technology was effective in this setting
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Recurrence free survival and overall survival – which were the primary endpoints of the relevant trials
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not	No

apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA558?	No
22. How do data on real-world experience compare with the trial data?	Limited real world data has been formally published but that seem is largely in line with the clinical trial data
Equality	
23a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Adjuvant treatment of Stage 3 melanoma has been shown to reduce risk of recurrence and improve long term survival in patients
- Nivolumab is one of the available agents which have shown this benefit and is a standard of care in England for this condition
- Patients need careful discussion of risk reduction and side effects to be able to make an informed decision to embark of adjuvant treatment
- Nivolumab is the only agent which has been proven to be of benefit in the resected stage 4 melanoma setting
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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

Cancer Drugs Fund Review

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and drafted the summary, background and clinical results sections
Samantha Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and assisted with drafting the clinical results sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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List of Abbreviations

ACD	Appraisal consultation document
AE	Adverse event
AJCC	American Joint Committee on Cancer
CDF	Cancer Drugs Fund
CGP	Corrected group prognosis
CS	Company submission
ECOG	Eastern Cooperative Oncology Group
ERG	Evidence review group
FAD	Final appraisal determination
HR	Hazard ratio
HRG	Healthcare resource group
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
LY	Life-years
NHS	National Health Service
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD1	Anti-programmed cell death protein 1
PH	Proportional hazards
PLD	Patient level data
PR	Post-recurrence
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
QALY	Quality-adjusted life-year
RF	Recurrence-free
RFS	Recurrence-free survival
SACT	Systemic Anti-Cancer Therapy
ToE	Terms of Engagement

1 Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides a critique of the adherence to committee's preferred assumptions from the Terms of Engagement (ToE) in the company's submission. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 and 1.4 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are presented in the main ERG report (Section 2 onwards).

All issues identified represent the ERG's view and should not be mistaken for the opinion of NICE.

1.1 Critique of the adherence to committee's preferred assumptions from the Terms of Engagement in the company's submission

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the ToE, although the updated overall survival (OS) data from CheckMate 238 remain immature. The clinical data presented by the company includes the ToE required later data cut from the company's randomised controlled trial of nivolumab versus ipilimumab, CheckMate 238. In addition, the company presented a summary of the observational data that were also required to be collected by Public Health England during the period of managed access for nivolumab, hereafter referred to as the Systemic Anti-Cancer Therapy (SACT) data set.

The data from CheckMate 238 now comprise a minimum follow-up period of [redacted] months and include more mature data for OS, recurrence-free survival (RFS) and subsequent therapies but these data remain immature, particularly for OS. The SACT data set reports on subsequent therapies but these data are also limited as only 25 patients in the cohort received subsequent therapies.

The company updated the patient level data (PLD) meta-regression indirect treatment comparisons (ITCs) used in the economic model with the updated data from CheckMate 238 and the ITC for OS now uses the CheckMate 238 OS data. The ERG notes that, like the ERG, the committee preferred the ITC analyses of RFS that censored patients on ipilimumab in CA184-029, a study informing the ITC, at 1-year but who continued treatment beyond 1-year. However, the ERG notes that the company does not apply the 1-year censoring of ipilimumab from CA184-029 in the ITC analysis for

OS used in their new base case, and the ERG considers it important to use the 1-year censoring for consistency with the RFS analyses. The ERG also remains concerned that the population in the ITC may not be fully reflective of clinical practice in terms of disease stage due to the exclusion of Stage IV patients from CA184-029 and Stage IIIa patients from CheckMate 238.

Table 1 presents a summary of the ERG's key issues.

Table 1. Summary of key issues

Issue number	Summary of issue	Report sections
Issue 1	**Staging of patients AJCC v8:** The absence of Stage IV patients from CA184-029 potentially limits the validity of the ITC results for the comparison of nivolumab with routine surveillance in this subgroup.	Section 3.1.3
Issue 2	**Survival data:** OS & RFS from CheckMate 238 remain immature.	Section 3.1.1
Issue 3	**Subsequent treatments:** Subsequent treatment data from SACT cohort immature.	Section 3.1.2
Issue 4	**OS ITC:** OS in the company ITC does not include censoring after 1 year of treatment for ipilimumab patients from CA184-029.	Section 3.1.3 and 4.1.4
Issue 5	**Model structure for decision making:** The company's updated PSM is considered more appropriate than the updated state-transition model for decision making.	Section 4.1.3 and 4.1.4
Issue 6	**Hazard of death for patients on routine surveillance:** The OS ITC in the PSM potentially overestimates the survival benefit of adjuvant nivolumab compared with routine surveillance as survival estimates for placebo patients in CA184-029 are outdated.	Section 4.1.4

Abbreviations: AJCC, American Joint Committee on Cancer; ITC, indirect treatment comparison; OS, overall survival, PSM, partitioned survival model; RFS, recurrence-free survival; SACT, Systemic Anti-cancer Treatment.

1.2 Overview of key model outcomes

In the Single Technology Appraisal 558 (TA558), most of the issues with the company's approach to estimating the cost-effectiveness of adjuvant nivolumab for patients with completely resected melanoma with lymph node involvement or metastatic disease were resolved. However, the key issues of OS and subsequent treatments were expected to be addressed in the Cancer Drugs Fund (CDF) data collection period. As such, the overview presented here is focussed on the updates the company's cost-effectiveness analyses from TA558. All cost-effectiveness analyses presented in this report are inclusive of the company's patient access scheme (PAS) simple discount of [redacted].

Overall, the technology is modelled to affect quality-adjusted life-years (QALYs) by:

- increasing OS and RFS compared with patients on routine surveillance.

Overall, the technology is modelled to affect costs by:

- its higher unit price compared with monitoring alone;
- being given intravenously at hospital compared with monitoring alone.

The updated modelling assumption that has the greatest effect on the ICER is:

- the size of the OS benefit.

1.3 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG's four key issues that relate to the clinical effectiveness evidence are detailed below in Tables 2 to 5. It should be noted that Issue 4 affects both the clinical and cost-effectiveness evidence and the implications for each are discussed separately in Sections 1.3 and 1.4.

Table 2. Issue 1: Absence of Stage IV patients from CA184-029

Report section	3.1.3
Description of issue and why the ERG has identified it as important	The absence of Stage IV patients from CA184-029 potentially limits the validity of the ITC results for the comparison of nivolumab with routine surveillance in this subgroup. The ERG also notes that Stage IIIa patients were excluded from CheckMate 238 but the new AJCC v8 criteria used to assess disease stage mean that some Stage IIIb patients in CheckMate 238 would now likely be classed as Stage IIIa. Nivolumab is approved for use in Stage III and IV patients and so the absence of Stage IV data for placebo limits the applicability of the ITC.
What alternative approach has the ERG suggested?	The ERG does not have a suggested alternative approach as the data are limited by the patient characteristics in the trials.
What is the expected effect on the cost-effectiveness estimates?	Without data on the relative effectiveness of adjuvant nivolumab for patients with the missing stages, the ERG is unable to predict what the impact on the ICER is likely to be.
What additional evidence or analyses might help to resolve this key issue?	The ERG does not consider it possible to obtain additional data from CheckMate 238 or CA184-029 to help resolve this issue.

Abbreviations: AJCC, American Joint Committee on Cancer; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison.

Table 3. Issue 2: Overall Survival (OS) & Recurrence-Free Survival (RFS) from CheckMate 238 remain immature

Report section	3.1.1
Description of issue and why the ERG has identified it as important	OS & RFS from CheckMate 238 remain immature, and [redacted] The ERG notes that RFS and OS are the key clinical outcomes used to inform the clinical effectiveness of nivolumab in the economic model.
What alternative approach has the ERG suggested?	The ERG has no suggested alternative approach as the issue is a result of immature clinical data and so the ERG's preference would be to wait until a later data cut from CheckMate 238 with mature data for OS and RFS is available.
What is the expected effect on the cost-effectiveness estimates?	If the trends of the latest data cut continue into the future, then it is likely that the availability of mature data from CheckMate 238 will reinforce the current ICERs or potentially improve them. However, if after a few years there is a decline in RFS and OS, it will likely cause the ICERs to increase substantially.
What additional evidence or analyses might help to resolve this key issue?	Later data cuts from CheckMate 238 would help to address the uncertainty in OS and RFS.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; RFS, recurrence-free survival.

Table 4. Issue 3: Subsequent treatment data from SACT cohort immature

Report section	3.1.2
Description of issue and why the ERG has identified it as important	Subsequent treatment data from SACT cohort are limited to 25 patients due to the lim ited follow-up to date. The ERG notes that these data were requested as part of the Terms of Engagement to help inform the modelling of treatments used in clinical practice.
What alternative approach has the ERG suggested?	The ERG's clinical experts reported that the company's approach of using the subsequent treatments from CheckMate 238 is reasonable.
What is the expected effect on the cost-effectiveness estimates?	As the ERG's clinical experts deem the subsequent treatment data from CheckMate 238 to be reasonable, there is no impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Additional data collection from the SACT could be considered to further validate the subsequent therapies used in clinical practice.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; SACT, Systemic Anti-cancer Treatment.

Table 5. Issue 4: OS in the company ITC does not include 1-year censoring for ipilimumab patients from CA184-029

Report section	3.1.3
Description of issue and why the ERG has identified it as important	The company's ITC analysis of OS used in their base case does not include censoring at 1-year for ipilimumab patients from CA184-029 who received treatment beyond 1-year. This is inconsistent with the data the company uses for RFS and creates a mismatch in the ipilimumab treatment duration in the ITC as patients in CheckMate 238 only received up to 1-year ipilimumab and in CA184-029 it was up to 3 years of ipilimumab.
What alternative approach has the ERG suggested?	The ERG recommends that censoring after 1 year of treatment with ipilimumab in CA184-029 is used in the ITC for OS and the ITC for RFS.
What is the expected effect on the cost-effectiveness estimates?	Implementing the 1-year censored OS ITC analysis in the PSM increases the ICER from £14,301 to £17,404.
What additional evidence or analyses might help to resolve this key issue?	The company supplied the appropriate ITC and relevant scenario analyses in their clarification response to address this issue.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OS, overall survival, PSM, partitioned survival model; RFS, recurrence-free survival.

1.4 The cost-effectiveness evidence: summary of the ERG's key issues

Table 7 to Table 8 present the ERG's key issues of the company's updated cost-effectiveness analyses. Please note that as previously discussed, Issue 4 affects both the clinical and cost-effectiveness evidence.

Table 6. Issue 4: One-year censoring of OS for ipilimumab patients from CA184-029 for the OS ITC

Report section	4.1.4
Description of issue and why the ERG has identified it as important	The company's base case analysis for the OS ITC includes the ITT populations for the two trials used, where different maximum treatment durations for ipilimumab were allowed. In CheckMate 238, ipilimumab treatment was restricted to 1 year, whereas, in CA184-029, ipilimumab treatment could go on for up to 3 years. For the RFS ITC, the company censored ipilimumab patients from CA184-029 after 1 year of treatment. The ERG considers that consistency in methods should be implemented for the RFS and OS ITC. The company stated that it is inappropriate to informatively censor ipilimumab patients who are on treatment for more than 1 year as these patients are likely to have the best prognosis at 1 year as they are able to continue treatment. Additionally, as treatment is given until disease recurrence, OS patients who are censored are more likely to be in the recurrence-free state. As such, the informative censoring is likely to favour routine surveillance.
What alternative approach has the ERG suggested?	An OS ITC analysis in which ipilimumab patients from CA184-029 are censored after 1 year of treatment was requested by the ERG to ensure that RFS and OS outcomes are aligned in the model. The ERG agrees that informative censoring may introduce the bias described by the company. However, in the company's base case analysis, by not censoring patients still receiving ipilimumab at 1 year, the same potential bias favours nivolumab.
What is the expected effect on the cost-effectiveness estimates?	Implementing the 1-year censored OS ITC analysis increases the ICER from £14,301 to £17,404.
What additional evidence or analyses might help to resolve this key issue?	Mature OS data from CheckMate 238 and Keynote 054 could be used to provide an alternative analysis to estimate survival for patients on routine surveillance that does not rely on ipilimumab as a common comparator.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; OS, overall survival, PSM, partitioned survival model; RFS, recurrence-free survival.

Table 7. Issue 5: Model structure for decision making

Report section	4.1.3 and 4.1.4
Description of issue and why the ERG has identified it as important	In TA558, the company's PSM and state-transition model (previously known as the Markov II option) were considered appropriate for decision making. With updated survival data from CheckMate 238, the ERG considers that the focus of the cost-effectiveness analysis should be on the results obtained from the PSM as it includes OS based on longer follow-up from the trial (albeit immature) in an OS ITC with RS. Apart from the updated RFS ITC and subsequent treatment proportions from CheckMate 238, the state-transition model remains unchanged from TA558.
What alternative approach has the ERG suggested?	The ERG's preference is for the PSM to be used as the basis of decision making for the CDF review.
What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER for the PSM is lower than the ICER for the state-transition model. However, as there is more flexibility to perform scenarios around OS in the PSM, comparing ICERs between the two different models with changes implemented is not meaningful.
What additional evidence or analyses might help to resolve this key issue?	Mature OS data from CheckMate 238, where post-recurrence survival could be estimated and implemented in the state-transition model would have been needed to help resolve some of the original uncertainty highlighted in TA558.

Abbreviations: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OS, overall survival, PSM, partitioned survival model; RFS, recurrence-free survival.

Table 8. Issue 6: Hazard of death for patients on routine surveillance

Report section	4.1.4
Description of issue and why the ERG has identified it as important	Appropriate modelling of OS for the routine surveillance arm has been a key issue in determining the cost-effectiveness of adjuvant nivolumab. In TA558, clinical experts considered that OS from the placebo arm of CA184-029 does not reflect the current survival outcomes for routine surveillance patients due to advances in the subsequent treatment pathway. As such, the OS ITC in the PSM potentially overestimates the survival benefit of adjuvant nivolumab compared with routine surveillance.
What alternative approach has the ERG suggested?	To estimate the impact on the ICER from improved survival for patients on routine surveillance, scenarios were explored in which it was assumed that the hazard of death for routine surveillance was equal to the hazard of death estimated from the CGP adjusted OS ITC survival curve for nivolumab after a) 3 years and b) 2 years. The ERG acknowledges that the scenarios exploring the hazard of death are based on strong assumptions but considers that they provide a basis for a plausible range of ICERs for the committee to consider in lieu of mature OS data from either CheckMate 238 or Keynote 054.
What is the expected effect on the cost-effectiveness estimates?	The range in the ICERs from varying the time point by which the hazard of death is equal between adjuvant nivolumab and routine surveillance is between £22,487 (3 years) and £28,809 (2 years). When the scenarios are combined with the 1-year censoring of ipilimumab OS patients from CA184-029 in the OS ITC, the range increases to £29,011 (3 years) to £37,371 (2 years).
What additional evidence or analyses might help to resolve this key issue?	Mature OS data from CheckMate 238 and Keynote 054 could be used to provide an alternative analysis to estimate survival for patients on routine surveillance.

Abbreviations: CGP, corrected group prognosis; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OS, overall survival, PSM, partitioned survival model.

1.5 Summary of ERG's preferred assumptions and resulting ICER

One of the key uncertainties expected to be resolved during the time nivolumab was in the CDF was OS. While the company has provided an update to OS from CheckMate 238, the data are still considered immature. The latest data cut of OS from CheckMate 238 is only used in the PSM, and, as such, the PSM is the only model that allows scenarios around OS to be performed to help inform committee. Thus, the ERG does not consider that the state-transition model helps resolve the uncertainties relating to OS.

Due to the uncertainties around OS estimates, the ERG presents a range of deterministic ICERs, varying the assumptions around OS in the PSM model for the committee to review. The ERG considers that the true ICER falls within the range presented (Table 9). The ICER range incorporates the company's patient access scheme (PAS) simple discount of [redacted]. A limitation of the probabilistic sensitivity analysis (PSA) is that it takes several hours to run when using a large sample size and, due to paucity of time, a PSA range of ICERs could not be presented. However, the ERG ran a test of the PSA for the scenario of equal hazard of death after 3 years and found that the PSA ICER was not dissimilar to the deterministic ICER.

Table 9. ERG preferred assumptions

Scenario	Incremental costs	Incremental QALYs	ICER (change from company base case
Company base case (post clarification)	[redacted]	[redacted]	**14,301**
Assuming the hazard of death and subsequent treatments for patients on routine surveillance is the same as nivolumab patients after 3 years (**Issue 6**)	[redacted]	[redacted]	22,487
Assuming the hazard of death and subsequent treatments for patients on routine surveillance is the same as nivolumab patients after 2 years (**Issue 6**)	[redacted]	[redacted]	28,809
One-year censoring of ipilimumab OS patients and assuming the hazard of death and subsequent treatments for patients on routine surveillance is the same as nivolumab patients after 3 years (**Issue 4 and Issue 6**)	[redacted]	[redacted]	29,011
One-year censoring of ipilimumab OS patients and assuming the hazard of death and subsequent treatments for patients on routine surveillance is the same as nivolumab patients after 2 years (**Issue 4 and Issue 6**)	[redacted]	[redacted]	37,371

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival, QALYs, quality-adjusted life-years.

2 Introduction and Background

2.1 Introduction

Melanoma is an aggressive type of skin cancer that refers to a malignant tumour of melanocytes, the melanin-producing cells found mostly in the skin.[1, 2] As with other forms of cancer, melanoma is divided into stages describing the extent to which the cancer has spread. The staging system most commonly used for melanoma is the American Joint Committee on Cancer (AJCC) system based on Tumour (T), Node (N), and Metastasis (M) categories. This system has recently been updated to the 8th edition.[3]

In England, approximately 8% of patients are diagnosed at Stage III or IV disease.[4] The Stage III or IV patients are initially treated with surgery, if possible, and it is estimated that surgery leads to completely resected disease in 80% of Stage III patients[5] and 8.6% of Stage IV patients.[6] Where the primary tumour has been successfully removed and patients have been declared disease free, the aim of adjuvant treatment is to prevent recurrence of disease. Despite surgical clearance of macroscopic disease, micro-metastatic disease is often present and either loco-regionally or distantly can result in later disease progression.

Nivolumab (OPDIVO®) is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to PD-1, an immune checkpoint receptor that may be present in melanoma. Nivolumab has European marketing authorisation for use as monotherapy, 'for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.' Nivolumab has been available via the Cancer Drugs Fund (CDF) since 2019.

Nivolumab is currently recommended for use within the CDF for adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (TA558).[7] Nivolumab is also a recommended treatment option in routine National Health Service (NHS) practice for the treatment of advanced (unresectable or metastatic) melanoma in adults both as monotherapy (TA384)[8] or in combination with ipilimumab (TA400).[9] Here, this report comprises a review of the latest clinical and cost-effectiveness evidence for adjuvant nivolumab in melanoma.

2.2 Background

The clinical-effectiveness evidence for adjuvant nivolumab in the original company submission (CS) for TA558 was from the CheckMate 238 randomised controlled trial (RCT) of nivolumab versus

ipilimumab in patients aged ≥ 15 years of age who had undergone complete surgical resection of Stage IIIB, IIIC or IV melanoma. The ERG notes that the European marketing authorisation for nivolumab allows its use for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. The ERG considers the use of adjuvant nivolumab in CheckMate 238 is consistent with the company's proposed positioning of adjuvant nivolumab therapy in clinical practice; although the ERG notes that patients with Stage IIIa melanoma will also be eligible for adjuvant nivolumab. The ERG also notes that the maximum duration of adjuvant nivolumab is 12 months.

The company has reported that the dose of nivolumab for adjuvant treatment of melanoma has changed since TA558. The previous dose of adjuvant nivolumab was 3 mg/kg, which was consistent with the dose used in CheckMate 238. The new dose of adjuvant nivolumab is 240 mg every 2 weeks or 480 mg every 4 weeks. The ERG's clinical experts reported that they would not expect the change in dose to have any major impact on the clinical outcomes from CheckMate 238. The ERG's clinical experts also reported that they would expect most patients in UK clinical practice to receive the 4 weekly dose and that this is due to resource limitations as well as patient preference to minimise hospital visits.

2.3 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

In general, the ERG considers that the company has adhered to the committees preferred assumptions from the Terms of Engagement, although OS data from CheckMate 238 remains immature. The ERG's critique of the company's adherence to the committee's preferred assumptions from the Terms of Engagement is provided in Table 10.

