NICE National Institute for Health and Care Excellence

Single Technology Appraisal

STA Nivolumab in combination with ipilimumab for treating advanced melanoma [ID848]

Committee papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

STA Nivolumab in combination with ipilimumab for treating advanced melanoma [ID848]

Contents:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The company has proposed that nivolumab plus ipilimumab is suitable for the first line treatment of advanced melanoma regardless of BRAF mutation status. Where in the clinical pathway is this combination therapy likely to be used and what are the most relevant comparators?
- Given that pembrolizumab has been recommended for metastatic melanoma (TA366 and 357) and was included in the scope for this appraisal, does the committee consider it to be a relevant comparator.
- The company used 2 arms from CheckMate 067 study for this submission. CheckMate 067 included a third study arm in which patients received nivolumab monotherapy. Nivolumab monotherapy was not in the scope for this appraisal (as it had not been appraised by NICE at the time). Does the committee consider this to be important?

- In the scope for this appraisal, vemurafenib and dabrafenib were listed as comparators. How relevant are these comparators to nivolumab plus ipilimumab?
- Nivolumab plus ipilimumab is associated with more frequent and severe adverse effects compared with ipilimumab monotherapy. What is the committee's view on these adverse effects?
- The CheckMate 067 and 069 studies included people with ECOG performance score of 0-1. Is there a population of patients that are fit enough to tolerate this treatment that can be defined in clinical practice?
- Checkmate 067 measured tumour PD-L1 expression. Is this relevant to the current appraisal?
- The company has assumed that treatment with nivolumab would not exceed 2 years. Is this a plausible assumption?

Cost effectiveness

- In the comparison with ipilimumab the company used a semi Markov model, using time-to-progression (TTP), pre-progression survival (PrePS) and post-progression survival (PPS). In the company's model, PPS is dependent on TTP. However, the company also assumed equal PPS for nivolumab plus ipilimumab and ipilimumab monotherapy..
  - The ERG did not agree with this assumption because the TTP times were different between the nivolumab plus ipilimumab and ipilimumab alone, which meant that PPS would be different for each. In its exploratory analyses, the ERG assumed that PPS survival was not dependent on TTP and therefore equal for both nivolumab plus ipilimumab and ipilimumab monotherapy arms, basing the extrapolation of post-progression mortality only on clinical trial data. The ERG considered it more reasonable to have an equal PPS which they estimated was 1.7 undiscounted life years for both. What is the committee's preferred approach for modelling PPS?
- The company's ICER for nivolumab plus ipilimumab compared with ipilimumab alone, using the list prices, was £10,433 per QALY gained for patients with BRAF mutation-negative melanoma. In its exploratory analyses, the ERG made the following changes to the company's base case:

- using the data from the CheckMate 067 to estimate the probability of receiving one of the 4 subsequent treatments considered by the company (i.e. pembrolizumab, ipilimumab, dabrafenib and vemurafenib)
- removing the long-term data nesting and basing the extrapolation of post-progression mortality only on clinical trial data
- assuming equal pre-progression mortality between nivolumab plus ipilimumab and ipilimumab monotherapy by averaging the Kaplan Meier curves
  - ◊ Because beneficial treatment effect on PrePS of nivolumab plus ipilimumab over ipilimumab monotherapy had not been demonstrated,
  - ◊ By doing this, it removes the difference in the tails of the Kaplan Meier curves for the 2 therapies which persisted over the entire time horizon
- removal of flat dose reduction of nivolumab including the equal PPS
  - ◊ the ERG did not find the company's justification around the assumption of a constant reduction over time in the nivolumab resource use and cost to be sufficient to grant a reduction in costs equal to approximately 10% of the total costs associated with the drug acquisition costs of nivolumab

These changes resulted in an ICER using the list price of £19,322 per QALY gained. These ICERs will be affected by the patient access schemes in place for the comparators.

- In the comparison with BRAF inhibitors monotherapies, the company used a series of complex methods to compare nivolumab plus ipilimumab to dabrafenib and vemurafenib.
  - The company modelled the OS curve for BRAF mutation-positive patients for the first 3 years for nivolumab plus ipilimumab and ipilimumab by combining TTP, PPS, and PrePS using patient characteristics from the vemurafenib arm in the BRIM-3 trial.
  - For dabrafenib and vemurafenib, the company used pseudo-patient level data from the BRIM-3 study to generate Kaplan-Meier PFS and OS data. The company assumed that the 2 BRAF inhibitors have the same PFS and OS, and the Kaplan-Meier data from the BRIM-3 trial were used to fit parametric curves.
  - An area under the curve model was used for the BRAF inhibitor monotherapies.

The ERG did not consider this comparison robust and emphasised the uncertainty of any ICERs using two different model structures and different assumptions on treatment effectiveness.. For this reason the ERG only presented short-term (5 year) exploratory results? What is the committee's view of the reliability of the company's model?