Table 10. Preferred assumptions from Terms of Engagement

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	ERG comment
Model	Following consultation, the company submitted two updated models comparing adjuvant nivolumab with routine surveillance: a partitioned survival model and a Markov model (which was an updated version of the Markov II model in its original submission). The committee concluded that, potentially, both model structures presented were acceptable for decision making. **The company should explore both model structures**	Yes — cost-effectiveness results for both the partitioned survival model and state-transition model (previously referred to as Markov II model) have been provided by the company.	N/A	No structural changes have been made to the models. The company has made minor corrections as a result of updates made to the model, but the corrections did not have a substantial impact on the final ICERs presented for TA558. Thus, the ERG is satisfied that the models used for the current analysis are the same as the final models submitted for TA558.
Overall survival	The company estimated overall survival using recurrence-free survival in a surrogacy analysis. The committee considered it was reasonable to expect that the recurrence-free survival benefit seen in CheckMate 238 would be translated to some extent into an overall survival benefit, but the extent is very uncertain. **The overall survival data from CheckMate 238 should be analysed in comparison with routine surveillance in a robust indirect treatment comparison.**	Yes — for the partitioned survival model the company has produced and implemented an indirect treatment comparison for OS based on updated data from CheckMate 238	N/A	The company submission included data from CheckMate 238 for OS from a [redacted] An indirect treatment comparison was conducted using the OS data from CheckMate 238 and pre-existing data from CA184-029 and has been implemented in the partitioned survival model for the first 10 years of the model. After 10 years, AJCC 8th edition data have been used for long-term estimation of survival, as per the methods used in TA558. The ERG considers the indirect treatment comparison for OS should use 1-year censoring of ipilimumab for patients in CA184-029 for consistency with the analyses of RFS and to account for the discrepancy in ipilimumab treatment duration between the studies.
Indirect treatment comparison	The company's updated indirect treatment comparison for RFS for the period between 12 weeks and 10 years is suitable to inform			No changes have been made in relation to disease staging and the indirect treatment comparison for RFS. The changes made

	decision making. However, the committee considered that differences in the inclusion criteria for CheckMate 238 and CA184-029 about what stage disease people had were potentially not fully accounted for. **The company may consider accounting for these differences in its updated indirect treatment comparison.**			include that the indirect treatment comparison has been updated based on the latest data cut from CheckMate 238 for RFS and OS data from CheckMate 238 are now used to inform the indirect treatment comparison for OS.
Long-term recurrence-free survival	Overall, the committee considered that the methodologies used to estimate RFS after 10 years for the comparison of interest were extremely 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 RFS considering the updated CheckMate 238 data.**	In their clarification response, the company state that, "*Despite having additional follow-up for RFS and more mature data, the clinical trial data only goes up to 54-months and is therefore still associated with some uncertainty in the long-term should it be extrapolated for the whole time horizon of 60 years. Therefore, BMS made the decision to stick with the most conservative option and use long-term data available in the literature at 10 years*".	N/A	No changes have been made to the methodology used for estimating long-term RFS. The only change made is the update to the indirect treatment comparison based on the latest data cut from CheckMate 238.
Survival extrapolations	Due to the immaturity of the clinical trial data, the committee concluded it was not able to judge whether any of the extrapolated clinical outcomes predicted by the model were plausible. **The company should re-explore the most appropriate clinical extrapolations.**	The company have re-run all survival analyses from the original company submission using updated RFS and OS data from CheckMate 238.	N/A	Extrapolations of RFS and OS are still based on immature data. For OS, there remains a substantial amount of uncertainty around whether the extrapolations are clinically plausible, and this has not been entirely addressed during the CDF review period.
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 as adjuvant treatment will change the treatment pathway for Stage III melanoma. 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.	SACT data on subsequent treatments have been analysed against updated subsequent treatment data from CheckMate 238.	N/A	Subsequent treatment data have been collected from SACT but are immature. Updated data on subsequent treatments in CheckMate 238 have also been collected and presented in the company submission. No adjustments have been made to overall survival data from CheckMate 238 to account for the impact of subsequent treatments. Methodologies for implementing

	The committee concluded that more real-world data on subsequent treatment used after adjuvant nivolumab in clinical practice would help to validate the model assumptions. The committee noted that the results of the Markov model were highly dependent on the subsequent treatments that patients had, and neither the company's nor the Evidence Review Group's analyses fully captured the true complexity of the post-recurrence treatment pathway. **The company should explore adjusting the results of the CheckMate 238 trial data to reflect the clinical costs and outcomes of the subsequent treatments used in NHS practice.**			subsequent treatment data in both the PSM and state-transition model remain unchanged from TA558.
Most plausible ICER	It was not possible to specify a plausible incremental cost-effectiveness ratio range at the time of the original appraisal because of the immaturity of the data.	In their clarification response, the company state that the updated ICERs implement more mature OS data from CheckMate 238 (24 months vs 48 months) and the results demonstrate a clear and robust improvement in OS. In addition, the company explain that the new data cut from CheckMate 238 resulted in a reduction in both the PSM and state-transition model ICERs.	N/A	The ERG considers that because OS data is still very immature, the uncertainty in the ICERs presented in TA558 that was to be addressed by the CDF review still remains. Through scenarios requested from the company, the ERG explored different assumptions around OS in the PSM model to put forward a potentially plausible range of ICERs, however strong assumptions were used for the scenarios.
Additional data	Another ongoing trial, Keynote 054 (which is looking at the comparative efficacy of adjuvant pembrolizumab and placebo) may provide useful evidence at the National Institute for Health and Care Excellence (NICE) review.	RFS data from Keynote 054 have been used to validate the indirect treatment comparison RFS extrapolations for the routine surveillance arm of the model.	N/A	Mature OS data from Keynote 054 is unavailable and as such could not be used in the analysis as a way to robustly model the routine surveillance arm. As such, the uncertainty around the survival estimates for routine surveillance remain the same as in TA558.
End of life	Nivolumab does not meet the criteria for end of life treatment.	No mention is made in the company's CDF submission for end of life.	N/A	N/A
Abbreviations: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; N/A, not applicable; OS, overall survival; RFS, recurrence-free survival.				

3 Clinical effectiveness

3.1 Critique of new clinical evidence

The new clinical data provided by the company for this Cancer Drugs Fund (CDF) review comprise updated overall survival (OS) and regression-free survival (RFS) data from the CheckMate 238 randomised controlled trial (RCT), along with data on the proportion of patients retreated with nivolumab in the metastatic setting. In addition, the company submission (CS) includes data from the Systemic Anti-Cancer Therapy (SACT) database on the subsequent therapies received by patients after adjuvant nivolumab in National Health Service (NHS) practice and time to next treatment data.

The data provided for CheckMate 238 are from the 30 January 2020 data-cut and include a minimum of 48-months' follow-up. The company reports that the data are still immature, and CheckMate 238 is ongoing. The ERG asked the company to clarify the timing of the next data-cut and estimated study completion date, but the company replied that these are still being revised and the previous estimated completion date was [redacted]. The ERG notes that the data included in the original review of TA558 were from the [redacted] data-cut and comprised a minimum of [redacted]-months follow-up. The data from the SACT database comprise only 25 patients who have received subsequent therapies. Further details of both studies are discussed below.

The company has also conducted updated indirect treatment comparisons (ITCs) for the outcomes of OS and RFS using the new data from CheckMate 238 and the pre-existing data from the CA184-029 study (ipilimumab versus best supportive care) to provide clinical data for use in the economic model for the comparison of adjuvant nivolumab versus routine surveillance. The ITCs are discussed further in Section 3.1.3.

3.1.1 CheckMate 238

CheckMate 238 is an international double-blind phase III RCT of adjuvant nivolumab compared to adjuvant ipilimumab. Nivolumab was administered at a dose of 3 mg/kg every 2 weeks and the ipilimumab dose was 10 mg/kg every 3 weeks for four doses, then 12 weekly. Both treatments were allowed to be given in CheckMate 238 for up to a maximum of 1 year. CheckMate 238 was assessed in TA558 to be of high methodological quality and low risk of bias by both the company and the ERG.

Patients enrolled in CheckMate 238 were aged 18 years or over and were required to have had complete surgical resection of Stage IIIB, IIIC or IV melanoma, according to the 2009 classification of

the American Joint Committee on Cancer (AJCC) 7th edition. The AJCC has since been updated to the 8th edition, which means that some patients in CheckMate 238 would now be classed as being in a different stage to that they were classified in CheckMate 238. This difference is important in relation to the use of the clinical data in the ITC as some patients from CheckMate 238 are likely to be classed as Stage IIIa (instead of Stage IIIb). The ITC is discussed further in Section 3.1.3.

In response to a clarification question, the company provided details of the duration of treatment for patients in CheckMate 238 for the January 2020 data cut although, the ERG notes that, based on the earlier 15 May 2017 data cut, all 905 treated patients had discontinued or completed the 12-month study drug period. The data on treatment duration remain as reported from the earlier data cut but patients who have remained in the study have now been followed-up for longer.

Duration of treatment was calculated from first to last exposure to treatment. [redacted] As previously noted in the original ERG report, these differences in treatment duration are not unexpected given [redacted].

Table 11. Duration of treatment in CheckMate 238 for the 48-month minimum follow-up data cut (Reproduced from company response to clarification, Table 10).

Treatment	N	Median	IQR (25^{th}, 75^{th} percentile)	Mean (SD)
Ipilimumab	453	[redacted]	[redacted]	[redacted]
Nivolumab	452	[redacted]	[redacted]	[redacted]

Abbreviations: IQR, interquartile range; SD, standard deviation.

Overall survival

The OS Kaplan–Meier plots from the January 2020 data cut (48 months' minimum follow-up) of CheckMate 238 are presented in Figure 1 with summary statistics presented in Table 12. The company reported that, despite the updated OS data cut from CheckMate 238, the study results for OS still remain immature and underpowered: 302 events were anticipated in order to provide 88% power to detect a hazard ratio (HR) of 0.7 (critical HR 0.76) under an overall alpha of 0.05 (hierarchical testing after RFS). [redacted]

The ERG notes that the Kaplan–Meier curves for nivolumab and ipilimumab [redacted] The HR for the minimum 48-month follow-up data suggests [redacted] for patients treated with nivolumab compared with those treated with ipilimumab (HR [redacted], 95% confidence interval [CI]: [redacted]).

The ERG notes that in addition to the company's concerns regarding the immaturity of the data that the company also highlight [redacted] The subsequent treatments in CheckMate 238 are discussed further later in Section 3.1.1.

Figure 1. CheckMate 238 Kaplan–Meier curves for overall survival by treatment arm, 48-month minimum follow-up (Reproduced from CS, Figure 1)

Key: ipi, ipilimumab; nivo, nivolumab.

Table 12. CheckMate 238 summary statistics for overall survival by treatment arm, 48-month minimum follow-up (Reproduced from CS, Table 4)

Treatment	Subjects	Events	Censored	Median (95% CI)	HR (95% CI)
Ipilimumab	453	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	453	[redacted]	[redacted]	[redacted]	

Notes: Hazard ratio <1 favours nivolumab. Hazard ratio >1 favours ipilimumab.
Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available.

The company provided forest plots with summary data for OS in various subgroups (based on age, sex, BRAF status, PD-L1 status, disease stage, Eastern Cooperative Oncology Group (ECOG) status

and geographical region) in their response to clarification (Company response to clarification, figure 21). The ERG notes that the only stratification factors in CheckMate 238 were disease stage (Stage IIIB or IIIC vs Stage IV M1a or M1b vs Stage IV M1c) and PDL1 status (<5% / Indeterminate vs ≥5%) and many of the subgroups comprise small patient numbers which limit their suitability for drawing conclusions. Nevertheless, the ERG considers [redacted].

Recurrence-free survival

The RFS results from the January 2020 data-cut, after a minimum of 48 months of follow-up, [redacted], with nivolumab demonstrating [redacted] in RFS compared with ipilimumab (HR: [redacted] Figure 2 and Table 13). The company provided forest plots with summary data for RFS in various subgroups, which included age, sex, BRAF status, PD-L1 status, disease stage, ECOG status and geographical region (CS, Figure 16 and response to clarification, Figure 20). Similar to OS, the ERG notes that the only stratification factors in CheckMate 238 were disease stage (Stage IIIB or IIIC vs Stage IV M1a or M1b vs Stage IV M1c) and PDL1 status (<5% /Indeterminate vs ≥5%) and many of the subgroups comprise [redacted] which limit their suitability for drawing conclusions. Nevertheless, the ERG considers [redacted]

In the January 2020 data cut of CheckMate 238, median RFS was [redacted] months (95% CI: [redacted] However, as for OS, the company report that the data for RFS also remain immature [redacted]

The company provided forest plots with summary data for RFS in various subgroups which included age, sex, BRAF status, PD-L1 status, disease stage, ECOG status and geographical region (CS, Figure 16 and response to clarification, Figure 20). Similar to OS, the ERG notes that the only stratification

factors in CheckMate 238 were disease stage (Stage IIIB or IIIC vs Stage IV M1a or M1b vs Stage IV M1c) and PDL1 status (<5% /Indeterminate vs ≥5%) and many of the subgroups comprise of small patient numbers which limit their suitability for drawing conclusions. Nevertheless, the ERG considers [redacted]

Figure 2. CheckMate 238 Kaplan–Meier curve for recurrence-free survival by treatment arm (48-month minimum follow-up) (Reproduced from CS, Figure 2)

Key: Ipi, ipilimumab; Nivo, nivolumab.

Table 13. CheckMate 238 summary statistics for recurrence-free survival by treatment arm (48-month minimum follow-up) (Reproduced from CS, Table 5)

Treatment	Subjects	Events	Censored	Median (95% CI; months)	HR (95% CI)
Ipilimumab	453	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	453	[redacted]	[redacted]	[redacted]	

Notes: Hazard ratio <1 favours nivolumab. Hazard ratio >1 favours ipilimumab.
Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available.

Subsequent treatment

The company reported that the update of subsequent treatments from CheckMate 238 based on the January 2020 data cut (48-month minimum follow-up) are derived using the same assumptions as the original submission, with data separated based on whether the recurrence is a local/regional or a distant recurrence (TA558 Document B, Section B3.5, Page 158). Patients who have a local/regional

recurrence before developing a distant recurrence were included in both groups. This was done by including the subsequent treatment records from the time of local up until distant recurrence in the local recurrence group, and any subsequent treatments after the distant recurrence were included in the distant recurrence group. Table 14 presents the updated subsequent treatment data from CheckMate 238.

The ERG notes that the subsequent treatment frequencies are similar to those in the original submission and that the majority of patients in the nivolumab arm go on to receive dabrafenib plus trametinib ([redacted], local/regional recurrence and distant recurrence; respectively) or ipilimumab ([redacted]) as systemic therapy. In comparison, [redacted] of patients in the ipilimumab arm received dabrafenib plus trametinib ([redacted] local/regional recurrence and distant recurrence; respectively) and pembrolizumab ([redacted]). The ERG's clinical experts reported that generally the subsequent treatments are reasonable, although a few of the less frequently used treatments in CheckMate 238 are never or very rarely used in UK clinical practice, for example, cisplatin, interferon and interleukin. The ERG's clinical experts considered the use of ipilimumab, nivolumab and dabrafenib + trametinib in CheckMate 238 to be reasonable and reflective of the likely subsequent therapies patients would receive in clinical practice based on the baseline characteristics of patients in CheckMate 238.

Table 14. Subsequent treatment splits by treatment arm from CheckMate-238 (48-month minimum follow-up) (Reproduced from CS, Table 6)

	Local/regional recurrence		Distant recurrence*	
	Nivolumab	Ipilimumab	Nivolumab	Ipilimumab
Patients who received subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]

Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent surgery	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]

Note: * Includes patients who had a distant recurrence following a local recurrence.

Re-treatment with nivolumab

The ERG notes that in TA558 there was uncertainty around the timing for re-challenging patients with nivolumab or other anti-PD1s if they have disease recurrence following adjuvant treatment with nivolumab. Clinical opinion suggested that, in practice, patients would most likely be re-challenged with PD-1 inhibitors 2 years after adjuvant nivolumab.[7] The ERG interprets this as 2 years from last treatment with a PD-1 inhibitor as opposed to time from relapse. The ERG's clinical experts reported that they would typically consider anti-PD1 re-challenge in patients beyond 1 year from last adjuvant treatment with nivolumab but possibly earlier depending on clinician and patient preference as well as other clinical and disease-related factors. The ERG's clinical experts also reported that the longer a patient remains in remission the more likely they would re-challenge with nivolumab.

The company has provided data from CheckMate 238 for the CDF review to show the time from recurrence to first anti-PD-1 subsequent therapy following adjuvant nivolumab treatment in the trial (Table 15). The ERG notes that anti-PD1 subsequent therapy is given to treat disease recurrence following adjuvant nivolumab and considers time from last dose of adjuvant nivolumab to first anti-PD1 subsequent therapy would be more useful to enable a comparison of data from CheckMate 238 with clinical practice. This is because disease recurrence could occur prior to completion of 12 months' adjuvant nivolumab and it is the length of time off PD1 inhibitors that is used by clinical experts to determine subsequent therapies at disease recurrence.

The ERG notes that the data from CheckMate 238 demonstrate that [redacted]% of patients in the nivolumab arm who received subsequent therapies were re-treated with anti-PD-1s before 6 months following recurrence and [redacted]% were re-treated prior to 2 years following recurrence. The ERG also notes that the median RFS in CheckMate 238 was [redacted] months and median duration of treatment with nivolumab was [redacted] months. The ERG considers that if disease recurrence occurs beyond 36 months and a patient completed the full 12 months' adjuvant nivolumab then they will have been off PD1 inhibitors for over 2 years at the point of disease recurrence.

Table 15. Timing of anti-PD-1 re-challenge in the nivolumab arm of CheckMate 238 (Reproduced from CS, Table 7)

Time from recurrence to first anti-PD-1 subsequent therapy	Number of patients (%)*	Mean time of 1st anti-PD-1 therapy (months)	Mean line of 1st anti-PD-1 therapy
< 6 months	[redacted]	[redacted]	[redacted]
≥ 6 months to < 12 months	[redacted]	[redacted]	[redacted]
≥ 12 months to < 24 months	[redacted]	[redacted]	[redacted]
≥ 24 months	[redacted]	[redacted]	[redacted]

Notes: [redacted]. Anti PD-1 treatment includes both monotherapy and anti-PD1 treatment used in combination therapy.
* Denominator for the percentage is [redacted] which is the total number of patients who had any systemic subsequent therapy after a recurrence event.

3.1.2 SACT

Systemic Anti-Cancer Therapy patient cohort

There were 284 eligible patients for analysis who had been enrolled in the SACT database between 30 November 2018 and 29 October 2019.[10] A summary of patient characteristics included in the SACT cohort is presented in the Appendix 8.1, Table 36, alongside the baseline characteristics of the patients in the nivolumab arm of CheckMate 238.

The patients in the SACT cohort are slightly older than patients in CheckMate 238 (median 63 versus 56 years, respectively) and the ECOG performance status was slightly worse in the SACT cohort (23% had an ECOG performance status of > 0 versus 9% in the CheckMate 238 cohort). The ERG's clinical experts reported that these differences were not unexpected as typically patients in clinical trials such as CheckMate 238 are fitter than those treated in practice. A further notable difference in baseline characteristics between the two studies was in the BRAF status, with 78% BRAF V600 negative in the SACT cohort and 44% BRAF V600 negative in CheckMate 238. The company reported that a possible explanation for this is that dabrafenib plus trametinib is available in clinical practice to patients who are BRAF V600 positive. The company also reported that retrospective analyses have confirmed that nivolumab has similar efficacy and safety outcomes regardless of BRAF mutation status[11] and therefore they consider the difference in BRAF status is unlikely to affect outcomes. The ERG's clinical experts also agreed that BRAF mutation status is unlikely to impact on outcomes with nivolumab.

Finally, the ERG notes that there was also a marked difference in disease stage between the SACT cohort and CheckMate 238, with 35% of the SACT cohort having Stage IV disease and only [redacted]% in CheckMate 238. However, the ERG notes that in CheckMate 238 the data have been reclassified to

use the AJCC v8 to match the data from the SACT cohort but the mapping of patients from v7 to v8 may have resulted in the incorrect staging of some patients and the likely directions of any resulting errors is unknown.

Subsequent therapies

The data on subsequent therapies in the SACT patient cohort comprise only 27 unique records relating to 25 patients who received adjuvant nivolumab and then went on to receive subsequent therapies (Table 16). However, 205 patients in the SACT cohort are still on treatment with adjuvant nivolumab and have not received any subsequent treatment, which is a reflection of the short follow-up of the SACT cohort. The ERG thus notes that the subsequent treatment data from the SACT patient cohort are immature and comprise a very small cohort of patients that may not fully reflect clinical practice. The ERG's clinical experts also reported that they would not expect patients in their clinical practice to receive some of the subsequent treatments given to patients in the SACT cohort, for example, bleomycin, capecitabine and cisplatin + dacarbazine + vinblastine.

The median follow-up time for subsequent therapies from a patient's last nivolumab cycle in the SACT cohort was 154 days (range: 28 to 262 days) and for patients who received a subsequent therapy the median time from a patient's last nivolumab cycle date to receiving their next treatment regimen was 35 days (range: 13 to 197 days).

Of the 9% of patients that received subsequent therapies in the SACT cohort, the most frequently received treatments were ipilimumab + nivolumab (5%), single agent ipilimumab (1%) and dabrafenib + trametinib (1%). The ERG notes that dabrafenib + trametinib use in the SACT cohort was lower compared to in CheckMate 238, which likely reflects the difference in the proportions of patients with BRAF V600 mutation positive patients between the studies (a higher proportion was observed in CheckMate238). Single agent ipilimumab after nivolumab adjuvant treatment was also frequently used as a subsequent treatment in CheckMate 238 similar to in the SACT cohort. However, ipilimumab + nivolumab combination therapy usage was lower in CheckMate 238 compared to in the SACT cohort, which may be a reflection of the longer follow-up and the larger proportion of patients who have had multiple lines of subsequent treatment, whereas the SACT cohort only has two patients who had more than one subsequent treatment.

Table 16. Distribution of subsequent treatment in the Systemic Anti-Cancer Therapy data cohort (Reproduced from CS, Table 8)

Regimen	SACT cohort (n = 284)
Still on treatment	205 (72%)
Stopped treatment	79 (28%)
Patients receiving at least one subsequent treatment	25 (9%)
Ipilimumab + nivolumab	13 (5%)
Ipilimumab	4 (1%)
Dabrafenib + trametinib	3 (1%)
Binimetinib + encorafenib	2 (1%)
Bleomycin	1 (<1%)
Capecitabine	1 (<1%)
Cisplatin + dacarbazine + vinblastine	1 (<1%)
Pembrolizumab	1 (<1%)
Talimogene laherparepvec	1 (<1%)

Abbreviations: n, number; SACT, Systemic Anti-Cancer Therapy.

3.1.3 ITC

The company used the CA184-029 study of ipilimumab versus placebo (data cut date: 13 May 2016) to conduct an indirect treatment comparison (ITC) between nivolumab, from the CheckMate 238 study, and routine surveillance, via the common comparator of ipilimumab. The ERG notes that the ITC is used for both OS and RFS, whereas in the original submission the company had used a surrogacy analysis to estimate OS for nivolumab due to immaturity of the OS data from CheckMate 238. The data used in the ITC for OS are now based on the CheckMate 238 outcome data for OS, although as discussed in Section 3.1.1, the OS data for nivolumab are still very immature. The ERG also considers it important to highlight that in TA558, clinical experts considered that OS from the placebo arm of CA184-029 does not reflect the current survival outcomes for routine surveillance patients due to advances in the subsequent treatment pathway.

The company's primary ITC was performed using a patient level data (PLD) meta-regression and a sensitivity analysis was conducted using the Bucher methodology.[12] The company reported that the differences between CheckMate 238 and CA184-029 studies were consistent with their original submission and the most notable differences are as follows:

- CheckMate 238 did not include patients with Stage IIIA disease and CA184-029 did not include patients with Stage IV disease;

- CA184-029 defined disease stage based on the 6th edition of the American Joint Committee on Cancer (AJCC) Staging Manual, while CheckMate 238 study used the 7th edition AJCC staging and as discussed previously there is now an 8th edition of the AJCC staging;
- Ipilimumab treatment in CA184-029 was for up to 3 years, whereas in CheckMate 238 ipilimumab treatment was only permitted for 1 year. In total, 25% of patients in CA184-029 received ipilimumab treatment beyond 1 year.

ITC methodology

The company reported that they used the same methodology for the PLD meta-regression as they used in their original submission for TA558 and highlighted that it was also in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14. The ERG notes that the PLD meta-regression in the new submission is conducted for OS in addition to RFS. In summary the methodology used by the company is as follows:

- Parametric curves were fitted in the meta-regression (exponential, Weibull, Gompertz, log-normal, log-logistic, and generalised gamma) to estimate the treatment effect of nivolumab in comparison with routine surveillance (placebo) for use in the partitioned survival model.
- Proportional hazards and accelerated failure time were not assumed because PLD were available for both studies. The ERG notes that the company provided log-cumulative hazard plots to assess proportional hazards and quantile–quantile (QQ)-plots to assess accelerated failure time in the appendix of the CS and they reported that they were provided for completeness.
- The covariates included in the PLD meta-regression were:
    - Treatment (nivolumab, ipilimumab or placebo [treatment effect was applied to two parameters for each parametric model with the exception of the one parameter exponential model]);
    - Sex (male or female);
    - Age (<65 or ≥65 years);
    - Disease stage (Stage IIIA, Stage IIIB, Stage IIIC or Stage IV [three patients in CheckMate 238 had unknown/other disease stage and were excluded from analysis]);
    - Trial (CA184-029 or CheckMate 238; trial was included as a covariate in the RFS ITC PLD meta-regression analysis only).

- The covariates were applied to the analysis of both OS and RFS and incorporated into the cost-effectiveness model using the corrected group prognosis method.
- RFS data were rebased at 12 weeks due to clustering of events at the time of first disease assessment and Kaplan–Meier data were used directly for the first 12 weeks. Clustering of events was not observed for OS and so rebasing was not required in the analyses of OS.
- The same criteria as in the original submission were used to select the most plausible curve fits and these included an assessment of statistical fit using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values. In addition, a visual review of the fitted curves was conducted to ensure that the curves for treatments within trials don't cross during trial follow up and to ensure the time at which the OS and RFS curves meet in the model for the routine surveillance arm are clinically plausible.
- In the analysis of RFS, the company applied censoring to any patients in CA184-029 who remained on ipilimumab after 12 months to coincide with the treatment duration seen in CheckMate 238, but this 1-year censoring was not applied in the analyses of OS. The company did, however, provide an analysis for OS with ipilimumab censoring at the request of the ERG at the clarification stage. The results of both analyses are presented below and the analyses with the consistent approach of 1-year censoring for both OS and RFS being preferred by the ERG.

ITC Results – overall survival

The goodness-of-fit statistics indicated that the generalised gamma model provided the best statistical fit to the data, as it has the lowest AIC and BIC values. The company reported that, "*when considering the extrapolated period for each survival curve, the Gompertz and generalised gamma curves produced the most optimistic estimates for the placebo data, with the generalised gamma, exponential and log-normal curves producing the most optimistic estimates for nivolumab*." The generalised gamma curve provided the best visual and statistical fit to the data and was therefore selected by the company as the base case for the economic model. The ERG notes that the use of the generalised gamma curve for OS is consistent with the original submission despite the inclusion of CheckMate 238 data in the new submission.

The fitted generalised gamma curves for OS are presented in Figure 3 and Figure 4 for the nivolumab (CheckMate 238) and placebo (CA184-029) arms, respectively, alongside the relevant Kaplan–Meier curves. The ERG notes that the fitted curves appear to fit the Kaplan-Meier data well. The corrected

group prognosis (CGP) method was used to calculate the final parametric survival curves used in the economic model and the resulting curves are presented in Figure 6. The ERG notes that once patient demographics for each of the treatment arms were matched to the model population (using the CGP method) nivolumab appears to have improved OS compared with placebo (Figure 5).

Figure 3. CheckMate 238 overall survival ITC PLD meta-regression model – generalised gamma survival extrapolations for the nivolumab arm (Reproduced from CS, Figure 3)

Abbreviations: ITC, indirect treatment comparison; Nivo, nivolumab; PLD, patient level data.

Figure 4. CA184-029 overall survival ITC PLD meta-regression model – generalised gamma survival extrapolations for the placebo arm (Reproduced from CS, Figure 4)

Abbreviations: ITC, indirect treatment comparison; KM, Kaplan–Meier; PBO, placebo; PLD, patient level data.

Figure 5. ITC OS final curve using matched population (Reproduced from CS, Figure 8)

Abbreviations: IPD, individual patient-level data; ITC, indirect treatment comparison; OS, overall survival.

As part of the clarification questions, the ERG requested the company provide ITC PLD meta-regression plots with data for nivolumab and routine surveillance in the same figure, including a shaded area around each plot designating the 95% confidence interval around the estimates for the outcomes of OS, which unfortunately the company did not provide. The company instead used a mean of covariates approach to provide graphical estimates of uncertainty around the extrapolations. Within the mean of covariates analysis, the patient population was matched for both treatment arms. The resulting ITC PLD meta-regression extrapolations using the generalised gamma distribution for OS are presented in Figure 6 with the graphical estimates of uncertainty. The ERG considers it important to highlight that the results from the mean of covariates approach produces similar but not identical results to the matched extrapolations presented in Figure 5. The results shown in Figure 6 demonstrate the uncertainty in the OS analyses as the shaded areas consistently overlap for nivolumab and placebo.

Figure 6. OS PLD meta-regression (generalised gamma) extrapolations using matched population (Reproduced from company response to clarification, Figure 7).

Abbreviations: nivo, nivolumab.

The company also reported that they conducted an exploratory analysis to explore the external validity of the ITC model for OS. The exploratory analysis comprised matching the modelled patient characteristics to the COMBI-AD study (a Phase III study comparing dabrafenib plus trametinib with placebo in BRAF-positive Stage III melanoma)[13] using a simulated treatment comparison (STC). The company reported that in this exploratory analysis the model accurately fitted the observed placebo arm, which was interpreted as the model providing a reasonable estimate outside of the CheckMate 238 and CA184-029 studies for OS. Due to time constraints the ERG was unable to review this analysis and thus is unable to comment on its suitability or the applicability of the COMBI-AD study.

The results of the Bucher indirect comparison using CheckMate 238 and CA184-029 for OS showed that treatment with nivolumab had a significantly reduced hazard of death compared with treatment with placebo ( ) based on the ITT population. The ERG considers this to be broadly consistent with the results of the PLD meta-regression ITC.

ITC Results – OS for ipilimumab censored after 1 year of treatment

The ERG requested the company conduct an analysis of OS in which patients from CA184-029 who had received ipilimumab treatment beyond 1 year were censored at 1 year of treatment, similar to the analysis of RFS used by the company in their base case. The company highlighted that the limitations for this OS analysis are similar to those observed for the corresponding RFS analysis, with

informative censoring being the key issue. This is because the censored patients are likely to be those with the best prognosis at 1 year (i.e., still alive and recurrence-free) and therefore biases the results against ipilimumab. Similar to the analysis of RFS, the ERG considers that the subsequent ITC would, therefore, potentially underestimate the difference in OS between nivolumab and routine surveillance.

Figure 7 presents the OS for the observed ITT population in CA184-029 alongside the OS for the ITT population where *all* patients are censored at 1 year if they were still receiving treatment (either ipilimumab or placebo). The ERG considers it important to highlight that only the ipilimumab arm data are censored at 1 year for use in the ITC. As can be observed in Figure 7, [redacted] The ERG considers the 1 year censoring of patients on ipilimumab in the ITC analysis is the most appropriate data set from CA184-029 and is consistent with the approach the company has used for the analysis of RFS in their base case.

Figure 7. CA184-029 overall-free survival Kaplan–Meier for the observed ITT population and for the observed ITT population in which ipilimumab patients are censored after 1 year of treatment (Reproduced from company response to clarification, Figure 3).

Notes: Dashed line indicates 1 year after randomization; patients typically started treatment a few days after randomization.
Abbreviations: HR, hazard ratio; Ipi, ipilimumab 10 mg; ITT, intention-to-treat KM, Kaplan–Meier; PBO, placebo; TRT, treatment; yr, year.

The goodness of fit statistics for the OS PLD meta-regression in which patients are censored in CA184-029 if still on treatment after 1 year indicate that the generalised gamma curves are still associated with the lowest AIC and BIC values. The fitted generalised gamma curves and Kaplan–Meier curves (nivolumab from CheckMate 238 and placebo from CA184-029) are presented in Figure 8 and Figure 9 for nivolumab and placebo, respectively. [redacted]

The revised comparison of nivolumab versus placebo for the matched population (using the CGP method) used in the partitioned survival model are presented in Figure 10 and [redacted]

Figure 8. CheckMate 238 overall survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – generalised gamma survival extrapolations for the nivolumab arm (Reproduced from company response to clarification, Figure 4)

Figure 9. CA184-029 overall survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – generalised gamma survival extrapolations for the placebo arm (Reproduced from company response to clarification, Figure 5)

Figure 10. Model OS and RFS with ipilimumab treatment censoring at 1 year in CA184-029 – partitioned survival model (Reproduced from company response to clarification, Figure 26).

Abbreviations: OS, overall survival; RFS, recurrence-free survival

The company also provided the results of the ITC using the Bucher method and the 1-year censoring of patients on ipilimumab in CA184-029 alongside the results using the ITT data from CA184-029 (Table 17). The results indicate that,

[redacted]

Table 17. Within trial and Bucher indirect analysis results for overall survival (observed results and results where ipilimumab patients are censored after 1 year of treatment in CA184-029) (Reproduced from company response to clarification, Table 3).

Comparison	Study	Observed ITT HR (95% CI)	Ipilimumab censored analysis* HR (95% CI)
Nivolumab vs ipilimumab	CheckMate 238	[redacted]	[redacted]
Placebo vs ipilimumab	CA184-029	[redacted]	[redacted]
Nivolumab vs placebo	Bucher indirect comparison	[redacted]	[redacted]

Notes: * ipilimumab patients censored after 1 year of treatment in CA184-029; Presented hazard ratios are unstratified.

ITC Results – RFS for ipilimumab censored after 1 year of treatment

As discussed previously, the patient level meta-regression for RFS was updated using the 48-month data cut of CheckMate 238. The goodness-of-fit statistics for the newly resulting fitted parametric survival curves for RFS indicated that the log-logistic model provided the best statistical fit to the data, as it had the lowest AIC and BIC values. The company also considered it to fit well with the clinical data and therefore selected it for use as the base case for the economic model, which the ERG notes is consistent with curve selected for use in the original CS. The fitted log-logistic curves are presented in Figure 11 and Figure 12 alongside the Kaplan–Meier plots for nivolumab (CheckMate 238) and placebo (CA184-029), respectively. The ERG considers it important to highlight that the data from CA184-029 used in the ITC for RFS in the company base case are from the 1 year censored ipilimumab analysis (patients censored after 1-year of ipilimumab treatment).

Figure 11. CheckMate 238 recurrence-free survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 – nivolumab arm (Reproduced from CS, Figure 5)

Abbreviations: ITC, indirect treatment comparison; KM, Kaplan–Meier; Nivo, nivolumab; PLD patient level data.
Note: KM from baseline is displayed, log-logistic curve is fitted from 12 weeks onwards.

Figure 12. CA184-029 recurrence-free survival (ipilimumab patients censored after 1 year of treatment) ITC PLD meta-regression model – log-logistic survival extrapolations rebased at Week 12 – placebo arm (Reproduced from CS, Figure 6)

Abbreviations: ITC, indirect treatment comparison; KM, Kaplan–Meier; PBO, placebo; PLD, patient level data.
Note: KM from baseline is displayed, log-logistic curve is fitted from 12 weeks onwards.

As for OS, the CGP method was used to calculate the final parametric survival curves used in the economic model and the resulting curves show nivolumab is associated with improved RFS compared to placebo(Figure 13).

Figure 13. ITC RFS final curve using matched population (Reproduced from CS, Figure 7)

Abbreviations: IPD, individual patient-level data; ITC, indirect treatment comparison; RFS, recurrence-free survival.

Similar to OS, as part of the clarification questions, the ERG requested the company provide ITC PLD meta-regression plots with data for nivolumab and routine surveillance in the same figure including a shaded area around each plot designating the 95% CI around the estimates for the outcome of RFS, which unfortunately the company did not provide. The company instead used a mean of covariates approach to provide graphical estimates of uncertainty around the extrapolations and it should also be noted that the company did not include data for the first 12 weeks as patients were rebased at 12 weeks within this analysis.

The resulting ITC PLD meta-regression extrapolations using the log-logistic distribution for RFS are presented in Figure 14 with the graphical estimates of uncertainty. The ERG considers it important to highlight that the mean of covariates approach produces slightly different results to the matched extrapolations but still indicates a clear benefit in RFS with nivolumab compared to placebo.

Figure 14. RFS PLD meta-regression (log-logistic) extrapolations using matched population (Reproduced from company response to clarification, Figure 6)

Abbreviations: nivo, nivolumab.

The company also reported that, as for OS, they conducted an exploratory analysis to investigate the external validity of the ITC model for RFS. The exploratory analysis comprised matching the modelled patient characteristics to the COMBI-AD study (a Phase III study comparing dabrafenib plus trametinib with placebo in BRAF-positive Stage III melanoma)[13] using a STC. The company reported that in this exploratory analysis the model accurately fitted the observed placebo arm, which indicated that the model provided reasonable estimates outside of the CheckMate 238 and CA184-029 studies for RFS. However, due to time constraints the ERG was unable to review this analysis and thus is unable to comment on its suitability or the applicability of the COMBI-AD study.

The results of the Bucher indirect comparison using the updated CheckMate 238 data for RFS (ipilimumab patients censored after 1 year of treatment) indicated that treatment with nivolumab had a significantly reduced hazard of an RFS event compared with treatment with placebo (HR [redacted]) based on the ITT population. The ERG notes that the results of the updated Bucher indirect comparison for RFS are [redacted]; ipilimumab patients censored after 1 year of treatment).

ITC Results – BRAF mutation status subgroup analyses

Following advice from clinical experts, the ERG requested that the company conduct subgroup analyses based on BRAF mutation status for the ITCs used in the economic model. The ERG notes that approximately 15% patients in the nivolumab arm and 10% of patients in the ipilimumab arm of

CheckMate 238 did not have BRAF status reported and as such would be excluded from this analysis. However, the company reported that BRAF status was only collected retrospectively in CA184-029 and approximately 85% of patients did not have a BRAF status reported. The company therefore decided to conduct two alternative analyses in which the subgroups of BRAF mutant and BRAF wild type were separately compared to the ITT population of CA184-029 for both RFS (ipilimumab patients censored after 1 year of treatment) and OS (ipilimumab patients were not censored after 1 year of treatment within the OS analysis). The ERG considers that the results of these analyses are of limited value as they assume that BRAF status has no impact on RFS or OS with ipilimumab in CA184-029, although the relevant ipilimumab subgroup data from CheckMate 238 have been used. The ERG requested the analyses to help identify whether or not BRAF status may affect treatment outcomes and does not consider it possible to draw conclusions from the results of the analyses presented by the company. In addition, the analyses for OS do not include the ERG's preferred 1-year censoring of ipilimumab from CA184-029. The ERG thus does not discuss the results of these subgroup analyses further.

3.2 Conclusions of the clinical effectiveness section

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the ToE, although the updated OS data from CheckMate 238 remain immature. The uncertainty from TA558 in terms of the effect of nivolumab on OS that was to be resolved during the CDF data collection period has not been resolved.

The clinical data presented by the company includes the ToE required later data cut from CheckMate 238 for OS and RFS, and the observational SACT data that were also required to be collected by Public Health England during the period of managed access for nivolumab. The ERG agrees that the company has focussed on the required Stage III and IV completely resected melanoma population and the key comparator of observation (placebo).

The ERG notes that the marketing authorisation approved licensed dose of nivolumab for adjuvant therapy has been changed to 240 mg every 2 weeks or 480 mg every 4 weeks from a weight-based dose of 3 mg/kg. The weight-based dose was used in the original CS for TA558 and in the CheckMate 238 clinical trial. The ERG's clinical experts reported that they would expect the new dose to be equivalent to the weight-based dose in terms of efficacy and safety.

CheckMate 238 now comprises a minimum follow-up period of [redacted] months and includes later data-cuts for OS, RFS and subsequent therapies. However, the ERG also notes that the updated data from CheckMate 238 remain immature, particularly for OS. The SACT data set comprises data on subsequent therapies for only 25 patients and thus is also immature and unfortunately of limited value. The ERG therefore considers there is still uncertainty in the clinical data, despite the later data-cut from CheckMate 238 and new data from the SACT.

The ERG is concerned that the population in CheckMate 238 differs from the population in SACT, particularly in relation to the proportion of patients with a BRAF mutation and the distribution of disease stage, and thus CheckMate 238 may not reflect expected clinical practice in England. The ERG's clinical experts reported that they considered the SACT data set to be more representative of patients in clinical practice in England who would receive nivolumab. However, the SACT data set does not provide information on RFS or OS as its purpose was to collect data on subsequent therapies and the follow-up duration is limited for this purpose.

The ERG also notes that, as detailed in the original ERG report, differences in the eligibility criteria for CheckMate 238 and CA184-029 may also have had an impact on both the comparability of the trials in the ITC and their applicability to clinical practice. CheckMate 238 did not include Stage IIIa patients and CA184-029 did not include Stage IV patients. In addition, the ERG notes that the AJCC has now been updated to v8 and so some patients previously classed as IIIb may now be classed in clinical practice as Stage IIIa. These discrepancies remain as in the original submission for TA558 and the impact of any resulting bias is unknown. In TA558 clinical experts also considered that OS from the placebo arm of CA184-029 does not reflect the current survival outcomes for routine surveillance patients due to advances in the subsequent treatment pathway.

In response to clarification questions, the company conducted ITC analyses of OS using censoring at 1 year of treatment for patients in the ipilimumab arm of CA184-029 which the ERG considers to be more suitable than using the full ITT population data from CA184-029. This is because of the ipilimumab treatment discrepancy between CheckMate 238 and CA184-029: in CheckMate 238 ipilimumab was given for up to 1 year, whereas in CA184-029 it could be given for up to 3 years and 25% of patients received treatment beyond 1 year. The ERG acknowledges that the use of the 1-year censoring for patients on ipilimumab in CA184-029 may result in a conservative estimate of OS for nivolumab from the ITC but considers this to be preferable to potentially over-estimating OS for nivolumab. In addition, the ERG notes that the 1-year censoring is used in the analyses of RFS and

considers the consistent use of the 1-year censoring in the analyses of OS should be used in the economic model.

In summary, the ERG considers the results of the analyses of OS with nivolumab compared to placebo (routine surveillance) still to be uncertain due to the immaturity of the nivolumab data from CheckMate 238 and the potentially outdated comparator data for placebo from CA184-029. In addition, the ERG is concerned about the potential mismatch in patient characteristics between CheckMate 238 and the patients expected in clinical practice in England in terms of disease stage. The ERG, nevertheless, considers the updated ITC analyses presented by the company for OS, where 1-year ipilimumab censoring is applied for patients from CA184-029, to be more suitable for decision making than the previously presented analyses of OS.

4 Cost effectiveness

4.1 Summary and critique of the company's submitted economic evaluation by the ERG

The company's submission (CS) for the cancer drugs fund (CDF) review of nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease was mostly unchanged from the approach in the original Single Technology Appraisal 558 (TA558).[14] The key updates made in the both the partitioned survival model (PSM) and the state-transition model (which previously was referred to as Markov option 2) were as follows:

- The licensed dose for nivolumab has changed to a flat dose of either 240 mg once every 2 weeks or 480 mg once every 4 weeks. Previously, the dose was based on weight and was 3 mg/kg once every 2 weeks.[14, 15]
    - The company state that, as the dose is no longer weight-based, the administration cost should reflect the simpler dosing and as such has updated the NHS reference cost code to SB12Z: 'Deliver Simple Parenteral Chemotherapy at First Attendance' (£259.76), from the previous cost code, which was SB13Z: ''Deliver more Complex Parenteral Chemotherapy at First Attendance' (£299.68).[16]
- For both models, a more recent data cut (30 January 2020) of recurrence-free survival (RFS) from the CheckMate 238 trial has been used to update the original indirect treatment comparison (ITC) of routine surveillance using a patient level data (PLD) meta-regression, including censoring of ipilimumab patients if treated beyond 1 year.
- For the PSM, a new ITC for overall survival (OS) based on the January data cut from CheckMate 238 was implemented in the model, applying the same methodology used for the RFS ITC but without censoring of ipilimumab patients if treated beyond 1 year.
- For the state-transition model, proportions of patients receiving post-recurrence subsequent therapies have been updated using the January data cut from CheckMate 238, resulting in updated post-recurrence survival and costs of subsequent therapies.

In addition to the key changes, the company made some minor corrections that were identified when updating the economic models for the CDF submission and were as follows:

- For the corrected group prognosis (CGP) analysis of the RFS ITC survival curves, the trial covariate for CA184-029 was applied to estimate the extrapolations for routine surveillance

in the original analysis, whereas the CheckMate 238 trial covariate should have been used for it to be comparable with nivolumab and this has now been updated;

- For the cost calculations of subsequent therapies (before re-challenge) for the nivolumab arm, second-line subsequent treatments were omitted but have now been included in the calculations.

The impact of the model corrections on the final base case incremental cost effectiveness ratio (ICER) from TA558 are minimal and are presented in Table 18 and Table 19, alongside the company's uncorrected final base case results from TA558 and the new updated base case ICERs for the PSM and state-transition model. All results presented in this report are inclusive of the company's patient access scheme (PAS) simple discount of [redacted].

Table 18. Company's deterministic cost effectiveness results – partitioned survival model

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Final base case results from TA558[7]							
Routine surveillance	[redacted]	17.83	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,423
Final base case from TA558 – corrected							
Routine surveillance	[redacted]	17.83	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,870
Updated base case results							
Routine surveillance	[redacted]	18.65	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,301

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 19. Company's deterministic cost effectiveness results – state-transition model

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Final base case results from TA558[7]							
Routine surveillance	[redacted]	14.19	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,018
Final base case from TA558 – corrected							
Routine surveillance	[redacted]	14.34	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,235
Updated base case results							
Routine surveillance	[redacted]	14.27	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,171

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

4.1.1 Population

The population used for both the updated PSM and state transition models remains unchanged from that accepted by the committee in TA558.[7] Briefly, the population in the model includes adult patients with melanoma who have undergone complete tumour resection. The matched population of the ITC is based on the trial populations of CheckMate 238 and CA184-029 and includes patients with stage IIIA-IV disease (no evidence of disease), though for both trials there was no overlap in patients for stage IIIA (missing from CheckMate 238) and IV (CA184-029) disease. In the ITC, the company included a covariate adjustment in the meta-analysis to allow for estimation of RFS and OS for the unobserved populations. Please refer to Section 3.1.6 for further detail on the ITC methods.

4.1.2 Interventions and comparators

Since the company's original submission, the licensed dose for nivolumab has changed from a weight-based dose of 3 mg/kg once every 2 weeks, to a flat dose of either 240 mg once every 2 weeks or 480 mg once every 4 weeks. In the company's analysis, the regimen of 240 mg once every 2 weeks was implemented.

The ERG consulted with its clinical experts to ascertain if the change in dose would have an impact on clinical outcomes and also what regimen for the flat dose they would use in clinical practice. The ERG's clinical experts unanimously agreed that the dose change would have no impact on clinical outcomes and, to limit the burden on the NHS, the flat dose of 480 mg once every 4 weeks would

likely be preferred. The company supplied scenarios that explored the impact on the ICER of the change in dosing regimen, but this had minimal impact on the ICER.

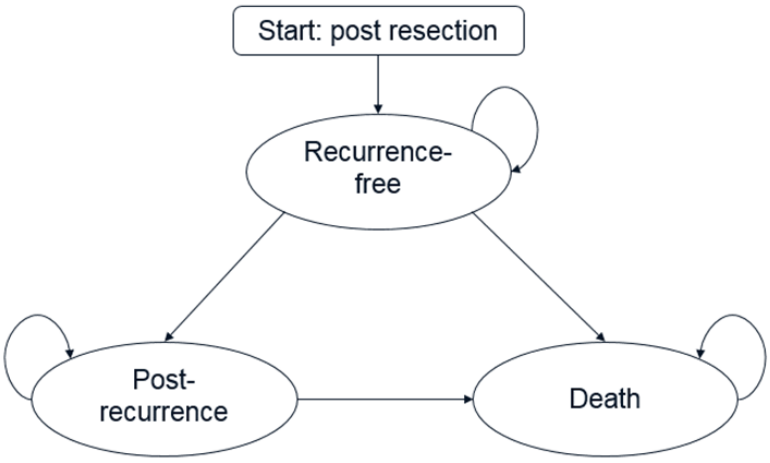
Routine surveillance is the main comparator to adjuvant nivolumab for adult patients with melanoma who have undergone complete tumour resection, which was accepted by the committee for TA558 and remains unchanged from the company's original submission.

4.1.3 Modelling approach and model structure

As mentioned previously, the final base case analyses submitted by the company for TA558 were based on an economic model that used partitioned survival analysis of RFS and OS data to inform the proportion of patients in the model health states per cycle (PSM) and a Markov model that estimated per-cycle transition probabilities between the health states (state-transition model). Both model structures were accepted by the committee as being potentially suitable for decision making and remain unchanged in the updated analysis submitted by the company.

Figure 15 presents the model structure used for both the PSM and the state-transition model. Both structures are formed on the basis of three health states defined as recurrence-free (RF), post-recurrence (PR) and death.

Figure 15. Model schematic obtained from the company's economic model



The model has a time horizon of 60 years and a cycle length of 28 days. The perspective of the analysis is the NHS and personal social services. Costs and benefits have been discounted at 3.5%.

The area of greatest uncertainty is with regards to OS. The ERG considers that the PSM facilitates an exploration of scenarios concerning OS as it implements data on OS directly (albeit immature) using

an OS ITC, whereas the state-transition model uses subsequent treatment-specific post-recurrence survival from published sources to estimate OS. As such, the ERG prefers the PSM analyses over the cost-effectiveness estimates produced by the state-transition model.

4.1.4 Treatment effectiveness

Recurrence free survival (PSM and state-transition model)

Using the later data cut for RFS from CheckMate 238, the company updated their final ITC (with ipilimumab patients in CA184-029 censored after 1 year of treatment) to produce revised parametric survival curves for use in the economic analyses and maintained their original approach as described in TA558 (please refer to Section 3.1.6.1 and Section 3.1.6.4 for further details).[14]

As per the company's original approach, the CGP method was used to weight and produce the final parametric survival curves for the PSM and state-transition model. Based on the company's re-evaluation of the survival curves, the log-logistic distribution was selected, consistent with the company's original approach and accepted by the ERG previously. The company provided a comparison of RFS estimates from the previous log-logistic curves based on the 24-month data cut from CheckMate 238 and the updated analysis (presented in Section 5.1.3, Table 31). The ERG reviewed the plots of the RFS log-logistic extrapolations from TA558 and the company's updated log-logistic extrapolation (Figure 13) and considers the results to be consistent.

As mentioned previously, methods for implementing RFS in both economic models remain unchanged. In the original analysis, the company rebased the RFS data at 12 weeks, at which point there was substantial change in hazard. For the first 12 weeks of the model, Kaplan–Meier (KM) data from the CheckMate 238 trial were used directly for the nivolumab group. For the routine surveillance group, a hazard ratio (HR) was derived by fitting a Cox proportional hazards (PHs) model to the ipilimumab groups of the CheckMate 238 and CA184-029 trials, with censoring applied at 12 weeks. The resulting HR was [redacted] and this was applied to 12-week KM data from the placebo group of the CA184-029 trial to derive the RFS estimates for RS for the first 12 weeks of the model. After 12 weeks and up to 10 years in the model, the CGP adjusted log-logistic extrapolations were implemented. Post 10 years, a HR for RFS relative to OS was implemented. The company estimated the HR by fitting a Cox PH model to digitised KM data from the Argawala *et al.* 2017 trial, which assessed interferon in the adjuvant setting.[17] The resulting HR was [redacted], which was applied to overall survival (OS) data from the American Joint Committee on Cancer version 8 registry data.[3]

In TA558, the committee stated that, "*the methodologies used to estimate recurrence-free survival after 10 years for the comparison of interest were extremely complex and relied to some extent on data sources that were potentially inappropriate*".[7] The committee's overall conclusion was that the RFS extrapolation may be reasonable but the benefit of adjuvant nivolumab over the longer term was uncertain and wanted the company to explore the most appropriate methodology to estimate long-term RFS considering the updated CheckMate 238 data as part of the CDF terms of engagement. However, the ERG considers that the company has only explored the validation of their RFS extrapolations for the 12 weeks to 10-year period, which the ERG and the committee accepted during TA558.

In response to clarification questions, the company explained that, despite having additional follow-up for RFS (54-months), there is still uncertainty around the long-term estimates and whether it is appropriate for the trial RFS to be extrapolated over a 60-year time horizon. As such, the company stated that it was more conservative to maintain their original approach using a HR applied to registry data, but supplied a scenario using the log-logistic extrapolation for the remainder of the model time horizon after 12 weeks, which reduced the ICER from [redacted] to [redacted] for the PSM and from [redacted] to [redacted] for the state-transition model. Given the company's justification, the ERG agrees that their base case approach is more conservative and that RFS, even though RFS data from CheckMate 238 are based 54-months of follow-up, has only [redacted] for nivolumab arm and so extrapolations of these data over a longer time horizon may not be robust.

Overall survival (PSM)

As part of the updated analysis, the company produced an OS ITC using PLD meta-regression for nivolumab compared with routine surveillance, with ipilimumab as the common comparator between CheckMate 238 and CA184-029. Unlike the ITC for RFS, ipilimumab data from CA184-029 were not censored for patients on treatment beyond 1 year. Please refer to Section 3.1.6 for further details of the methodology and results of the OS ITC.

The company selected the generalised gamma distribution, but recognised that for both nivolumab and routine surveillance, this distribution produced optimistic estimates. As with RFS, the company adjusted the curves using the CGP method. Figure 5 presents the CGP-adjusted generalised gamma survival curves for nivolumab and routine surveillance and Table 20 in Section 5.1.3 presents a validation of the company's OS estimates compared with real world data. One of the ERG's clinical

experts considered that 10-year survival rates for routine surveillance and nivolumab would be 55% and 65%, [redacted]. However, it should be noted that even though the OS ITC analysis uses the latest data cut from 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.

The CGP generalised gamma survival curves for both arms of the model are implemented for the first 10 years of the model, after which point long-term estimates of survival for both arms of the model are derived from the American Joint Committee on Cancer version 8 registry data.[3]

Appropriate modelling of OS for the routine surveillance arm has been a key issue in determining the cost-effectiveness of adjuvant nivolumab. In TA558, clinical experts considered that OS from the placebo arm of CA184-029 does not reflect the current survival outcomes for routine surveillance patients due to advances in the subsequent treatment pathway. Furthermore, the recommendations the ERG made in TA558 to help resolve the issue of modelling OS, such as using mature data from CheckMate238 and Keynote 054, a trial evaluating ad juvant pembrolizumab versus placebo in patients with resected high-risk stage III melanoma (which will provide recent data for patients on placebo), for modelling survival have not been possible to implement as they are currently unavailable.[14] As such, through scenarios requested during the clarification stage (described below), the ERG has sought to explore different assumptions around OS that predominantly adjust the estimates for the routine surveillance arm of the PSM model.

Ipilimumab patients from CA184-029 are censored after 1 year of treatment

As described in Section 3.1.6.3, an OS ITC analysis in which ipilimumab patients from CA184-029 are censored after 1 year of treatment was requested by the ERG to ensure that RFS and OS outcomes are aligned in the model. The company stated that it is inappropriate to informatively censor ipilimumab patients who are on treatment for more than 1 year as these patients are likely to have the best prognosis at 1 year as they are able to continue treatment. Additionally, as treatment is given until disease recurrence, OS patients who are censored are more likely to be in the recurrence-free state. As such, the informative censoring is likely to favour routine surveillance. The ERG agrees that informative censoring may introduce the bias described by the company. However, in the

company's base case analysis, by not censoring patients still receiving ipilimumab at 1 year, the same potential bias favours nivolumab. As committee has accepted that OS data for routine surveillance from CA184-029 is outdated, the ERG prefers to make this adjustment in order to mitigate this to some degree. As such, using an analysis that maintains consistency in methods for estimating RFS and OS but may favour the routine surveillance arm could be considered conservative and so should minimise the risk of overestimating the treatment effect of nivolumab.

The hazard of death for routine surveillance is equal to nivolumab using different time points

Scenarios assuming the hazard of death for routine surveillance is equal to the hazard of death estimated from the CGP adjusted OS ITC survival curve for nivolumab after a) 3 years, b) 2 years and c) from baseline were requested by the ERG at clarification stage and were provided by the company in their clarification response. That is, up to the cut-off point, the CGP ITC OS survival curves for nivolumab and routine surveillance are implemented in the model, but after the cut-off point the hazard of death is the same for both arms and reflects the hazards for nivolumab patients.

The 3- and 2-year thresholds were chosen by the ERG as surrogates for potential re-challenge by immunotherapies. That is, as discussed in Section 3.1.4, clinical experts informed the ERG that patients receiving adjuvant nivolumab would not be re-challenged until 2 years after completing treatment (or at the earliest 1 year after completing treatment). In theory, this means that after a maximum of 1 year of treatment with adjuvant nivolumab, patients between 2 and 3 years could be re-challenged with a PD-1 inhibitor and so potentially the therapies received from this point onwards could be considered comparable between the nivolumab arm and the routine surveillance arm.

For each scenario, subsequent treatments for nivolumab reflect the nivolumab arm of CheckMate 238 (where re-challenge with an anti-PD-1 treatment may happen within 2 years) and for routine surveillance reflect the ipilimumab arm of CheckMate 238 up until the cut-off point where routine surveillance and nivolumab hazard of death is equal, after which subsequent treatment data for the nivolumab arm of CheckMate 238 are used.

In response to the request for the scenarios, the company stated that uncertainty around the impact of subsequent treatment on OS for routine surveillance has been appropriately modelled in the state-transition model. Furthermore, for scenario (c), the company stated there is no evidence to suggest that adjuvant nivolumab has no survival benefit compared to patients on routine surveillance and the scenario is clinically implausible. The clinical experts for TA558 suggested that

even though OS data are immature, they expect to see RFS benefit to be translated to some extent into an OS benefit.[7] However, the ERG considers that scenario (c) is relevant for consideration if the main benefit of adjuvant nivolumab is the increase in RFS rather than OS, as it is potentially confounded by the impact of subsequent treatments but the ERG acknowledges this is a conservative assumption in relation to clinical expert opinion.

The company also provided a range of scenarios combining the OS ITC in which ipilimumab patients are censored after 1 year of treatment and varying the time point at which the hazard of death is equal for nivolumab and routine surveillance. All ERG requested scenarios are presented in Table 20 along with the company's base case ICER. A detailed breakdown of the scenario results is presented in Table 29, Section 5.1.2. The ERG acknowledges that the scenarios exploring the hazard of death are based on strong assumptions but considers that they provide a basis for a plausible range of ICERs for the committee to consider in lieu of mature OS data from either CheckMate 238 or Keynote 054.

Table 20. Overall survival scenario results

Scenario	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	[redacted]	**14,301**
One-year censoring of ipilimumab OS patients	[redacted]	[redacted]	[redacted]	17,404
Equal hazard of death – three years	[redacted]	[redacted]	[redacted]	22,487
Equal hazard of death – two years	[redacted]	[redacted]	[redacted]	28,809
OS censoring & Equal hazard of death – three years	[redacted]	[redacted]	[redacted]	29,011
OS censoring & Equal hazard of death – two years	[redacted]	[redacted]	[redacted]	37,371
Equal hazard of death from baseline (RFS benefit only)	[redacted]	[redacted]	[redacted]	75,489
OS censoring & equal hazard of death from baseline (RFS benefit only)	[redacted]	[redacted]	[redacted]	75,562

Abbreviations: ICER, incremental cost effectiveness ratio; LY, life-year; OS, overall survival; QALY, quality-adjusted life-year.

Overall survival (state-transition model)

In the company's updated analysis, no changes in sources used to estimate post-recurrence survival based on individual subsequent treatments have been made, only changes in the proportions of patients on each individual subsequent treatment based on the later data cut from CheckMate 238, resulting in a updated base case ICER that is not dissimilar to what was presented in the final analyses for TA558.[14]

As mentioned previously, the area of greatest uncertainty is with regards to OS. Mature OS data from CheckMate 238 would have helped to address the uncertainty around post-recurrence survival in the state-transition model, as it was acknowledged in TA558 that the pathway is complex and it is unknown how adjuvant treatment impacts the efficacy of metastatic treatment.[7]

The ERG prefers the PSM analyses of OS as it implements data from CheckMate 238 in an OS ITC (albeit immature), making the most use of the trial data and facilitates an exploration of scenarios concerning OS, which are not possible in the state transition model.

4.1.5 Subsequent treatments

For the revised analysis, the implementation of the subsequent therapy data is unchanged from the company's final analyses submitted after the first appraisal committee meeting.[7] However, the company has updated the models with the latest subsequent treatment data from the January 2020 data cut from CheckMate 238, presented in Section 3.1.3, Table 14.

In the company's original economic analysis (PSM and state-transition model), subsequent treatment data informing the analyses were from Checkmate 238 (please refer to Section 3.1.3 for more detail). The company assumed that the ipilimumab group of the trial reflects the proportions of subsequent treatments routine surveillance. For the PSM, nivolumab data from CheckMate 238 was used to reflect the proportions of subsequent treatments after nivolumab. For the state-transition model, for nivolumab, re-challenge with a PD1 inhibitor was assumed to occur if recurrence happened after 2 years of treatment with adjuvant nivolumab. As such, subsequent therapy data for the nivolumab cohort of CheckMate 238 was used for the period before re-challenge and usage of any PD1 inhibitor treatments, that is, nivolumab, nivolumab plus ipilimumab, and pembrolizumab would have costs (applicable in both models) and survival rates (only applicable in the state-transition model) determined by ipilimumab data for the duration of the set threshold period. After the 2-year threshold, subsequent treatment usage was the same as the routine surveillance group, that is, subsequent treatment data from the ipilimumab group of the CheckMate 238 trial.

In the PSM and state-transition model, subsequent treatment data were stratified by site of recurrence(local/regional and distant). As mentioned in Section 3.1.3, the company included patients who first have a local/regional recurrence but then have a distant recurrence in both groups and any records after the distant recurrence were included in the distant recurrence group.

For the PSM, the updated subsequent treatment data only affected the estimation of costs of subsequent treatment for nivolumab and routine surveillance. Costs of the individual subsequent treatments remain unchanged and can be found in TA558.[14] Table 21 presents the original and updated costs of subsequent treatment used in the PSM.

Table 21. Subsequent treatment costs in the partitioned survival model

Recurrence type	Nivolumab	Routine surveillance
Final base case – TA558		
Local/regional	[redacted]	[redacted]
Distant	[redacted]	[redacted]
Updated base case		
Local/regional	[redacted]	[redacted]
Distant	[redacted]	[redacted]

In the final appraisal determination (FAD) document, the committee was concerned about the lower use of immunotherapy than might be expected in clinical practice, and as a consequence felt that subsequent treatment costs for nivolumab were too low.[7]

As mentioned in Section 3.1.3, based on the updated data cut from CheckMate 238, the ERG's clinical experts reported that generally the subsequent treatments are reasonable, although a few of the less frequently used treatments in CheckMate 238 are never or very rarely used in UK clinical practice, for example, cisplatin, interferon and interleukin. Furthermore, the costs of subsequent therapy for local/regional recurrence are similar for nivolumab and routine surveillance, but distant recurrences are more costly in the routine surveillance arm due to the greater use of pembrolizumab (see Table 14).

For the state-transition model, the update in the proportion of patients on different subsequent treatments for each arm of the model only affects the estimation of post-recurrence survival, but the underlying survival data used for each treatment remains unchanged from the company's original analysis. In the FAD, it is noted that with regards to subsequent therapy usage and post-recurrence survival, particularly around re-challenge with nivolumab, "*the committee recognised the company's efforts in trying to address these issues. It also accepted the remaining uncertainty about which treatments people would have if their disease recurred after adjuvant nivolumab, together with the lack of evidence to support the assumption that giving PD-1 inhibitors for a second time, 2 years after adjuvant nivolumab, would be equally effective as when these treatments are used for the first time in the metastatic setting (as assumed in the model). The committee concluded that*

neither the company's nor the ERG's analyses fully captured the true complexity of the post-recurrence treatment pathway".[7]

As part of the CDF review, data on subsequent treatments was collected through the Systemic Anti-Cancer Therapy (SACT) database. However, out of 284 patients, only 25 patients received subsequent treatment. The company deemed the SACT data too immature for use in the economic analysis (please refer to Section 3.1.5.2 for more details).

In its response to the company comments on the appraisal consultation document (ACD), the ERG recommended that to account for the uncertainty around subsequent treatments and the influence on OS, mature OS data from the CheckMate 238 trial would be needed to demonstrate a benefit over ipilimumab and would facilitate a robust comparison between the CheckMate 238 trial (for nivolumab) and the Keynote 054 trial (for routine surveillance), in which Keynote 054 trial would include currently available post-recurrence subsequent treatments. However, OS data from CheckMate 238 are immature and OS data from Keynote 054 are unavailable for comparison. As such, the ERG's uncertainty around the impact of subsequent treatments on OS remains unchanged from TA558.[7, 14]

4.1.6 Adverse events

Adverse events (AE) included in the model remain unchanged from the company's original analysis. The company included immune-related AEs of any grade, diarrhoea of grade 2 or above, and any other AE of grade 3 or above. AE data from CheckMate 238 was used for the nivolumab arm and CA184-029 placebo data adjusted for the difference in risks across the ipilimumab arms of both trials was used for routine surveillance.

In the original ERG report, the ERG was concerned that the method of adjustment AE risks for the routine surveillance group was incorrect, but concluded that the resulting estimates were not implausible and similar to the unadjusted placebo data from CA184-029 and thus the impact on the ICER was likely to be minimal. Furthermore, AEs are not a primary driver of cost-effectiveness in the model.

4.1.7 Health-related quality of life

Utilities applied in the both economic models remain unchanged from the company's original submission and were accepted by the committee in TA558.[14] EQ-5D-3L data were obtained directly

from CheckMate 238 and used in both models for nivolumab and routine surveillance. Utility values for the recurrence-free and post recurrence health states for both arms of the model were 0.86 and 0.77, respectively. Disutilities for AEs were also included and were estimated from published data sources.

4.1.8 Resource use and costs

In the company's updated base case analysis, three cost categories have been revised. The updated categories include drug acquisition and administration cost for nivolumab as a result of the licensed dose change (discussed below), and subsequent therapy costs based on the later data cut from CheckMate 238 (discussed in Section 4.1.5). All other resource use and costs remain unchanged from the company's original submission and were accepted by the committee in TA558.[14] The cost price year reflects 2016/17 as per the company's original submission.

Drug acquisition and administration cost

The licensed dose for nivolumab has changed to a flat dose of either 240 mg once every 2 weeks or 480 mg once every 4 weeks. Previously, the dose was based on weight and was 3 mg/kg once every 2 weeks.[14, 15] Table 22 presents the unit costs of nivolumab by vial size based on the list price and the company's PAS, which is a simple discount of *** on the list price.

For the base case analysis, the company has assumed the regimen for the flat dose to be 240 mg once every 2 weeks, thus costs are based on the 24 ml vial. However, the ERG's clinical experts were unanimous in their agreement that, in UK clinical practice, nivolumab would be given as a flat dose of 480 mg once every 4 weeks. As such, during the clarification stage, the company updated their base case to reflect the ERG's clinical expert view on the regimen, though this had minimal impact on the ICERs from the PSM and state-transition model.

Table 22. Nivolumab unit costs

Nivolumab	4ml vial	10ml vial	24ml vial
Dose per vial (10mg/ml)	40mg	100mg	240mg
Unit cost (list price)	£439.00	£1,097.00	£2,633.00
Unit cost (PAS)	[redacted]	[redacted]	[redacted]

Abbreviations: mg, milligram; ml, millilitre; PAS, patient access scheme.

The company state that, as the dose is no longer weight-based, the administration cost should reflect the simpler dosing and as such has updated the NHS reference cost code to SB12Z: 'Deliver

Simple Parenteral Chemotherapy at First Attendance' (£259.76), from the previous cost code, which was SB13Z: ''Deliver more Complex Parenteral Chemotherapy at First Attendance' (£299.68).[16]

However, for the first appraisal committee meeting of this topic, NHS England made a submission to NICE that stated, "*the NHS England chemotherapy delivery tariff in 2017/18 for nivolumab is coded as SB13Z*".[14] No mention was made for the chosen tariff by NHS England as related to weight-based dosing, but specifically for nivolumab as an adjuvant treatment. The company provided a scenario that explored the use of the code SB13Z for the revised base case analyses, but this had minimal impact on the ICER. Furthermore, in their clarification response, the company explained that the administration cost applied in their base case reflects the flat dose and is in line with the HRG cost code list in the NHS OPCS-4 coding standards for chemotherapy 2017-2018, which upon review, the ERG agrees is correct.[18]

5 Cost effectiveness results

5.1 Company's cost effectiveness results

The company's updated base case results for the partitioned survival model (PSM) and state-transition model as presented in Table 23 and Table 24, respectively.

Table 23. Company's deterministic cost effectiveness results – partitioned survival model

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	18.65	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,301

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 24. Company's deterministic cost effectiveness results – state-transition model

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	14.27	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,171

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

5.1.1 Company's sensitivity analyses

Probabilistic sensitivity analysis

The company provided a PSA based on 1,000 samples, to assess the impact of parameter uncertainty when all parameters are varied simultaneously in the economic model. The results of the PSA are given in Table 25 and Table 26, and cost effectiveness planes for the PSM and state-transition model are presented in Figure 16 and Figure 17, respectively. Based on a willingness-to-pay threshold of £30,000 per QALY gained, the probability of nivolumab being the most cost-effective treatment option was [redacted] in the PSM and [redacted] with the state-transition model.

Table 25. Company's probabilistic cost effectiveness results – partitioned survival model (Reproduced from company response to clarification, Table 28)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	19.28	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,566

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 26. Company's probabilistic cost effectiveness results – state-transition model (Reproduced from company response to clarification, Table 28)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	14.46	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,954

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Figure 16. Cost-effectiveness plane – partitioned survival model (Reproduced from company response to clarification, Figure 33)

Figure 17. Cost-effectiveness plane – state-transition model (Reproduced from company response to clarification, Figure 34)

One-way sensitivity analysis

The company also conducted a range of one-way sensitivity analyses to assess the impact of varying each parameter individually. The results of these are shown in the tornado plot in Figure 18 for the PSM and Figure 19 for the state-transition model.

Figure 18. Tornado plot – partitioned survival model (Reproduced from company response to clarification, Figure 35)

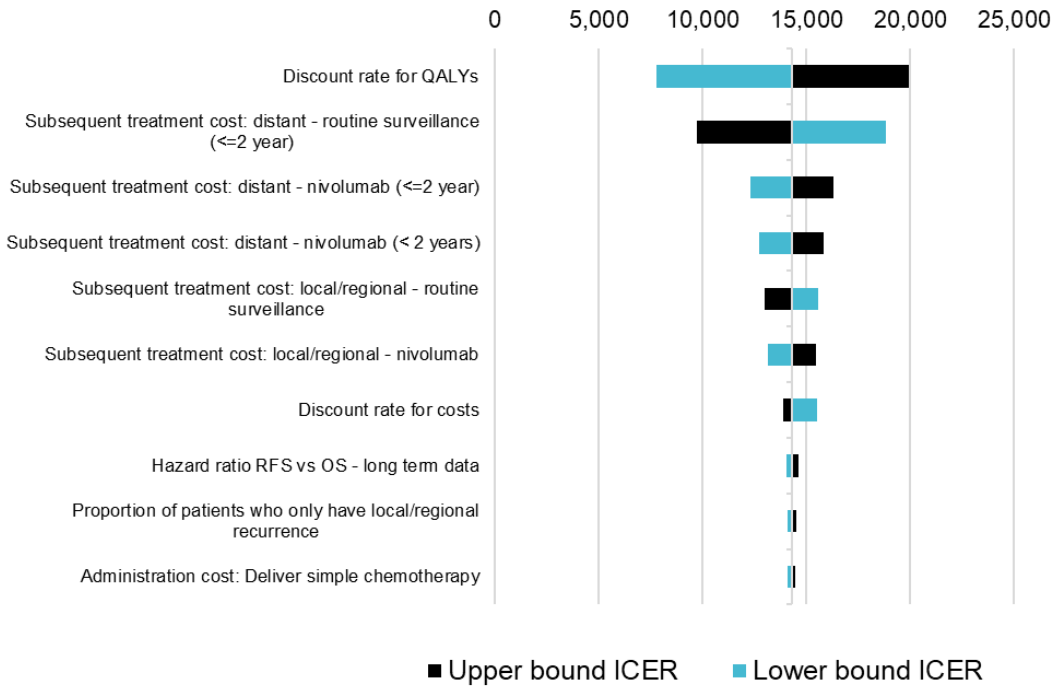
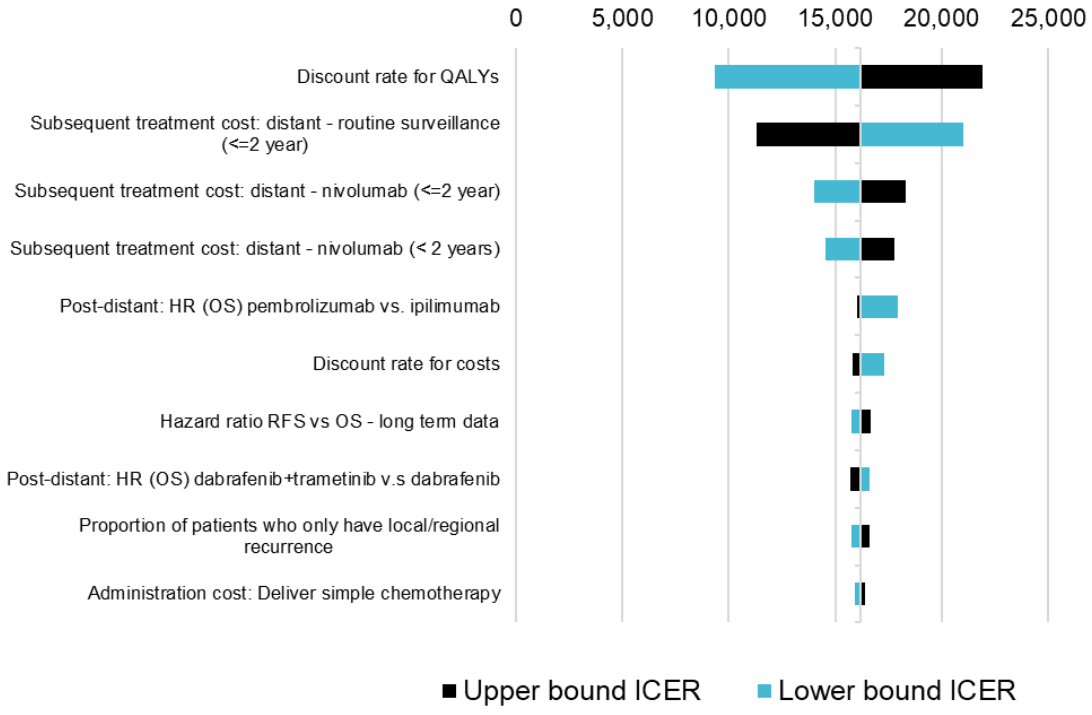


Figure 19. Tornado plot – state-transition model (Reproduced from company response to clarification, Figure 36)



5.1.2 *Company scenario analyses*

Results of key scenario analyses conducted by the company in the PSM and state transition model are presented in Table 27 and Table 28, respectively.

Table 27. Company's scenario analyses - partitioned survival model (Reproduced from company response to clarification, Table 29)

Parameter	Base case	Scenario	Incremental results vs Routine surveillance			ICER (£/QALY)
			Costs (£)	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	14,301
Population	Patient characteristics: (CA184-029 and CheckMate 238) Stage proportions: CA184-029 & CheckMate 238 adjusted RFS for nivolumab and routine surveillance: ITC (CA184-029 and CheckMate 238)	CheckMate 238 CheckMate 238 Nivo: CheckMate 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	12,504
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	13,648

Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	14,827
		50 years	[redacted]	[redacted]	[redacted]	14,403
Nivolumab dosing	240 Q2W	3 mg/kg Q2W	[redacted]	[redacted]	[redacted]	14,935
		240 mg Q2W	[redacted]	[redacted]	[redacted]	14,195
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	14,195
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	14,199
Nivolumab administration cost reference	SB12Z	SB13Z	[redacted]	[redacted]	[redacted]	14,301
Subsequent treatment (local/regional)	CheckMate 238	CA184-029	[redacted]	[redacted]	[redacted]	14,304
Nivolumab subsequent treatment (distant)	CheckMate 238	SACT data	[redacted]	[redacted]	[redacted]	11,520
RFS ITC method	ITC 48-month DBL (subgroup 1-year ipi treatment in 029)	ITC 48-month DBL	[redacted]	[redacted]	[redacted]	7,726
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	18,545
		Gompertz	[redacted]	[redacted]	[redacted]	14,426
		Log-normal	[redacted]	[redacted]	[redacted]	13,545
		Generalised gamma	[redacted]	[redacted]	[redacted]	13,933
		Weibull	[redacted]	[redacted]	[redacted]	14,938
Long-term survival adjustment	Gershenwald, applied after10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	12,790
		No long-term adjustment to RFS	[redacted]	[redacted]	[redacted]	13,515
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	18,458
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	12,958
		Balch, 5 years	[redacted]	[redacted]	[redacted]	26,282
		Balch, 10 years	[redacted]	[redacted]	[redacted]	17,331
		Balch, 20 years	[redacted]	[redacted]	[redacted]	13,848
		OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	14,655
		Balch, OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	17,932
OS distribution (all)	Generalised gamma	Exponential*	[redacted]	[redacted]	[redacted]	12,706
		Gompertz*	[redacted]	[redacted]	[redacted]	29,962
		Log-normal	[redacted]	[redacted]	[redacted]	14,646
		Log-logistic	[redacted]	[redacted]	[redacted]	15,007
		Weibull	[redacted]	[redacted]	[redacted]	15,172
Long-term-data curve selection	Gershenwald, Generalised gamma	Balch, Exponential*	[redacted]	[redacted]	[redacted]	24,581
		Balch, Generalised gamma	[redacted]	[redacted]	[redacted]	17,331
		Balch, Gompertz	[redacted]	[redacted]	[redacted]	14,104

		Balch, log-normal	[redacted]	[redacted]	[redacted]	19,971
		Balch, log-logistic	[redacted]	[redacted]	[redacted]	19,933
		Balch, Weibull*	[redacted]	[redacted]	[redacted]	21,361
		Exponential*	[redacted]	[redacted]	[redacted]	18,142
		Gompertz	[redacted]	[redacted]	[redacted]	13,723
		Log-normal	[redacted]	[redacted]	[redacted]	15,903
		Log-logistic	[redacted]	[redacted]	[redacted]	16,315
		Weibull*	[redacted]	[redacted]	[redacted]	17,104
End-of-life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	14,186
Utilities source	Observed EQ-5D Apply same utility to across treatments Separate stage covariate Include AE disutilities: yes	Include AE disutilities: No	[redacted]	[redacted]	[redacted]	14,276
		Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	14,439
		Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	14,464
		Middleton et al.	[redacted]	[redacted]	[redacted]	11,747
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	14,517
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	14,685
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	14,301
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	14,464
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	14,448

Note: The curve fits that are indicated (*) are those that fit the data poorly.

Abbreviations: AE, adverse event; DBL, database lock; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; ipi, ipilimumab; ITC, indirect treatment comparison; LY, life year; nivo, nivolumab; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival; SACT, Systemic Anti-Cancer Therapy.

Table 28. Company's scenario analyses – state-transition model (Reproduced from company response to clarification, Table 30)

Parameter	Base case	Scenario	Incremental results vs Routine surveillance			ICER (£/QALY)
			Costs (£)	Lys	QALYs	
Base case			[redacted]	[redacted]	[redacted]	16,171
Population	Patient characteristics: (CA184-029 and CheckMate 238) Stage proportions: CA184-029 & CheckMate 238 adjusted	CheckMate 238 CheckMate 238 Nivo: CheckMate 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	13,421

	RFS for nivolumab and routine surveillance: ITC (CA184-029 and CheckMate 238)					
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	15,608
Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	16,572
		50 years	[redacted]	[redacted]	[redacted]	16,254
Nivolumab dosing	240 Q2W	3 mg/kg Q2W	[redacted]	[redacted]	[redacted]	17,919
		240 mg Q2W	[redacted]	[redacted]	[redacted]	17,120
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	17,120
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	16,171
Nivolumab administration cost reference	SB12Z	SB13Z	[redacted]	[redacted]	[redacted]	16,173
Subsequent treatment (local/regional)	CheckMate 238	CA184-029	[redacted]	[redacted]	[redacted]	16,160
Nivolumab subsequent treatment (distant)	CheckMate 238	SACT data	[redacted]	[redacted]	[redacted]	9,394
		Wilmington	[redacted]	[redacted]	[redacted]	10,772
		IPSOS	[redacted]	[redacted]	[redacted]	11,837
RFS ITC method	ITC 48-month DBL (subgroup 1-year ipi treatment in CA184-029)	ITC 48-month DBL	[redacted]	[redacted]	[redacted]	14,826
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	30,887
		Gompertz	[redacted]	[redacted]	[redacted]	16,889
		Log-normal	[redacted]	[redacted]	[redacted]	14,576
		Generalised gamma	[redacted]	[redacted]	[redacted]	15,419
		Weibull	[redacted]	[redacted]	[redacted]	17,868
Long-term survival adjustment	Gershenwald, applied after 10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	15,017
		No long-term adjustment to RFS	[redacted]	[redacted]	[redacted]	15,004
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	20,037
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	15,105
		Balch, 5 years	[redacted]	[redacted]	[redacted]	28,202
		Balch, 10 years	[redacted]	[redacted]	[redacted]	19,484
		Balch, 20 years	[redacted]	[redacted]	[redacted]	16,019
		OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	16,725
		Balch, OS/RFS HR from CA184-029 trial	[redacted]	[redacted]	[redacted]	20,683
Long-term-data curve selection	Gershenwald, Generalised gamma	Balch, exponential*	[redacted]	[redacted]	[redacted]	23,573
		Balch, Generalised gamma	[redacted]	[redacted]	[redacted]	19,484

		Balch, Gompertz	[redacted]	[redacted]	[redacted]	15,701
		Balch, log-normal	[redacted]	[redacted]	[redacted]	21,504
		Balch, log-logistic	[redacted]	[redacted]	[redacted]	21,495
		Balch, Weibull*	[redacted]	[redacted]	[redacted]	22,185
		Exponential*	[redacted]	[redacted]	[redacted]	20,221
		Gompertz	[redacted]	[redacted]	[redacted]	15,140
		Log-normal	[redacted]	[redacted]	[redacted]	18,152
		Log-logistic	[redacted]	[redacted]	[redacted]	18,583
		Weibull*	[redacted]	[redacted]	[redacted]	19,330
End-of-life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	16,008
Utilities source	Observed EQ-5D Apply same utility to across treatments Separate stage covariate Include AE disutilities: Yes	Include AE disutilities: No	[redacted]	[redacted]	[redacted]	16,141
		Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	16,306
		Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	16,337
		Middleton et al.	[redacted]	[redacted]	[redacted]	13,819
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	16,334
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	16,503
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	16,170
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	16,337
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	16,332
Data used for Markov model curves	CheckMate 067 and other sources	Metastatic NMA	[redacted]	[redacted]	[redacted]	13,247
Post-distant long-term dataset	Balch 2009	Balch 2001	[redacted]	[redacted]	[redacted]	15,638
Dacarbazine hazard ratio applied	HR (OS) vemurafenib vs dacarbazine	HR (OS) ipi vs gp100	[redacted]	[redacted]	[redacted]	16,550
OS HR pembrolizumab vs ipilimumab source	Bucher comparison	KEYNOTE 006	[redacted]	[redacted]	[redacted]	16,746
Re-challenge scenario	Yes	No	[redacted]	[redacted]	[redacted]	14,979
Re-challenge scenario time-point	2.00	0.50	[redacted]	[redacted]	[redacted]	15,561
		1.00	[redacted]	[redacted]	[redacted]	15,861
		60.00	[redacted]	[redacted]	[redacted]	17,125
Note: The curve fits that are indicated (*) are those that fit the data poorly.						

Abbreviations: AE, adverse event; DBL, database lock; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; ipi, ipilimumab; LY, life year; nivo, nivolumab; NMA, network meta-analysis; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival; SACT, Systemic Anti-Cancer Therapy.

In their clarification response, the company provided a number of scenarios upon the request of the ERG, presented in Table 29 for the PSM and Table 30 for the state-transition model.

Table 29. ERG Scenarios requested during the clarification stage – partitioned survival model

	Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
0	**Company base case**							
	Routine surveillance	[redacted]	17.83	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,301
1	**One-year censoring of OS ipilimumab patients in CA184-029 (B2)**							
	Routine surveillance	[redacted]	19.29	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,404
2a	**Hazard of death equal for nivolumab and routine surveillance after two years (B3a)**							
	Routine surveillance	[redacted]	21.00	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,809
2b	**Hazard of death equal for nivolumab and routine surveillance after three years (B3b)**							
	Routine surveillance	[redacted]	20.39	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,487
2c	**Hazard of death equal for nivolumab and routine surveillance from baseline (B3c)**							
	Routine surveillance	[redacted]	22.26	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	75,489
3a	**Scenario 1 and 2a**							
	Routine surveillance	[redacted]	21.32	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,371
3b	**Scenario 1 and 2b**							
	Routine surveillance	[redacted]	20.85	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,011
3c	**Scenario 1 and 2c**							
	Routine surveillance	[redacted]	22.11	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	75,562
4	**RFS ITC for entire model time horizon post 12 weeks (B4)**							
	Routine surveillance	[redacted]	18.65	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,515

5	**OS ITC for entire model time horizon (B5)**							
	Routine surveillance	[redacted]	17.77	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,790

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 30. ERG Scenarios requested during the clarification stage – state-transition model

	Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
0	**Company base case**							
	Routine surveillance	[redacted]	14.27	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,171
1	**RFS ITC for entire model time horizon post 12 weeks (B4)**							
	Routine surveillance	[redacted]	13.91	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,004
2	**OS ITC for entire model time horizon (B5)**							
	Routine surveillance	[redacted]	13.67	[redacted]	-	-	-	-
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,017

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

5.1.3 *Model validation and face validity check*

The company performed internal validation, as well as using external sources of data to validate projections of outcomes. The company performed internal validation by comparing the model outcomes against the CheckMate 238 and CA184–029 trial outcomes. These are summarised for RFS in Table 31, and for OS in CA184-029 in Table 32.

Table 31. Recurrence-free survival – Trial vs state-transition model estimates (Reproduced from CS, Table 40)

	Median (years)	Year 1	Year 2	Year 3	Year 4
Routine surveillance – CA184-029					
KM RFS	1.43	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – updated analysis*	1.69	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – original analysis*	1.46	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab – CheckMate 238					
KM RFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – updated analysis**	4.37	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – original analysis**	4.29	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Trial data medians were sourced from trial clinical study report.
* Patient characteristics were based on CA184-029.
** Patient characteristics were based on CheckMate 238.
Abbreviations: KM, Kaplan–Meier; RFS, recurrence-free survival; NA, not available.

Table 32. Overall survival – Trial vs PSM estimates (Reproduced from CS, Table 41)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year7
CA84-029							
Trial '029 OS – placebo (KM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – routine surveillance*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 238							
Trial CheckMate 238 OS – nivolumab (KM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model RFS – nivolumab**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: * Patient characteristics were based on CA184-029.
** Patient characteristics were based on CheckMate 238.
Abbreviations: KM, Kaplan–Meier; OS, overall survival.

The company performed external validation using long term OS data for nivolumab and routine surveillance from the AJCC 7th edition data (Balch *et al.* 2009) and the AJCC 8th edition data (Gershenwald *et al.* 2017).[3, 19] A comparison of the base case model outputs for the PSM and state-transition model against various subgroups from these two sources are shown in Table 33 and Table 34, respectively.

Furthermore, the company compared extrapolated RFS and OS curves for nivolumab and routine surveillance against KM data from KEYNOTE-054 (RFS only) and COMBI-AD (RFS and OS) and are presented in Figure 41 and Figure 42 of the company's CDF submission.

Table 33. External validation of overall survival – PSM (Reproduced from CS, Table 42)

Source	Year 1	Year 2	Year 5	Year 10	Year 15
Balch 2009 Stage IIIA	97.8%	91.6%	77.3%	67.7%	66.5%
Balch 2009 Stage IIIB	95.5%	83.0%	58.4%	42.6%	37.1%
Balch 2009 Stage IIIC	85.5%	64.5%	40.3%	25.3%	22.6%
Balch 2009 Stage III (weighted) – AJCC 7v	**89.0%**	**74.4%**	**52.9%**	**38.9%**	**32.1%**
Balch 2009 Stage IV abnormal LDH	33.3%	19.4%	9.7%	7.5%	NA
Balch 2009 Stage IV normal LDH	69.4%	44.1%	24.2%	18.8%	NA
Gershenwald 2017 Stage III – AJCC v8	**97.8%**	**91.3%**	**79.3%**	**71.7%**	**NA**
Nivolumab OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Routine surveillance OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AJCC, American Joint Committee on Cancer Staging Manual; LDH, lactate dehydrogenase; NA, not available; OS, overall survival.

Table 34. External validation of overall survival – state-transition model (Reproduced from CS, Table 43)

Source	Year 1	Year 2	Year 5	Year 10	Year 15
Balch 2009 Stage IIIA	97.8%	91.6%	77.3%	67.7%	66.5%
Balch 2009 Stage IIIB	95.5%	83.0%	58.4%	42.6%	37.1%

Balch 2009 Stage IIIC	85.5%	64.5%	40.3%	25.3%	22.6%
Balch 2009 Stage III (weighted) – AJCC 7v	**89.0%**	**74.4%**	**52.9%**	**38.9%**	**32.1%**
Balch 2009 Stage IV abnormal LDH	33.3%	19.4%	9.7%	7.5%	NA
Balch 2009 Stage IV normal LDH	69.4%	44.1%	24.2%	18.8%	NA
Gershenwald 2017 Stage III – AJCC v8	**97.8%**	**91.3%**	**79.3%**	**71.7%**	**NA**
Nivolumab OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Routine surveillance OS (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AJCC, American Joint Committee on Cancer Staging Manual; LDH, lactate dehydrogenase; NA, not available; OS, overall survival.

6 Additional economic analysis undertaken by the ERG

6.1 Model corrections

No model corrections were identified by the Evidence Review Group (ERG).

6.2 Exploratory and sensitivity analyses undertaken by the ERG

The company provided extensive sensitivity and scenario analyses for both the partitioned survival model (PSM) and the state-transition model. Furthermore, the ERG requested a number of scenarios during the clarification stage, which the company provided. Results of the key ERG requested scenarios can be found in Section 5.1.2, Table 29 for the PSM and Table 30 for the state-transition model.

6.3 ERG preferred assumptions

One of the key uncertainties expected to be resolved during the time nivolumab was in the Cancer Drugs Fund (CDF) was overall survival (OS). While the company has provided an update to OS from CheckMate 238, the data is still considered immature. The latest data cut of OS from CheckMate 238 is only used in the PSM, and, as such, the PSM is the only model that allows scenarios around OS to be performed to help inform committee. Thus, the ERG does not consider the state-transition model to help resolve the uncertainties relating to OS.

Due to the uncertainties around OS estimates, the ERG presents a range of deterministic incremental cost effectiveness ratios (ICERs), varying the assumptions around OS in the PSM model for the committee to consider and considers that the true ICER falls within this range (Table 35). The range of ICERs are based on the following assumptions:

- Censoring of ipilimumab patients in CA184-029 on treatment after 1 year for the OS indirect treatment comparison (ITC) – Section 4.1.4.
- Assuming the hazard of death and subsequent treatments for patients on routine surveillance is the same as nivolumab patients after 3 years – Section 4.1.4.
- Assuming the hazard of death and subsequent treatments for patients on routine surveillance is the same as nivolumab patients after 2 years – Section 4.1.4.

The ICER range incorporates the company's patient access scheme (PAS) simple discount of [redacted]. A limitation of the probabilistic sensitivity analysis (PSA) is that it takes several hours to run when using

a larger sample size and due to paucity of time, a PSA range of ICERs could not be presented. However, the ERG ran a test of the PSA for the scenario of equal hazard of death after 3 years and found that the PSA ICER was not dissimilar to the deterministic ICER.

Table 35. ERG's plausible range of deterministic ICERs

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	-	[redacted]	[redacted]	**14,301**
Equal hazard of death – three years	4.1.4	[redacted]	[redacted]	22,487
Equal hazard of death – two years	4.1.4	[redacted]	[redacted]	28,809
One-year censoring of ipilimumab OS patients & equal hazard of death – three years	4.1.4	[redacted]	[redacted]	29,011
One-year censoring of ipilimumab OS patients & equal hazard of death – two years	4.1.4	[redacted]	[redacted]	37,371

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year.

6.4 Conclusions of the cost effectiveness section

Between November 2018 and January 2020, adjuvant nivolumab treatment of completely resected melanoma with lymph node involvement or metastatic disease was made available through the CDF to enable further data collection from CheckMate 238 to be obtained by the company, as well as allow UK-based subsequent treatment data to be collected through Systemic Anti-Cancer Therapy (SACT) database.

In their CDF submission, the company updated their final PSM and state-transition model (which previously was referred to as Markov option 2) from TA558 with the latest data cut from CheckMate 238, which included recurrence-free survival (RFS), OS and subsequent treatment data with a minimum of 48 months of follow-up. Both models were mostly unchanged from the approach in the original Single Technology Appraisal 558 (TA558).[14] In the updated analyses, the licensed dose for nivolumab has changed to a flat dose of 480 mg once every 4 weeks, the original RFS ITC has been updated with the latest data from CheckMate 238, an OS ITC has been implemented in the PSM, and proportions of patients on subsequent treatments from CheckMate 238 has been updated in both models. Furthermore, the company identified some minor corrections to both models, but these had minimal impact on the final ICERs from TA558.

The most important outstanding issue that has not been rectified as part of the CDF review is OS. In TA558, OS data based on 24 months of follow up from CheckMate 238 were immature and with a

later data cut that has a minimum of 48-months of follow, the data are still immature. Furthermore, in TA558 the ERG considered that mature data from Keynote 054, a trial evaluating adjuvant pembrolizumab versus placebo in patients with resected high-risk stage III melanoma, may be useful to produce robust survival estimates for routine surveillance as it would reflect current practice for subsequent treatments (which was a key issue for the committee). However, mature OS data from Keynote 054 are not currently available. As such, the ERG considers that the uncertainty around the cost-effectiveness analyses from TA558 that was to be addressed during the CDF data collection period remains the same.

The committee for TA558 considered both the PSM and state-transition model were fit for decision making. However, the main change in the state-transition model in the company's CDF submission, aside from the updated RFS ITC, is an update to the proportion of patients on subsequent treatments based on the latest data cut from CheckMate 238, with the post-recurrence survival estimations unchanged from TA558. Thus, the updated company ICER for the state-transition model is not dissimilar to the final ICER from TA558. The latest data cut of OS from CheckMate 238 is only used in the PSM, and, as such, the PSM is the only model that allows scenarios around OS to be performed to help inform committee. Thus, the ERG does not consider the state-transition model to help resolve the uncertainties relating to OS.

The PSM was updated with a new OS ITC using the latest data cut for OS from CheckMate 238, which employed the same methods as the RFS ITC, as well as the updated RFS ITC. Unlike the RFS ITC, which censored ipilimumab patients after 1 year of treatment in CA184-029, the OS ITC used the entire intention to treat (ITT) population. The ERG requested that the company provide an OS ITC in which ipilimumab patients in CA184-029 are censored after 1 year of treatment to align RFS and OS outcomes in the model. The company stated that it is inappropriate to informatively censor ipilimumab patients who are on treatment for more than 1 year as these patients are likely to have the best prognosis at 1 year as they are able to continue treatment. Also, as treatment is given until disease recurrence, OS patients who are censored are more likely to be in the recurrence-free state. As such, the informative censoring is likely to favour the analysis for routine surveillance.

The ERG agrees that informative censoring may introduce the bias described by the company. However, in the company's base case analysis, by not censoring patients still receiving ipilimumab at 1 year, the same potential bias favours nivolumab. As committee has accepted that OS data for routine surveillance from CA184-029 is outdated, the ERG prefers to make this adjustment in order

to mitigate this to some degree. As such, using an analysis that maintains consistency in methods for estimating RFS and OS but may favour the routine surveillance arm could be considered conservative and so should minimise the risk of overestimating the treatment effect of nivolumab.

In addition to the censoring of the OS ITC analysis, the ERG requested several scenarios from the company assuming the hazard of death for routine surveillance is equal to the hazard of death estimated from the corrected group prognosis (CGP)-adjusted OS ITC survival curve for nivolumab for various time points in the model. The ERG acknowledges that adjusting OS for routine surveillance relies heavily on strong assumptions, but it is useful to provide the committee with a range of ICERs that could be considered plausible in lieu of mature OS data from either CheckMate 238 or Keynote 054.

The ERG considers that using the OS ITC in which ipilimumab patients are censored after 1 year of treatment and varying the timepoint (2 or 3 years) after which the hazard of death is equal for nivolumab and routine surveillance produces a plausible range of ICERs between £29,011 and £37,371, with the true ICER potentially falling within this range.

The ERG concludes that the company has attempted to deliver a robust cost-effectiveness analysis of adjuvant nivolumab with limited mature data and provided extensive sensitivity and scenario analyses around both models but as OS data from CheckMate 238 are still immature, many assumptions from the original analyses are still in place and could not be resolved during the time period of this CDF review. Thus, the uncertainty in the cost-effectiveness analyses remains the same as assessed in TA558.

7 References

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8 Appendices

8.1 Baseline characteristics of patients in the SACT cohort

Table 36. Systemic Anti-Cancer Therapy data cohort patient characteristics versus CheckMate 238 (Reproduced from CS, Table 20)

Patient characteristic	SACT cohort (N = 284)	CheckMate 238 – Nivolumab (N = 453)
Median age, n (range)	63 (Not reported)	56 (19–83)
Age category, n (%) < 40 years 40-49 years 50-59 years 60-69 years 70-79 years ≥80 years	 25 (9%) 32 (11%) 63 (22%) 81 (29%) 69 (24%) 14 (5%)	[redacted]
Sex, n (%) Male Female	 157 (55%) 127 (45%)	 258 (57%) 195 (43%)
ECOG performance status, n (%) 0 1 2 3 4 Unknown/missing	 199 (70%) 62 (22%) 2 (1%) 0 (0%) 0 (0%) 21 (7%)	 413 (91%) 40 (9%) 0 (0%) 0 (0%) 0 (%) 0 (%)
BRAF mutation status, n (%) V600 negative V600 positive Unknown/missing	 222 (78%) 62 (22%) 0 (0%)	 197 (44%) 187 (41%) 69 (15%)
Melanoma stage, n (%) [a] Stage IIIA Stage IIIB Stage IIIC Stage IIID Stage IV Not reported	 25 (9%) 73 (26%) 83 (29%) 5 (2%) 98 (35%) 0 (0%)	[redacted]

Notes: a CheckMate 238 data have been reclassified to the American Joint Committee on Cancer Staging Manual (AJCC) 8th edition for this Table. See company submission Section A.15.11 for details of the Stage re-classification. b Assuming all patients with Stage IV disease remain in Stage IV and are not reclassified using the AJCC 8th edition.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N, number; SACT, Systemic Anti-Cancer Therapy data.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 28 August 2020** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Relevance of CA184-029 OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.4, page 58 *"In TA558, clinical experts considered that OS from the placebo arm of CA184-029 does not reflect the current survival outcomes for routine surveillance patients due to advances in the subsequent treatment pathway."* Section 4.1.4, page 59 *"As committee has accepted that OS data for routine surveillance from CA184-029 is outdated, the ERG prefers to make this adjustment in order to mitigate this to some degree."*	The ERG should acknowledge that despite the committee's previous concerns, BMS have validated the OS ITC projections using available external data and that these projections are also in line with the ERGs clinical expert opinion. The current wording inaccurately suggests that BMS have not made attempts to validate the OS and therefore mitigate some of the uncertainty.	On page 58, the ERG confirm that the projections from the OS ITC are in line with their clinical expert opinion "*One of the ERG's clinical experts considered that 10-year survival rates for routine surveillance and nivolumab would be 55% and 65%,* [redacted]*."* In addition, BMS provided external validation, comparing the projected routine surveillance survival with the placebo survival from COMBI-AD once the patient characteristics have been matched to the trial population (see Section A.15.18, Figure 42 of the company submission). Furthermore, the ITC meta-regression includes a covariate for 'trial' which accounts for any differences between trials that could not otherwise be captured (including subsequent treatments). The projected routine surveillance curve takes this trial covariate into account producing outcomes as if this treatment were in the CheckMate 238 trial. Thus, differences in subsequent treatments	Not factually inaccurate, no change required.

		have been indirectly captured within the ITC meta-regression.	

Issue 2 State-transition model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4, page 18, Table 7 *"However, as there is more flexibility to perform scenarios around OS in the PSM, comparing ICERs between the two different models with changes implemented is not meaningful."* Section 1.5, page 19 *"The latest data cut of OS from CheckMate 238 is only used in the PSM, and, as such, the PSM is the only model that allows scenarios around OS to be performed to help inform committee. Thus, the ERG does not consider that the state-transition model helps resolve the uncertainties relating to OS."* Section 4.1.4, page 60 *"The ERG prefers the PSM analyses of OS as it implements data from CheckMate 238 in an OS ITC ([redacted]), making the most use of the trial data and facilitates an exploration of scenarios concerning OS, which*	The ERG need to clarify their statements in regards to why the state-transition model is not considered flexible enough to conduct scenarios around OS.	BMS consider these statements by the ERG to be factually incorrect given that state-transition models are considered to be more flexible than partitioned survival models. State-transition models explicitly model each of the transitions from RFS, and post-recurrence therefore allowing more flexibility for scenarios exploring assumptions for post-recurrence survival and impacts of subsequent treatments. Overall survival is a combination of RFS and post-recurrence survival (PRS), therefore modelling scenarios changing the OS, indirectly implies changes from both RFS and PRS without appropriately accounting for different assumptions to both end points. The ERG scenarios assume the same hazard of death after certain time points which are supposed to demonstrate re-challenge scenarios. However, any scenarios looking into subsequent treatments and re-challenge only impact PRS and subsequently will impact the OS. As	The ERG thanks BMS for their comment. In reference to the flexibility of the PSM to perform scenarios around OS, this specifically relates to being able to change assumptions used for the modelling of OS data directly from CheckMate 238. For the state transition model, the modelling of post-recurrence survival has not changed from TA558 and thus all exploratory scenarios for the state-transition model were presented in the original appraisal. As such there is no factual error and no change is required in the report.

are not possible in the state transition model."		such, the need to apply these scenarios to the OS in the PSM is subsided by the availability of the state-transition model where direct scenarios and assumptions can be applied directly to PRS.	

Issue 3 Subsequent treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.5, page 61 *"For nivolumab, re-challenge with a PD1 inhibitor was assumed to occur if recurrence happened after 2 years of treatment with adjuvant nivolumab. As such, subsequent therapy data for the nivolumab cohort of CheckMate 238 was used for the period before re-challenge and usage of any PD1 inhibitor treatments, that is, nivolumab, nivolumab plus ipilimumab, and pembrolizumab would have costs (applicable in both models) and survival rates (only applicable in the state-transition model) determined by ipilimumab data for the duration of the set threshold period. After the 2-year threshold, subsequent treatment usage was the same as the routine surveillance group, that is, subsequent treatment data from*	Please revise to *"For the PSM, nivolumab data from CheckMate 238 was used to reflect the proportions of subsequent treatments after nivolumab. For the state-transition model, for nivolumab, re-challenge with a PD1 inhibitor was assumed to occur if recurrence happened after 2 years of treatment with adjuvant nivolumab. As such, subsequent therapy data for the ipilimumab cohort of CheckMate 238 was used for the period before re-challenge and usage of any PD1 inhibitor treatments, that is, nivolumab, nivolumab plus ipilimumab, and pembrolizumab would have costs and survival rates determined by ipilimumab data for the duration of the set threshold period. After the 2-year threshold, subsequent treatment usage was the same as the routine surveillance group, that is, subsequent treatment data from the ipilimumab group of the*	To clarify that re-challenge was only applied within the state-transition model. For the partitioned survival model, subsequent treatments were informed directly from CheckMate 238 for the whole time period, where nivolumab was assumed to use the nivolumab subsequent treatment data and routine surveillance was assumed to have the same subsequent treatment proportions as the ipilimumab arm.	The ERG thanks the company for identifying the error. The ERG report has been amended as requested by the company.

the ipilimumab group of the CheckMate 238 trial."	*CheckMate 238 trial."*		
Section 4.1.5, page 63 *"However, [redacted] and OS data from Keynote 054 are unavailable for comparison. As such, the ERG's uncertainty around the impact of subsequent treatments on OS remains unchanged from TA558.[7, 14]"*	Despite Keynote 054 OS being unavailable for use within the model, data from the placebo arm of COMBI-AD was used to validate the OS projections of the placebo arm in the ITC. Using the CGP patient groups, these were changed to match the patient characteristics of those within the COMBI-AD trial. The model projections were then overlaid with the KM data from COMBI-AD (4 years available) which demonstrated a good match in comparison to routine surveillance model projections (see Section A.15.18, Figure 42).	The current wording inaccurately suggests no validation of the OS projects were performed due to data from Keynote 054 being unavailable. BMS would like the ERG to acknowledge that validations of the OS ITC projections were conducted with another well designed and recently conducted trial where subsequent treatment data would include currently available subsequent treatments.	Not factually inaccurate, no change required.

Issue 4 Plausible ICERs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.4, page 81 *"The ERG considers that using the OS ITC in which ipilimumab patients are censored after 1 year of treatment and varying the timepoint (2 or 3 years) after which the hazard of death is equal for nivolumab and routine surveillance produces a plausible range of ICERs between £29,011 and £37,371, with the true ICER potentially*	The correct plausible ICER range should also include estimates from the non-ipilimumab censored OS ITC and unadjusted OS curves. *"The ERG considers that using the OS ITC in which ipilimumab patients are censored after 1 year of treatment and varying the timepoint (2 or 3 years) after which the hazard of death is equal for nivolumab and routine surveillance produces plausible upper bound ICERs between £29,011 and £37,371.*	The ERG acknowledges that the ipilimumab censored analysis potentially underestimates the difference in OS between nivolumab and ipilimumab, therefore any plausible ICER range should also include the non-censored analysis. Page 41: *"This is because the censored patients are likely to be those with the best prognosis at 1 year (i.e., still alive and recurrence-free) and therefore biases the results against ipilimumab.*	Not factually inaccurate, no change required.

falling within this range."	*However, the ERG acknowledges that the ipilimumab censored analysis is bias against nivolumab, and the strong assumptions regarding the hazard of death are conservative, therefore the plausible range of ICERs are between £14,301 and £37,371, with the true ICER falling within this range."*	*Similar to the analysis of RFS, the ERG considers that the subsequent ITC would, therefore, potentially underestimate the difference in OS between nivolumab and routine surveillance."* In addition, the ERG acknowledges that the scenarios around the hazard of death are based on strong assumptions and therefore, would only ever represent an upper bound if they are considered plausible. Page 59: *"The ERG acknowledges that the scenarios exploring the hazard of death are based on strong assumptions but considers that they provide a basis for a plausible range of ICERs for the committee to consider"* BMS acknowledge that using the ipilimumab censored OS and adjustments to hazard of death may be the ERGs preferred analyses, however given prior statements around the potential bias against nivolumab that these analysis produces it will be important for any plausible ICER range to also consider OS without any censoring and adjustments to the hazard of death.	

Issue 5 Minor clarifications/changes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.1.3, page 39 *"The results shown in Figure 6 demonstrate the uncertainty in the OS analyses as the shaded areas consistently overlap for nivolumab and placebo."*	Please revise to: *"The results shown in Figure 6 shows the uncertainty in the OS analyses as the shaded areas consistently overlap for nivolumab and placebo up until 2.5 years. After 2.5 years, minimal overlap is observed."*	The statement is a misleading description of the figure, where minimal overlap is observed beyond 2.5 years.	Not factually inaccurate, no change required.
Section 3.1.3, page 41 *"Similar to the analysis of RFS, the ERG considers that the subsequent ITC would, therefore, potentially underestimate the difference in RFS between nivolumab and routine surveillance."*	*"Similar to the analysis of RFS, the ERG considers that the subsequent ITC would, therefore, potentially underestimate the difference in OS between nivolumab and routine surveillance."*	Minor typo	The ERG thanks the company for identifying the error. The ERG report has been amended as requested by the company.
Section 3.1.3, page 44 "… [redacted]	"… [redacted]	Minor typo	The ERG thanks the company for identifying the error. The ERG report has been amended as requested by the company.
Section 3.1.3, page 47 *"The ERG notes that the results of the updated Bucher indirect comparison for RFS are*	Please revise to: *"The ERG notes that the results of the updated Bucher indirect comparison for RFS are consistent with the results*	The presented HR refers to the Bucher comparison performed for the observed RFS analyses, where patients have not been censored in	The ERG thanks the company for identifying the error. The ERG report has been amended as requested by the company.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
consistent with the results presented in the original CS (HR 0.53, 95% CI: 0.41 to 0.68)"	*presented in the original CS (HR [redacted])"*	CA184-029 if still on treatment after 1 year of ipilimumab treatment. The revised text presents the HR where patients in CA184-029 were censored if still receiving ipilimumab treatment after 1 year.	
Section 4.1.4, page 59 *"Scenarios assuming the hazard of death for routine surveillance is equal to the hazard of death estimated from the CGP adjusted OS ITC survival curve for nivolumab after a) 3 years, b) 2 years and c) from baseline were provided by the company in their clarification response."*	Please re-phrase to clarify that these scenarios were provided as they were requested by the ERG. *"Scenarios assuming the hazard of death for routine surveillance is equal to the hazard of death estimated from the CGP adjusted OS ITC survival curve for nivolumab after a) 3 years, b) 2 years and c) from baseline were requested by the ERG at clarification stage. The company provided these in their clarification response."*	BMS feel it is inaccurate to present these scenarios are appropriate or plausible and therefore would like to clarify that they are only provided based on the request by the ERG. As stated in our response to clarification questions, BMS do not agree that these scenarios implicitly assume that re-challenge can happen after 2 or 3 years as the adjustment is made to the routine surveillance arm. The nivolumab curve uses the OS hazard derived from the ITC meta-regression from baseline and subsequent treatment costs from CheckMate 238 throughout, which as presented in Section A.6.1 in the CDF submission, demonstrates that patients are re-challenged with nivolumab within the first 2 years (including some patients within the first 6 months).	The ERG thanks the company for identifying the error. The ERG report has been amended as requested by the company.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Section 3.1.1, page 32 (last paragraph)	Data describing the re-treatment of nivolumab from CheckMate 238 should be marked AIC.	*"The ERG notes that the data from CheckMate 238 demonstrate that [redacted] of patients in the nivolumab arm who received subsequent therapies were re-treated with anti-PD-1s before 6 months following recurrence and [redacted] were re-treated prior to 2 years following recurrence. The ERG also notes that the median RFS in CheckMate 238 was [redacted] and median duration of treatment with nivolumab was [redacted] months."*	The ERG thanks the company for identifying the error. The ERG report has been amended as requested by the company.
Section 3.1.1 page 33	Proportion of patients who are Stage IV from CheckMate 238 should be redacted.	*"Finally, the ERG notes that there was also a marked difference in disease stage between the SACT cohort and CheckMate 238, with 35% of the SACT cohort having Stage IV disease and only [redacted] in CheckMate 238."*	The ERG thanks the company for identifying the error. The ERG report has been amended as requested by the company.

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Technical engagement response form

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **Thursday 24th September 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol Myers Squibb**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Staging of patients Nivolumab is approved for stage III and IV patients. The clinical evidence is based on CA184-029 and CheckMate 238. CA184-029 does not include stage IV patients, while CheckMate 238 does not include stage IIIa patients. However, new American Joint Committee on Cancer Staging Manual (AJCC) v8 criteria now apply - some Stage IIIb patients in CheckMate 238 would now likely be classed as Stage IIIa. The ERG does not have a suggested alternative approach as the data are limited by the patient characteristics in the trials and the ERG is unable to predict what the impact on the incremental cost-effectiveness ratio (ICER) is likely to be.	**NO**	The lack of overlap in disease Stage between CheckMate 238 and CA184-029 is a limitation in the analysis. However, clinical experts (from the advisory board used in the original submission) agreed that if resection is possible with Stage IV NED patients, then outcomes would be very similar to those of Stage IIIC patients.[1, 2] In addition, the within trial analyses in both CheckMate 238 (see Figure 20 [RFS] and Figure 21 [OS] in the ERG response document) and CA184-029 Figure 19 [RFS; CA184-029] in the submission dossier), and the KEYNOTE 054 study suggest that disease stage is not a treatment effect modifier.[3] In addition, published Bucher comparisons between nivolumab and placebo (based on data from CheckMate 238 and CA184-029) show consistent results between the ITT population and the subset of patients with Stage IIIB/C disease for a range of endpoints, suggesting that the inclusion of Stage IIIA and Stage IV patients do not modify the treatment effect between nivolumab and placebo.[4] The covariate adjustment in the meta-regression is therefore appropriate as it allows for estimation of RFS and OS for the unobserved populations (nivolumab with Stage IIIA disease and placebo with Stage IV NED disease), assuming that disease stage does not change the relative treatment effects within these populations.
Key issue 2: Survival data CheckMate 238 overall survival (OS) and recurrence free survival (RFS) data now have 48 months minimum follow-up,	**NO**	The smoothed hazard plots for OS (Figure 1) show [redacted]

however they remain immature, [redacted] RFS and OS are the key clinical outcomes used to inform the clinical effectiveness of nivolumab in the model. If the trends of the latest data cut continue into the future, then it is likely that the availability of mature data from CheckMate 238 will reinforce the current ICERs or potentially improve them. However, if after a few years there is a decline in RFS and OS, it will likely cause the ICERs to increase substantially.		[redacted] **Figure 1: Smoothed hazard plots – OS – CheckMate 238** [redacted] This increase in treatment effect over time was also observed when comparing the 24-month data cut, with the 48-month data cut. The observed trend in event rates with 2 years of additional data show that the hazard of death [redacted] (hazard ratio [HR]: [redacted] When compared with placebo via the indirect treatment comparison, [redacted]. Results of the Bucher

		comparison using the 48-month data show that treatment with nivolumab is associated with [redacted] The additional data for RFS shows consistent extrapolated outcomes using the 24-month data versus the 48-month data (see Figure 2), this demonstrates the robustness of the model meta-regression outcomes when using later data cuts. **Figure 2: 24-month versus 48-month RFS nivolumab model outcomes** [redacted] **Key:** KM, Kaplan-Meier; RFS, recurrence-free survival. **Notes:** Patient characteristics in the model reflect the CheckMate 238 population. In conclusion, the extra 24-months of data demonstrates potential improvements for nivolumab compared to ipilimumab OS and consistent RFS

<table>
<tr><td></td><td></td><td>outcomes from the model demonstrating the likelihood that further data cuts will provide similar trends if not in favour of nivolumab.</td></tr>
<tr><td>Key issue 3: Subsequent treatments
The implementation of the subsequent therapy data is unchanged from TA558, but updated data for subsequent treatment from CheckMate 238 are used.
Subsequent treatment data from the SACT cohort are immature - limited to 25 (9% ~ 25/284) patients due to the short follow-up.
The ERG’s clinical experts reported that the company’s approach of using the subsequent treatments from CheckMate 238 is reasonable.</td><td>YES</td><td>Since the re-submission a later version of the SACT subsequent treatment has become available (updated between 30 April 2020 to 1 August 2020). Data still remains relatively immature but has an additional 16 unique patients in the data set and an additional 24 subsequent treatment incidences. The table below shows the updated SACT data for the 14% (41/284) of patients who had subsequent treatments following adjuvant nivolumab.
Table 1: Distribution of subsequent treatments in SACT
<table>
<tr><th>Regimen</th><th>Previous SACT data (n=25)</th><th>New SACT data (n=41)</th></tr>
<tr><td>Ipilimumab + nivolumab</td><td>13 (52.0%)</td><td>14 (34.1%)</td></tr>
<tr><td>Ipilimumab</td><td>4 (16.0%)</td><td>12 (29.3%)</td></tr>
<tr><td>Dabrafenib + trametinib</td><td>3 (12.0%)</td><td>9 (22.0%)</td></tr>
<tr><td>Binimetinib + encorafenib</td><td>2 (8.0%)</td><td>6 (14.6%)</td></tr>
<tr><td>Bleomycin</td><td>1 (4.0%)</td><td>1 (2.4%)</td></tr>
<tr><td>Capecitabine</td><td>1 (4.0%)</td><td>1 (2.4%)</td></tr>
<tr><td>Cisplatin + dacarbazine + vinblastine</td><td>1 (4.0%)</td><td>1 (2.4%)</td></tr>
<tr><td>Dabrafenib</td><td>0 (0.0%)</td><td>1 (2.4%)</td></tr>
<tr><td>Dacarbazine</td><td>0 (0.0%)</td><td>1 (2.4%)</td></tr>
<tr><td>Hydroxycarbamide</td><td>0 (0.0%)</td><td>1 (2.4%)</td></tr>
<tr><td>Imatinib</td><td>0 (0.0%)</td><td>1 (2.4%)</td></tr>
<tr><td>Pembrolizumab</td><td>1 (4.0%)</td><td>1 (2.4%)</td></tr>
<tr><td>Talimogene laherparepvec</td><td>1 (4.0%)</td><td>1 (2.4%)</td></tr>
<tr><td>Trametinib</td><td>0 (0.0%)</td><td>1 (2.4%)</td></tr>
</table>
As per the previous SACT data cut, this shows that upon recurrence, most patients are re-treated with a PD-L1 treatment the most common being nivolumab in combination with ipilimumab (34.1%).</td></tr>
</table>

<table>
<tr><td></td><td></td><td>This data has been added to the economic model as an option, however due to the immaturity this has only been used in the sensitivity analysis. Based on the company base case ICERs (£14, 301 for the PSM and £16,171 for the STM), using the new SACT data reduces the ICERs to £8,956 and £11,248, respectively. The results are similar to the scenarios using the previous SACT data cut (£7,604 for the PSM and £10,275 for the STM).</td></tr>
<tr><td>Key issue 4: Indirect treatment comparison (ITC)
The company's ITC analysis of OS used in their base case does not include censoring at 1-year for ipilimumab patients from CA184-029 who received treatment beyond 1-year. This is inconsistent with the data the company uses for RFS and creates a mismatch in the ipilimumab treatment duration in the ITC as patients in CheckMate 238 only received up to 1-year ipilimumab and in CA184-029 it was up to 3 years of ipilimumab.
The ERG recommends that censoring after 1 year of treatment with ipilimumab in CA184-029 is used in the ITC for OS and the ITC for RFS.</td><td>Yes</td><td>The difference in ipilimumab treatment regimens is a potential source of clinical uncertainty between the two studies. However, the median duration of ipilimumab was shorter in CA184-029, the patients in the ipilimumab arms for both trials received the same median doses, and only 25% of patients assigned to receive ipilimumab in CA184-029 received ipilimumab beyond 1 year. Clinical opinion at the advisory board indicated that the difference in dosing between the trials would not impact the effectiveness of ipilimumab treatment.[1]
Table 2: Ipilimumab dosage and duration information
<table>
<tr><th>CheckMate 238</th><th>CA184-029</th></tr>
<tr><td>• Ipilimumab 10 mg/kg every 3 weeks for 4 doses, then every 3 months up to a maximum of 1 year or until disease recurrence, unacceptable toxicity, major protocol violation or treatment refusal
• Median duration = 2.7 months
• Median number of doses = 4</td><td>• Ipilimumab 10 mg/kg every 3 weeks for 4 doses, then every 3 months up to a maximum of 3 years or until disease recurrence, unacceptable toxicity, major protocol violation or treatment refusal
• Median duration = 2.1 months
• Median number of doses = 4
• 25% of patients received ipilimumab beyond 1 year</td></tr>
</table>
To investigate this difference further, analysis which censored ipilimumab patients in CA184-029 if they remained on treatment after 1 year was performed. However, a large limitation of this analysis is informative censoring,</td></tr>
</table>

which results in patients with the best prognosis being censored in CA184-029. This violates the assumption for the KM method which assumes there is no dependence between the time to event and the process which causes censoring. This bias was acknowledged by the ERG in the original submission who suggested the analysis would underestimate the efficacy between nivolumab and routine surveillance and would represent a 'worst case' scenario.[5]

For the analysis of OS, the effect of censoring patients is more pronounced than for RFS, as almost all patients who are censored are in the recurrence-free health state, whereas approximately [redacted]% of ipilimumab patients who are not censored are in the post-recurrence state, with the remaining patients having stopped ipilimumab treatment and were yet to start subsequent therapy (see Table 3), the patients in the post-recurrence state are likely to have increased risk of mortality than the patients in the pre-recurrence station. By definition, all patients who are not censored in the corresponding RFS analysis are recurrence-free.

Table 3 : Health state of patients 1 year after starting treatment -CA184-029

Health state - 1 year after starting treatment	Off-treatment 1 year after starting treatment		Still on treatment 1 year after starting treatment	
	Ipilimumab	Placebo	Ipilimumab	Placebo
Pre-recurrence - on treatment	[redacted]	[redacted]	[redacted]	[redacted]
Pre-recurrence - off treatment	[redacted]	[redacted]	[redacted]	[redacted]
Alive - censored RFS	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Censored OS	[redacted]	[redacted]	[redacted]	[redacted]
Died	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

When viewing the smoothed hazard plot for OS (Figure 3) it is observed that between [redacted] which is very unlikely given patients treated with ipilimumab had improved RFS and would have similar subsequent therapy options available. In addition, the hazards for ipilimumab for the observed data in [redacted] This supports the assumption that the increased duration of ipilimumab treatment in CA184-029 is unlikely to modify the relative treatment effect of ipilimumab for OS.

Figure 3: OS smoothed hazard plot

[redacted]

Based on the available data and clinical opinion the bias from the increased duration of ipilimumab in CA184-029 is small, however there is a bias against nivolumab if the censoring for ipilimumab in CA184-029 is applied, particularly for OS. In addition, the range of plausible ICERs presented by the ERG applied

		the censoring rule to ipilimumab, given the bias introduced by this analysis the 'true' ICER would be less than those presented by the ERG.
Key issue 5: Model structure In TA558, both the partitioned survival model (PSM) and state-transition model (STM) were considered appropriate for decision making. However, OS data (albeit immature) are now available from CheckMate234. The ERG considers the PSM to be more appropriate for decision making because STM does not include OS data (it only includes updated RFS data).	**YES**	The ERG made several statements regarding the STM and its lack of appropriateness for the decision problem. BMS acknowledge that the OS is still immature and therefore consider the STM to be useful to decision makers as it gives an alternative approach not relying on OS from CheckMate 238 but using subsequent treatment data directly and related scenarios around re-challenge. As stated in NICE TSD 19, in STMs, OS depends on all three individual transitions allowing a structural link between mortality and earlier recurrence rates, in addition, "*state transition modeling allows event rates and treatment effects on these event rates to be specified for individual components of the disease process. As a result, the use of state transition models can improve transparency around the mechanisms and processes underpinning results generated using extrapolation, and facilitate meaningful sensitivity analyses*"[6] Given that post-recurrence survival is a key uncertainty in the decision problem (linked to subsequent treatment usage and resulting survival post nivolumab), the STM separates the OS connected with RFS and post-recurrence survival which allows numerous scenarios regarding subsequent treatment usage linking both survival and cost outcomes. BMS acknowledge the limitations regarding the STM in its current approach to estimate PRS from subsequent treatment OS in the literature. As an alternative, PRS from CheckMate 238 has been used to inform PRS for both nivolumab and routine surveillance in the model. This provides another analysis using CheckMate 238 data which is considered an appropriate reflection of subsequent treatment usage as specified by the ERG clinical experts and therefore more reflective of clinical practice. This analysis also negates the use of CA184-029 to inform the OS for the routine surveillance arm. In this analysis, PRS from CheckMate 238 was pooled for both treatment arms and fitted with parametric curves using the same CGP method as the other parametric curves in the model. Given the immaturity of the data, pooling the treatment arms allows more data to be used to inform PRS. This analysis therefore assumes that once a patient has a recurrence their hazard of death is

		assumed to be the same between both treatment arms. Additionally, the subsequent treatment costs incurred represent the pooled CheckMate 238 data and is used for both treatment arms assuming that the same subsequent treatments are given irrespective of previous treatment. This assumption is reasonable given that the SACT data shows that patients are re-treated with anti-PD-L1 treatments after adjuvant nivolumab and the CheckMate 238 shows that most patients are re-treated with anti-PD-L1s within 6 months of recurring. Given that there are no Stage IIIA patients in the CheckMate 238 trial using the AJCC version 7, in order to model the full licenced population, the covariate from Stage IIIA in the OS meta-regression is used as a proxy. The curves fitted to the CheckMate 238 KM data and AIC/BIC fit statistics are presented in the Appendix. From these curves, log-normal had the best visual and statistical fit and therefore has been used for the PRS base case. Other curves are tested in scenarios and presented in the Appendix. Figure 4 presents the final curve for PRS when the model population is changed to reflect the CheckMate 238 population.

Figure 4: Final model PRS (CheckMate 238 population)

Key: PRS, post-recurrence survival

The results of this analysis are presented in Table 4. Assuming the same hazard of death and subsequent treatment cost after a patient recurs on both treatment arms gives an ICER of £16,064.

Table 4: Cost-effectiveness results (STM) using PRS from CheckMate 238

Treatment	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
RS	[redacted]	15.35	[redacted]				
Nivo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,064

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Nivo, nivolumab; QALYs, quality-adjusted life years; RS, routine surveillance; STM, state-transition model.

Key issue 6: Hazard of death for routine surveillance Routine surveillance OS modelling has been a key issue in determining the cost-effectiveness of adjuvant nivolumab. In TA558 clinical experts considered that placebo in CA184-029 does not reflect routine surveillance OS due to advances in the subsequent treatment pathway. As such, the OS ITC in the PSM potentially overestimates the survival benefit of nivolumab. The ERG explored scenarios assuming equal hazard of death for routine surveillance and nivolumab estimated from the corrected group prognosis adjusted OS ITC curve for nivolumab after a) 3 years and b) 2 years. These scenarios are based on strong assumptions, but the ERG considers they provide plausible range of ICERs in lieu of mature data. Mature CheckMate 238 and Keynote 054 OS data could provide an alternative analysis to estimate routine surveillance.	**YES**	BMS would like to respond to the comments around the relevance of CA184-029 OS to inform the routine surveillance arm. To further investigate the effect of the change of subsequent therapies between the CheckMate 238 and CA184-029 studies an additional analysis was performed.[7] The analysis aimed to adjusted overall survival in CA184-029 such that it reflected the one that would have been observed if the same subsequent therapies received by patients in CheckMate 238 were available. To do this, post-recurrence survival in the ipilimumab arms of CheckMate 238 and CA184-029 were modelled using a generalised gamma distribution adjusted for possible confounders, among them, age, disease stage and recurrence type. The generalised gamma distribution was chosen because this was the one with the lowest Akaike Information Criterion (AIC) compared to models assuming exponential, log-normal and Weibull distribution of error terms. After adjustment, a [redacted] average increase in post-recurrence survival was measured in CheckMate 238 compared to CA184-029. This factor was then used to increase post-recurrence survival for both ipilimumab and placebo in CA184-029, assuming that post-recurrence survival does not depend on the randomized treatment. To generate adjusted OS times in CA184-029, the original time from randomization to recurrence was used and was combined with the adjusted post-recurrence survival estimates. The Bucher method was then used to estimate the relative effect of nivolumab compared to placebo.[8] An accelerated failure time model assuming a generalized gamma distribution for the error terms was applied to compare post-recurrence survival between Ipilimumab in CheckMate 238 and Ipilimumab CA184-029. This distribution was chosen because this was the one with the lowest AIC compared to models assuming exponential, log-normal and Weibull distribution of error terms. To account for the variability around the acceleration factor used to adjust post-recurrence survival in CA184-029, a 95% confidence interval around the ITC HR was calculated via bootstrap method using 10000 samples.

		Since the adjustment in survival time was only applied to subjects who recurred in CA184-029 and recurrence may be related to prognostic factors, re-censoring was applied in all subjects in CA184-029 as the literature suggests to remove the possible bias associated with informative censoring. [9-11] Several sensitivity analyses were performed on the Placebo arm where the estimated subsequent therapy effect on post-recurrence survival was increased to be 10% and 20% larger and 10% worse than in Ipilimumab. The results of the adjusted KM curve (Figure 5), displays that after adjustment ipilimumab [redacted], and nivolumab displays a significantly reduced hazard compared to placebo (HR: [redacted]). These adjustments are consistent with the modelled OS outcomes from the meta-regression (Figure 5) for the placebo arm suggesting that the meta-regression analysis appropriately accounts for differences in for subsequent treatments between CA184-029 and 238 studies.

		Figure 5: Kaplan-Meier Plot of Overall Survival – CheckMate 238 and adjusted CA184-029  **Key:** Adj, adjusted; CI, confidence interval; HR, hazard ratio; OS, overall survival The results of the sensitivity analyses around the improvement of post-recurrence survival for placebo, also displays that nivolumab has a significantly

reduced hazard versus placebo even when assuming a more positive subsequent therapy effect in placebo than in the ipilimumab arm (Table 5).

Table 5: Assessment of the Impact of Subsequent Therapy on Overall Survival

Post-recurrence Survival Increase		ITC HR	95% CI
Ipilimumab in CA184-029	Placebo in CA184-029		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

BMS would also like to respond to the ERG scenarios and in particular the application of the scenarios which BMS have several issues with.

In the scenarios, the ERG adjusts the hazard of death for routine surveillance to be the same as nivolumab at the selected cut-offs. These cut-offs were *"chosen by the ERG as surrogates for potential re-challenge by immunotherapies".* This assumes that patient outcomes are the same between treatment arms regardless of prior therapy and hence adjuvant nivolumab does not impact outcomes on subsequent therapies. PFS2 data from CheckMate 238 suggests that nivolumab outcomes are statistically significantly better than ipilimumab PFS2 outcomes for next line therapy suggesting that this assumption could be conservative ([redacted]).

BMS strongly disagree that these scenarios are appropriate and required for the PSM given that a STM has been provided which can implement these scenarios in a more realistic manner. In the current company base case for the STM, re-challenge is assumed to happen for patients who recur after 2 years (and therefore the hazard of death and subsequent treatment costs for patients who recur after 2 years are the same in both treatment arms). Those who recur

before two years are assumed not to receive subsequent PD-L1 treatment after nivolumab. Both PRS and subsequent treatment costs are adjusted for the re-challenge assumption. These settings are more reflective of practice compared to the ERG scenario given that this takes into account the timing of patients who have a recurrence which is when subsequent therapy will be considered.

The ERG considered 2 or 3 years based on clinical feedback that patients would not be re-challenged until 2 years after completing treatment (or at the earliest 1 year after completing treatment). Further treatment is only given once a patient has a recurrence, therefore the ERG applying these cut-offs assuming all patients have one year of treatment and can be re-challenged after 1 year does not consider patients who are still recurrence-free at this time. From the CheckMate 238 trial, median RFS for nivolumab is [redacted] months (95% CI: [redacted]), which would provide a more plausible time point for an OS adjustment to all patients.

Applying this cut-off and assuming that patients can be re-challenged from this cut-off point gives an ICER of £18,789 and £23,853 using ipilimumab 12-month uncensored and censored OS, respectively (Table 6).

Table 6: Cost-effectiveness results (PSM) using cut-off from median RFS

Treatment	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
OS uncensored							
RS	[redacted]	19.83	[redacted]				
Nivo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,789
OS censoring patients after 12 months of ipilimumab treatment							
RS	[redacted]	20.37	[redacted]				
Nivo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,853

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Nivo, nivolumab; QALYs, quality-adjusted life years; RS, routine surveillance; STM, state-transition model.

		These results demonstrate that using a more plausible cut-off with the ERG approach, nivolumab is cost-effective versus routine surveillance at the £30,000 per QALY threshold. Moreover, even when applying the ipilimumab censored analysis, which is considered bias and as such an upper bound of the true ICER.

Issues from the technical team

Please use the table below to respond to issues raised by the technical team. You may also provide additional comments on that you would like to raise but which do not address the specific questions.

Technical team issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Nivolumab dose The licenced dose of nivolumab has changed to a flat dose of either 240 mg once every 2 weeks or 480 mg once every 4 weeks. Previously, the dose was based on weight and was 3 mg/kg once every 2 weeks since TA558. The ERG's clinical experts agreed that the dose change would have	**NO**	Flat dosing of 240 mg is considered to be similar to 3 mg/kg dose. 240 mg is same as 3 mg/kg for patients weighing 80 kg which is the median weight in Phase II and III clinical studies of nivolumab monotherapy 240 mg every 2 weeks (Q2W) is considered similar to 480 mg every 4 weeks (Q4W). The 240 mg Q2W dose was chosen to approximate the exposures achieved with 3 mg/kg in patients weighing 80 kg, the median body weight of patients across nivolumab trials. Nivolumab flat-dosing regimens are supported by well-established and robust population pharmacokinetic modelling and clinical safety data. Extensive population pharmacokinetic modelling data in patients with melanoma, renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), squamous and non-squamous non-small cell lung cancer (NSCLC), urothelial carcinoma (UC), hepatocellular carcinoma (HCC) and colorectal cancer (CRC) showed that distributions of nivolumab exposures after 3 mg/kg Q2W and 240 mg Q2W were similar and below the exposures observed with 10 mg/kg Q2W. No clinically meaningful relationship between body weight or nivolumab exposure and frequency or severity of AEs was observed.

no impact on clinical outcomes and expect most patients to receive the 4-weekly dose. The ERG incorporated the new flat 4 weekly dose in the model (ERG report page 53 – Section 4.1.2). The company incorporated the ERG's changes in its preferred base case post clarification questions (clarification questions page 54 – question B9).

Based on flat exposure-response relationships across indications, the benefit-risk profile of nivolumab 240 mg Q2W is likely to be similar to 3 mg/kg Q2W.[12-18]

Additionally a phase 3b/4 dose optimization trial of nivolumab 240 mg Q2W vs nivolumab 480 mg Q4W in patients with advanced or metastatic NSCLC who received up to 12 months of nivolumab monotherapy 3 mg/kg or 240 mg Q2W reported efficacy and safety (CheckMate 384). A total of 363 patients were randomized 1:1 to receive either nivolumab 240 mg Q2W or nivolumab 480 mg Q4W. Patients were stratified by tumor histology (squamous vs. non-squamous) and response to prior nivolumab therapy at randomization (PR/CR vs SD). The co-primary endpoints are progression-free survival (PFS) rates at 6 and 12 months. Data from an interim analysis (n = 329) are shown in Table 7 and

Table 8.[19, 20]

Table 7: Post-Randomization 6 Month PFS Rates by Subgroup in CheckMate 384

Subgroup	**480 mg Q4W 6 mo PFS rate, %**	**240 mg Q2W 6 mo PFS rate, %**	**Difference of 6 month PFS rates, % (one-sided 95% CI)[a]**
Overall (N = 329)			
Stratified	75	80	−1.9 (−10.0, NA)[b]
Unstratified	72	72	−0.4 (−9.4, NA)
Age			
<65 years (n = 130)	80	76	4.1 (−9.3, NA)
≥65 years (n = 199)	67	70	−3.4 (−15.2,NA)
Sex			
Male (n = 231)	70	72	−2.2 (−13.2, NA)
Female (n = 98)	76	72	4.1 (−11.6, NA)
Baseline ECOG PS			
0 (n = 134)	80	75	4.4 (−8.4, NA)
1 (n = 181)	65	68	−2.8 (−15.7, NA)
Histology			

Squamous (n = 114)	68	64	3.2 (−12.8, NA)
Non-squamous (n = 215)	74	76	−2.1 (−12.8, NA)
Lines of prior therapy			
1 (n = 213)	69	76	−7.0 (−18.2, NA)
2+ (n = 112)	76	61	14.5 (−1.5, NA)
Duration of prior NIVO treatment			
3–<6 mo (n = 176)	67	71	−4.5 (−17.2, NA)
6–<9 mo (n = 79)	71	74	−3.6 (−22.6, NA)
9–<12 mo (n = 55)	92	77	14.7 (−1.7, NA)
Response to prior NIVO at randomization			
CR/PR (n = 117)	84	88	−3.5 (−15.2, NA)
SD (n = 212)	65	64	0.6 (−11.3, NA)

Unstratified PFS rates from the randomized population unless otherwise noted; only groups with ≥10 patients per arm are included

Median follow-up (range) was 10.2 months (0.5–21.0) in the NIVO 480 mg Q4W arm (n = 136) and 9.4 months (0.0–22.7) in the NIVO 240 mg Q2W arm (n = 133).

CheckMate 384 was originally designed as a non-inferiority study. However, due to a reduced sample size, there was insufficient power to demonstrate non-inferiority, and the analysis is descriptive. Therefore, conclusions cannot be drawn about which subgroups benefit more from Q4W vs Q2W dosing based on this data.

a. The difference of PFS rates is 480 mg Q4W minus 240 mg Q2W

b. Adjusted for stratification factors: tumour histology (squamous vs non-squamous) and response category at randomization (CR/PR vs SD) and calculated using inverse variance as weights

Table 8: Safety Summary of Post-Randomization Treatment-Related AEs in CheckMate 384

TRAE,[a] n (%)	**480 mg Q4W (n = 164[b])**		**240 mg Q2W (n = 161[b])**	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	79 (48)	14 (8)	98 (61)	20 (12)

Serious TRAEs	7 (4)	6 (4)	9 (6)	8 (5)
TRAEs leading to discontinuation	10 (6)	3 (2)	14 (9)	8 (5)
Most frequent TRAEs (≥5%[c])				
Diarrhea	18 (11)	3 (2)	13 (8)	1 (1)
Hypothyroidism	14 (8)	0	11 (7)	0
Fatigue	13 (8)	1 (1)	21 (13)	1 (1)
Asthenia	8 (5)	0	9 (6)	1 (1)
Pruritus	7 (4)	0	14 (9)	1 (1)
Lipase increased	5 (3)	2 (1)	9 (6)	6 (4)
Dry skin	2 (1)	0	9 (6)	0
Treatment-related deaths	0		0	

Similar safety was observed across subgroups by weight; few patients were represented in the <50 kg and ≥110 kg subgroups.
The median duration of post-randomization study therapy was 7.5 months in the NIVO 480 mg Q4W arm and 7.1 months in the NIVO 240 mg Q2W arm.
a. Includes events reported between first dose and 30 days after last dose of study therapy
b. Treated population
c. In either group.
d. Duration between treatment discontinuation/cutoff date and first dose date.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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Appendix: Post-recurrence survival – CheckMate 238

Figure 6: Pooled post-recurrence survival from CheckMate 238

Key: KM, Kaplan-Meier

Table 9: AIC and BIC values – pooled post-recurrence survival from CheckMate 238

Model	AIC	BIC
Exponential	3291.828	3312.397
Generalised Gamma	3276.758	3305.553
Gompertz	3293.748	3318.43
Log-logistic	3280.743	3305.425
Log-normal	**3275.53**	**3300.213**
Weibull	3290.741	3315.423

Table 10: Cost-effectiveness results (STM) using pooled post-recurrence survival from CheckMate 238 – alternative curve distributions

	Nivolumab		Routine surveillance		Incremental		
Curve distribution	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER (£/QALY)**
Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,064
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,967
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,615
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,248
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,588
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,370
Key: QALYs, quality-adjusted life-years; STM, state-transition model;							

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Technical engagement response form

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **Thursday 24 September 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted] and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Ruth Plummer**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Staging of patients Nivolumab is approved for stage III and IV patients. The clinical evidence is based on CA184-029 and CheckMate 238. CA184-029 does not include stage IV patients, while CheckMate 238 does not include stage IIIa patients. However, new American Joint Committee on Cancer Staging Manual (AJCC) v8 criteria now apply - some Stage IIIb patients in CheckMate 238 would now likely be classed as Stage IIIa. The ERG does not have a suggested alternative approach as the data are limited by the patient characteristics in the trials and the ERG is unable to predict what the impact on the incremental cost-effectiveness ratio (ICER) is likely to be.	**YES/NO**	Checkmate 238 was unique in the adjuvant studies in including resected stage 4 patients, and therefore adjuvant nivolumab remains the only option for this group of patients. Resection of oligo-metastatic disease is considered a reasonable clinical option, and for some patients with melanoma the natural history of the disease can be with many months between any such recurrence, and Checkmate 238 demonstrated that resection and adjuvant treatment for one year showed a significant benefit to patients by delaying recurrence, and the clinical community is hoping this will also translate into the OS benefit when the data finally mature. The change in the AJCC criteria has raised the issue highlighted here. The v8 criteria is now what is used by all MDTs so we are offering adjuvant treatment to some patients who were not included in the trial, and likewise some patients do fall into slightly different stage groupings when discussing the Bluteq risk criteria. I agree there is not an alternative to this at present, and eventually we will have data on the benefits of adjuvant treatment

		using the new stage groupings if the data continues to be collected prospectively.
Key issue 2: Survival data CheckMate 238 overall survival (OS) and recurrence free survival (RFS) data now have 48 months minimum follow-up, however they remain immature, [redacted] RFS and OS are the key clinical outcomes used to inform the clinical effectiveness of nivolumab in the model. If the trends of the latest data cut continue into the future, then it is likely that the availability of mature data from CheckMate 238 will reinforce the current ICERs or potentially improve them. However, if after a few years there is a decline in RFS and OS, it will likely cause the ICERs to increase substantially.	**YES/NO**	It is a reasonable assumption that the data trend will continue on current lines with the benefit in RFS and assumption that this means OS. This is based on the fact that in this adjuvant setting patients who are going the recur do tend to do so within the first few years, late recurrences are relatively rare, although they do happen, but effect likely to be small. Also presentations at the ongoing ESMO conference from the other immunotherapy adjuvant studies continue to show an ongoing benefit, and therefore it is a reasonable assumption that another agent in the IO class will also continue to show benefit.
Key issue 3: Subsequent treatments The implementation of the subsequent therapy data is unchanged from TA558, but updated data for subsequent treatment from CheckMate 238 are used. Subsequent treatment data from the SACT cohort are immature - limited to 25 (9% ~ 25/284) patients due to the short follow-up. The ERG's clinical experts reported that the company's approach of using the subsequent treatments from CheckMate 238 is reasonable.	**YES/NO**	I agree, no significant changes in subsequent treatments for melanoma in the time period so this is reasonable. A key 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.
Key issue 4: Indirect treatment comparison (ITC) The company's ITC analysis of OS used in their base case does not include censoring at 1-year for ipilimumab patients from CA184-029 who received	**YES/NO**	This would seem reasonable to try and make the data evaluated consistent. I guess one caveat is that patients who stopped treatment at one year on CA184-029 may have either recurred or

treatment beyond 1-year. This is inconsistent with the data the company uses for RFS and creates a mismatch in the ipilimumab treatment duration in the ITC as patients in CheckMate 238 only received up to 1-year ipilimumab and in CA184-029 it was up to 3 years of ipilimumab. The ERG recommends that censoring after 1 year of treatment with ipilimumab in CA184-029 is used in the ITC for OS and the ITC for RFS.		had toxicity issues. If the censoring enriches the group for patients who recur will this alter the model? However only 25% patients went beyond 1 year so I think these are minor theoretical concerns
Key issue 5: Model structure In TA558, both the partitioned survival model (PSM) and state-transition model (STM) were considered appropriate for decision making. However, OS data (albeit immature) are now available from CheckMate234. The ERG considers the PSM to be more appropriate for decision making because STM does not include OS data (it only includes updated RFS data).	**YES/NO**	Absolutely outside my area of expertise!
Key issue 6: Hazard of death for routine surveillance Routine surveillance OS modelling has been a key issue in determining the cost-effectiveness of adjuvant nivolumab. In TA558 clinical experts considered that placebo in CA184-029 does not reflect routine surveillance OS due to advances in the subsequent treatment pathway. As such, the OS ITC in the PSM potentially overestimates the survival benefit of nivolumab. The ERG explored scenarios assuming equal hazard of death for routine surveillance and nivolumab estimated from the corrected group prognosis adjusted OS ITC curve for nivolumab after a) 3 years and b) 2 years. These scenarios are based on strong	**YES/NO**	Routine surveillance was our SOC before we started giving adjuvant treatment, and what is used for patients who opt not to have the treatment. Is it scanning frequency or clinical examination frequency which makes the placebo arm not SOC equivalent? Subsequent treatments have not significantly changed therefore the placebo arm does reflect SOC prior to the trial and subsequently

assumptions, but the ERG considers they provide plausible range of ICERs in lieu of mature data. Mature CheckMate 238 and Keynote 054 OS data could provide an alternative analysis to estimate routine surveillance.		

Issues from the technical team

Please use the table below to respond to issues raised by the technical team. You may also provide additional comments on that you would like to raise but which do not address the specific questions.

Technical team issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Nivolumab dose The licenced dose of nivolumab has changed to a flat dose of either 240 mg once every 2 weeks or 480 mg once every 4 weeks. Previously, the dose was based on weight and was 3 mg/kg once every 2 weeks since TA558. 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. The ERG incorporated the new flat 4 weekly dose in the model (ERG report page 53 – Section 4.1.2). The company incorporated the ERG's changes in its preferred base case post clarification questions (clarification questions page 54 – question B9).	**YES/NO**	It is very reasonable to switch to this recommended dose. This is clinically what we all have done. Patients are offered 2 or 4 weekly dosing, most choose 4 weekly for convenience. Both FDA and EMA were happy with the company's pharmacokinetic modelling justifying the change to flat dosing from weight based, and then the change in schedule and it is assumed that the efficacy/trail data will be unchanged.

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Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

BMJ TAG

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

ERG response to BMS technical engagement comments

September 2020

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 130570T.

1 Introduction

This document provides a review and critique of the company's response to the technical engagement (TE) process. The company's response addressed the following seven key issues presented for technical engagement:

1. Staging of patients;
2. Immature survival data from CheckMate 238;
3. Appropriate subsequent treatments;
4. Indirect treatment comparison used for the cost-effectiveness analysis;
5. Relevant model structure for decision making;
6. ERG scenarios exploring hazard of death for routine surveillance; and
7. Change to licensed dose of nivolumab.

The ERG's critique of the company's response to each of these issues is discussed in Section 2.

The company's base case (Table 1 for the partitioned survival model [PSM] and Table 2 for the state-transition model), remains unchanged from that presented in the ERG report.

Table 1. Company's deterministic cost effectiveness results – partitioned survival model

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	18.65	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,301

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 2. Company's deterministic cost effectiveness results – state-transition model

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	14.27	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,171

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

2 Key issues for engagement

2.1 Staging of patients

The absence of Stage IV patients from CA184-029 potentially limits the validity of the ITC results for the comparison of nivolumab with routine surveillance in this subgroup. The ERG also notes that Stage IIIa patients were excluded from CheckMate 238 but the new AJCC v8 criteria used to assess disease stage mean that some Stage IIIb patients in CheckMate 238 would now likely be classed as Stage IIIa. The ERG notes that the company has included covariate adjustment in the meta-regression to allow for estimation of RFS and OS for the unobserved populations (nivolumab with Stage IIIA disease and placebo with Stage IV disease), assuming that disease stage does not change the relative treatment effects within these populations. The view of the Evidence Review Group (ERG) is unchanged from the ERG report: the ERG does not consider it possible to obtain additional data from CheckMate 238 or CA184-029 to help resolve this issue, and no new data has been presented at technical engagement.

2.2 Survival data

In response to technical engagement, the company presented a smoothed hazard plots for OS (Figure 1). The company reported that [redacted]

The ERG is concerned that [redacted]

2 [redacted]

The ERG noted in the ERG report that despite the updated data cut from CheckMate 238, the study results for OS still remain immature and underpowered and the results for RFS also remain immature. The view of the ERG is unchanged from the ERG report.

Figure 1. Smoothed hazard plots for OS from CheckMate 238 (reproduced from company response to technical engagement, Figure 1)

Key: ipi, ipilimumab; nivo, nivolumab.

Figure 2. CheckMate 238 Kaplan–Meier curves for overall survival by treatment arm, 48-month minimum follow-up (Reproduced from CS, Figure 1)

Key: ipi, ipilimumab; nivo, nivolumab.

2.3 Subsequent treatments

Since the date of the company submission a later version of the SACT subsequent treatments has become available with an additional 6 months of data on subsequent treatments (updated from 31

October 2019 to 30 April 2020). Data on subsequent treatments for patients in the SACT cohort still remains relatively immature with only 14% (41/284) of patients who have had subsequent treatments following adjuvant nivolumab, although there are now an additional 16 patients with data (Table 3). The median follow-up time from a patient last nivolumab cycle in the updated SACT data is now 276 days (range: 49 days to 444 days), whereas it was previously only 154 days (range: 28 days to 262 days).

The ERG notes that there are still differences in the subsequent therapies received in SACT and CheckMate 238. In the nivolumab arm of CheckMate 238, of the people receiving systemic treatment subsequent to nivolumab, the most commonly used therapies were [redacted] ipilimumab + nivolumab was the most commonly used subsequent therapy in the SACT cohort (34.1% [14/41]). The ERG considers this difference may be a reflection of the longer follow-up and the larger proportion of patients who have had multiple lines of subsequent treatment in CheckMate 238, compared to in the SACT cohort.

The ERG notes that dabrafenib + trametinib use in the SACT cohort continues to [redacted] compared to in CheckMate 238, which as discussed in the ERG report, likely reflects the difference in the proportions of patients with BRAF V600 mutation positive patients between the studies [redacted]

Table 3: Distribution of subsequent treatments in SACT

Regimen	Previous SACT data (n=25)	New SACT data (n=41)
Ipilimumab + nivolumab	13 (52.0%)	14 (34.1%)
Ipilimumab	4 (16.0%)	12 (29.3%)
Dabrafenib + trametinib	3 (12.0%)	9 (22.0%)
Binimetinib + encorafenib	2 (8.0%)	6 (14.6%)
Bleomycin	1 (4.0%)	1 (2.4%)

Capecitabine	1 (4.0%)	1 (2.4%)
Cisplatin + dacarbazine + vinblastine	1 (4.0%)	1 (2.4%)
Dabrafenib	0 (0.0%)	1 (2.4%)
Dacarbazine	0 (0.0%)	1 (2.4%)
Hydroxycarbamide	0 (0.0%)	1 (2.4%)
Imatinib	0 (0.0%)	1 (2.4%)
Pembrolizumab	1 (4.0%)	1 (2.4%)
Talimogene laherparepvec	1 (4.0%)	1 (2.4%)
Trametinib	0 (0.0%)	1 (2.4%)

Abbreviations: SACT, systemic anti-cancer therapy.

The ERG notes that the company has added the updated SACT data to the economic model as an option in a sensitivity analysis and the resulting ICERs are slightly higher compared to the previous sensitivity analyses using the earlier SACT data. Nevertheless, the SACT data still reduces the ICERs compared to the company base case ICERs (updated SACT data ICERs £8,956 for the PSM and £11,248 for the STM, and company base case £14,301 for the PSM and £16,171 for the STM).

The view of the ERG is unchanged from the ERG report: the subsequent treatments from CheckMate 238 are generally consistent with expected clinical practice and the SACT data remain immature.

2.4 Indirect treatment comparison

The company's ITC analysis of OS used in their base case does not include censoring at 1-year for ipilimumab patients from CA184-029 who received treatment beyond 1-year, whereas censoring is applied in the analysis of RFS. The ERG's rationale for its preference for the 1-year censoring is that patients in CheckMate 238 only received up to 1-year ipilimumab while in CA184-029 ipilimumab treatment could continue for up to 3 years. The company presented data in their response to technical engagement that showed the median number of doses of ipilimumab in both CheckMate 238 and CA184-029 was 4 doses and the median duration of treatment was slightly longer in CheckMate 238 compared to in CA184-029 (2.7 months and 2.1 months, respectively). The ERG considers it important to highlight that these values are median values and 50% of patients in both studies will have received more doses and had a longer treatment duration. The company also reported that 25% of patients in CA184-029 received ipilimumab for longer than 1-year and the ERG

notes that in CheckMate 238 ipilimumab treatment was not permitted beyond 1-year. The ERG does not consider 25% of patients receiving ipilimumab beyond 1 year to be an insignificant proportion. The ERG therefore recommends that censoring after 1 year of treatment with ipilimumab in CA184-029 is used consistently for both RFS and OS, but the company base case only includes censoring for RFS.

The ERG agrees with the company that the 1-year censoring of ipilimumab patients in CA184-029 if they remained on treatment after 1 year results in informative censoring and considers that the ITC analyses for OS and RFS with the censored data are likely to underestimate the efficacy between nivolumab and routine surveillance. In contrast the ITC analyses without the censoring applied may overestimate the efficacy of nivolumab compared to routine surveillance. The company presented updated data on the health states of patients still on treatment after 1 year and for those off treatment after 1 year in CA184-029 in their response to technical engagement which shows the impact of the 1-year censoring on health state at 1-year after starting nivolumab (Table 4).

Table 4 : Health state of patients 1 year after starting treatment -CA184-029

Health state - 1 year after starting treatment	Off-treatment 1 year after starting treatment		Still on treatment 1 year after starting treatment	
	Ipilimumab	Placebo	Ipilimumab	Placebo
Pre-recurrence - on treatment	[redacted]	[redacted]	[redacted]	[redacted]
Pre-recurrence - off treatment	[redacted]	[redacted]	[redacted]	[redacted]
Alive - censored RFS	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Censored OS	[redacted]	[redacted]	[redacted]	[redacted]
Died	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

The company also provided a smoothed hazard plot for OS for the ipilimumab and placebo arms in CheckMate 238 and CA184-029 to show the impact of the 1-year ipilimumab censoring (Figure 3). The company highlights that between [redacted] and the ERG agrees with the company that this is unlikely given that patients treated with ipilimumab had improved RFS and would have similar subsequent therapy

options available. In addition, the company reported that the hazards for ipilimumab for the observed data in [redacted] The company report that this supports their view that the increased duration of ipilimumab treatment in CA184-029 is unlikely to modify the relative treatment effect of ipilimumab for OS. However, the ERG does not consider it possible to draw such a conclusion from the available data.

Figure 3. OS smoothed hazard plot

The view of the ERG is unchanged from the ERG report, although the ERG acknowledges that applying censoring rule to ipilimumab is likely to bias the ITC results for OS and RFS against nivolumab.

2.5 Model structure

In TA558, the company submitted two models, the partitioned survival model (PSM) and the state-transition model, to inform the cost-effectiveness of adjuvant nivolumab treatment for adult patients with melanoma who have undergone complete tumour resection. The committee for TA558 concluded that both models were potentially suitable for decision making. However, as part of the CDF review of adjuvant nivolumab, the ERG stated a preference for the PSM as it was updated to included OS data from CheckMate 238 and as such utilised more of the trial data compared with the state-transition model and facilitated scenarios to performed around modelled OS. In their response to the TE process, the company provided a scenario that explored the use of post-recurrence survival (PRS) data from CheckMate 238 for nivolumab and routine surveillance in the state-

transition model. Previously, PRS was based on weighted subsequent treatment-specific survival data obtained from published sources.

For the scenario, the company pooled PRS Kaplan-Meier (KM) data from Check238 for nivolumab and ipilimumab and fitted parametric distributions to the data, using corrected group prognosis (CGP) method, consistent with the methodology used for the extrapolation of RFS and OS data in both models. The company chose to pool PRS data due to the immaturity of the data for each treatment arm and thus assumes that once a patient has a recurrence, regardless of their previous treatment, their hazard of death is the same. Furthermore, to align subsequent treatments to PRS, the company pooled subsequent treatment data for nivolumab and ipilimumab and assumed subsequent treatment is the same regardless of previous treatment, resulting in equal subsequent treatment costs for each arm in the economic model. The company based the assumption of equivalence in subsequent treatments based on data from SACT and CheckMate 238, which they say demonstrates patients are retreated with anti-PD-L1 treatments after adjuvant nivolumab and within six months of disease recurrence.

Based on visual and statistical fit, the company selected the log-normal distribution to extrapolate the pooled PRS data (Figure 4). Using the log-normal distribution for PRS based on CheckMate 238 data in the state-transition model had minimal impact on the ICER, reducing it from £16,171 to £16,064. The company explored other parametric curves for PRS in scenario analyses, presented in the Appendix to the company's response to the technical engagement process.

Figure 4. Post-recurrence survival (PRS) based on pooled data from CheckMate 238 – state-transition model (Figure 4 from the company response to technical engagement)

Key: KM, Kaplan-Meier; PRS, post-recurrence survival.

The ERG investigated the impact the company's PRS scenario in the state-transition model had on life-years and presents a comparison of estimates for the company's state-transition model base case, PRS scenario and PSM base case in Table 5. In theory, as 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. The ERG is concerned that the state-transition model estimates xxxxx RFS for both treatment arms compared with the PSM, even though both use the same RFS ITC CGP survival curves and considers this is driving the difference between the two models and additionally why the state-transition model ICER was not sensitive to the company's PRS scenario (see

Figure 5). Furthermore, post-recurrence survival between the PRS scenario in the state-transition model and the PSM is not aligned, even though they are based on related survival data from CheckMate 238.

Table 5. Comparison of life years for the state-transition model base case and PRS scenario and the PSM

Health state and treatment arm	State-transition model – company base case	State-transition model – company PRS 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]

Abbreviations: PSM, partitioned survival model; PRS, post-recurrence survival.

Figure 5. Comparison of RFS extrapolations from the PSM and state-transition model

Key: KM, Kaplan-Meier; PSM, partitioned survival model; STM, state-transition model.

The PSM represents a more parsimonious model with fewer underlying assumptions to model survival, whereas the STM requires more steps in the estimation of the transition probabilities As such, the ERG has more confidence in the PSM as the basis for decision making as it is taking the proportions occupying the health states in the model directly from the survival curves and can be considered to provide more robust estimates of survival compared to the state-transition model.

The ERG considers that the state-transition model doesn't pass face validity and further investigation is needed into why estimates of RFS life-years for the state-transition model are markedly different compared to the PSM.

2.6 Hazard of death for routine surveillance

To address the ERG's concerns around OS for routine surveillance, the company conducted an analysis to adjust OS in CA184-029 to reflect the OS that might have been observed if the same subsequent therapies received in CheckMate 238 were available to patients in CA184-029. The analysis estimated that there was an average increase of [redacted] in post-recurrence survival for ipilimumab in CheckMate 238 compared with ipilimumab in CA184-029. The company then applied the estimate average increase to post-recurrence survival for both ipilimumab and the placebo arms in CA184-029 and ran an analysis to produce an ITC HR of [redacted]. The company than explored the impact on the HR when the estimated average increase was varied by -10%, 10% and 20% for the placebo arm. The resulting HRs ranged from [redacted]

to [redacted]. The company state that this additional analysis validates the OS outcomes from the meta-regression for placebo, suggesting that the impact of subsequent treatments between CheckMate 238 and CA184-029 is appropriately captured. The ERG considers more detail on the methods used by the company is need but estimating the HR when post-recurrence survival for both arms of CA184-029 has been inflated is unlikely to have much of an impact as the relative difference in survival is still the same and would have preferred to see estimated HRs when only post-recurrence survival for placebo was adjusted.

The ERG notes that the company has not implemented any of these analyses in either the PSM or state-transition model and as such no corresponding ICERs are provided for this additional analysis. However, the company provided an additional scenario exploring an equal hazard of death for nivolumab and routine surveillance using a threshold of [redacted] months, which reflects median RFS for nivolumab. The company state that using median RFS as the threshold for the scenario is more plausible for the OS adjustment as subsequent treatment is only given once a patient has a recurrence. The company provided two scenarios using the median RFS as the threshold for assuming hazard of death is equal between nivolumab and routine surveillance, one scenario where OS is uncensored for ipilimumab patients on treatment for more than one year and another scenario where OS is censored for ipilimumab patients on treatment for more than one year, with corresponding PSM ICERs of £18,789 and £23,853, respectively.

The aim of the hazard of death scenarios was 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. As mentioned in the ERG report, mature placebo data from Keynote-054, which is an ongoing trial looking at the comparative efficacy of adjuvant pembrolizumab and placebo, if available, would have been pivotal to addressing the uncertainty around OS outcomes for routine surveillance. As such, the ERG acknowledges that any assumptions around OS for routine surveillance will have a high degree of uncertainty. The company's base case analysis using the PSM is biased towards nivolumab and the resulting ICER of £14,301 can be considered optimistic and representative of the lower bound of cost-effectiveness.

The ERG has considered the company's scenario of using median RFS for nivolumab as a plausible threshold for assuming hazard of death is equal between nivolumab and routine surveillance but notes that RFS for patients on routine surveillances is substantially shorter, with a modelled median of 1.61 years. By using the nivolumab median RFS, there is a delay in improved overall survival for routine surveillance patients.

In order to estimate a plausible upper bound in the ICER, the ERG considers it is more useful to provide an illustrative scenario using the modelled median RFS for routine surveillance (rounded up to two years for simplicity) instead and presents the results of this scenario and the scenario combined with one-year censoring of ipilimumab OS patients in Table 6. For the scenarios, the ERG has assumed that after the two-year threshold patients on routine surveillance who experience a recurrence in their disease will receive the benefits and so incur the costs of an immunotherapy. For simplicity, the immunotherapy is assumed to be nivolumab and the hazard of death from this point onward is assumed to be the same as patients receiving adjuvant nivolumab.

The ERG prefers the scenario that included one-year censoring of ipilimumab patients, equal hazard of death after two years and nivolumab subsequent treatment costs for routine surveillance but acknowledges that the scenario employs strong assumptions that are potentially biased in favour of routine surveillance. As such, the ERG ran a threshold analysis around the estimated QALY gain for this scenario to determine what the minimum additional QALYs needed to be gained by treatment with nivolumab to bring the ICER to £30,000; this additional QALY gain was identified as approximately [redacted]. As such, if committee considers that resolving the likely bias in the scenario analysis would result in nivolumab gaining an additional [redacted] QALY benefit (or more) then the ICER would be at (or below) the £30,000 threshold.

Table 6. Overall survival scenario results

Scenario	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	[redacted]	**14,301**
1. One-year censoring of ipilimumab OS patients	[redacted]	[redacted]	[redacted]	17,404
2. Equal hazard of death – two years & nivolumab subsequent treatment costs for routine surveillance	[redacted]	[redacted]	[redacted]	40,009
1+2. OS censoring, equal hazard of death – two years & nivolumab subsequent treatment costs for routine surveillance	[redacted]	[redacted]	[redacted]	52,012

Abbreviations: ICER, incremental cost effectiveness ratio; LY, life-year; OS, overall survival; QALY, quality-adjusted life-year.

As mentioned previously the true benefit of an immunotherapy compared to routine surveillance is only likely to only be established once the ongoing Keynote-054 study for pembrolizumab compared with placebo reports and mature data are available.

2.7 Nivolumab dose

The licensed dose for nivolumab has changed from a weight-based dose of 3 mg/kg once every 2 weeks, to a flat dose of either 240 mg once every 2 weeks or 480 mg once every 4 weeks. In the company's analysis post clarification, the regimen of 480 mg once every 4 weeks was implemented and is considered appropriate by the ERG based on feedback from the ERG's clinical experts that in UK clinical practice the dose change would have no impact on clinical outcomes and, to limit the burden on the NHS, the flat dose of 480 mg once every 4 weeks would likely be preferred. In their TE response, the company provided additional evidence for the dose equivalence of 3 mg/kg once every 2 weeks, 240 mg once every 2 weeks and 480 mg once every 4 weeks. As such, the view of the ERG is unchanged from the ERG report.