- Following the clarification stage, the company produced a scenario with pembrolizumab. What is the committee's view of this exploratory comparison?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of nivolumab in combination with ipilimumab within its marketing authorisation for treating advanced, unresectable melanoma.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults with advanced (stage III or IV unresectable or metastatic) melanoma			
Int.	Nivolumab in combination with ipilimumab			
Com.	• Ipilimumab • Pembrolizumab • BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma	• Ipilimumab • BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma	Pembrolizumab was not considered to be a relevant comparator having only recently been recommended by NICE for use in NHS England after disease progression with ipilimumab. Recent prescribing data shows that it is rarely used in first line treatment of melanoma in clinical practice.	The company did not include pembrolizumab in its decision problem because when it was preparing its submission, pembrolizumab had not yet been recommended for use in the NHS by NICE and it had not been included in either the draft or pre-invitation scope for this appraisal. It was, however, included in the final scope. The company stated that prescribing data from December 2015 indicates that pembrolizumab is not established in routine use in clinical practice and therefore should not be considered standard care in the NHS in England. However, the company provided analyses comparing nivolumab plus ipilimumab with pembrolizumab at the clarification stage.

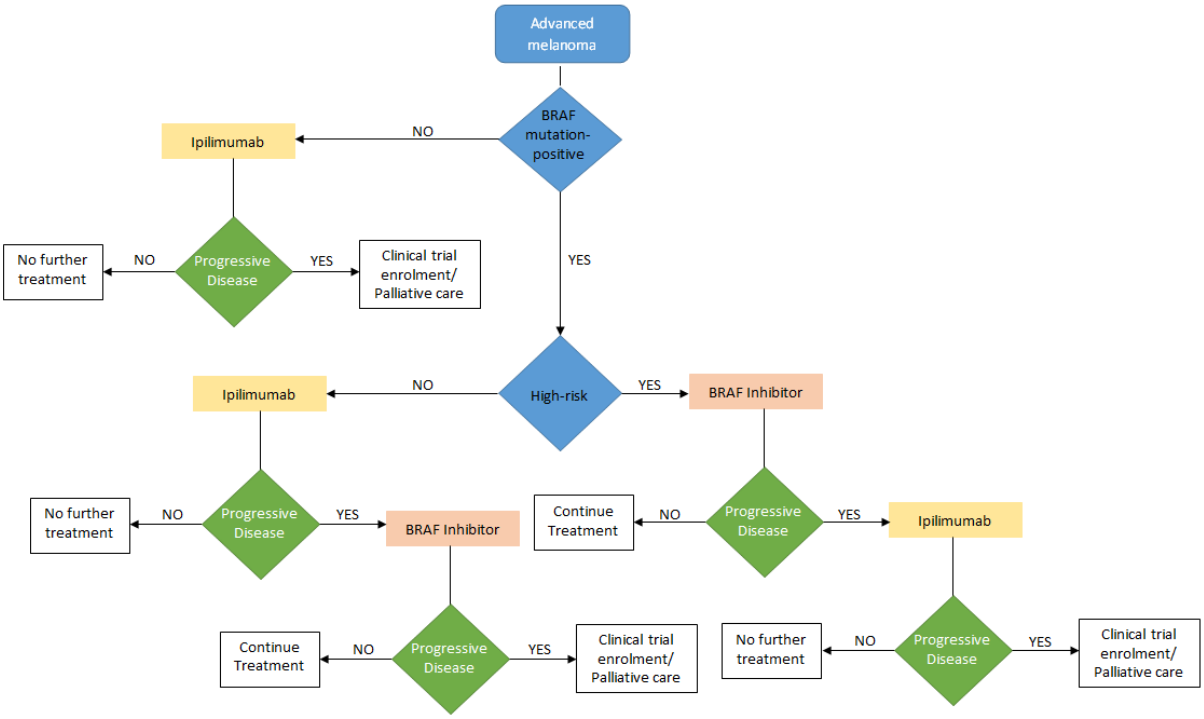
Out.	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.		

2 The technology and the treatment pathway

The technology

2.1 Nivolumab (Opdivo, Bristol-Myers Squibb) is a human monoclonal antibody (immunoglobulin G4) that blocks the programmed cell death-1 receptor (PD-1) and activates the immune system to attack cancer cells. Nivolumab is administered intravenously. Nivolumab currently has a marketing authorisation in the UK as a monotherapy 'for treating advanced (unresectable or metastatic) melanoma in adults'.

Figure 1 Treatment pathway before nivolumab plus ipilimumab (CS fig 4, pg 32)



2.2 The mainstay of treatment for advanced melanoma (unresectable or metastatic) is systemic immunotherapy with ipilimumab irrespective of BRAF 600 mutation status, or targeted therapy for BRAF mutation positive melanoma (with vemurafenib and dabrafenib). Technology appraisals 268 and 319 recommend ipilimumab as an option for treating advanced

(unresectable or metastatic) melanoma in people who have and have not had prior therapy respectively. NICE technology appraisal guidance 269 and 321 recommend vemurafenib and dabrafenib (respectively) as options for treating locally advanced or metastatic BRAF V600 mutation-positive unresectable or metastatic melanoma.

2.3 Technology appraisal 366 recommends pembrolizumab as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab. Technology appraisal 357 recommends pembrolizumab as an option for treating advanced (unresectable or metastatic) melanoma after the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF inhibitor (vemurafenib, dabrafenib) or MEK inhibitor (trametinib). Technology appraisal 384 recommends nivolumab monotherapy within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults.

Figure 2 Company's anticipated treatment pathway after the introduction of nivolumab plus ipilimumab (CS fig 5, pg 34)

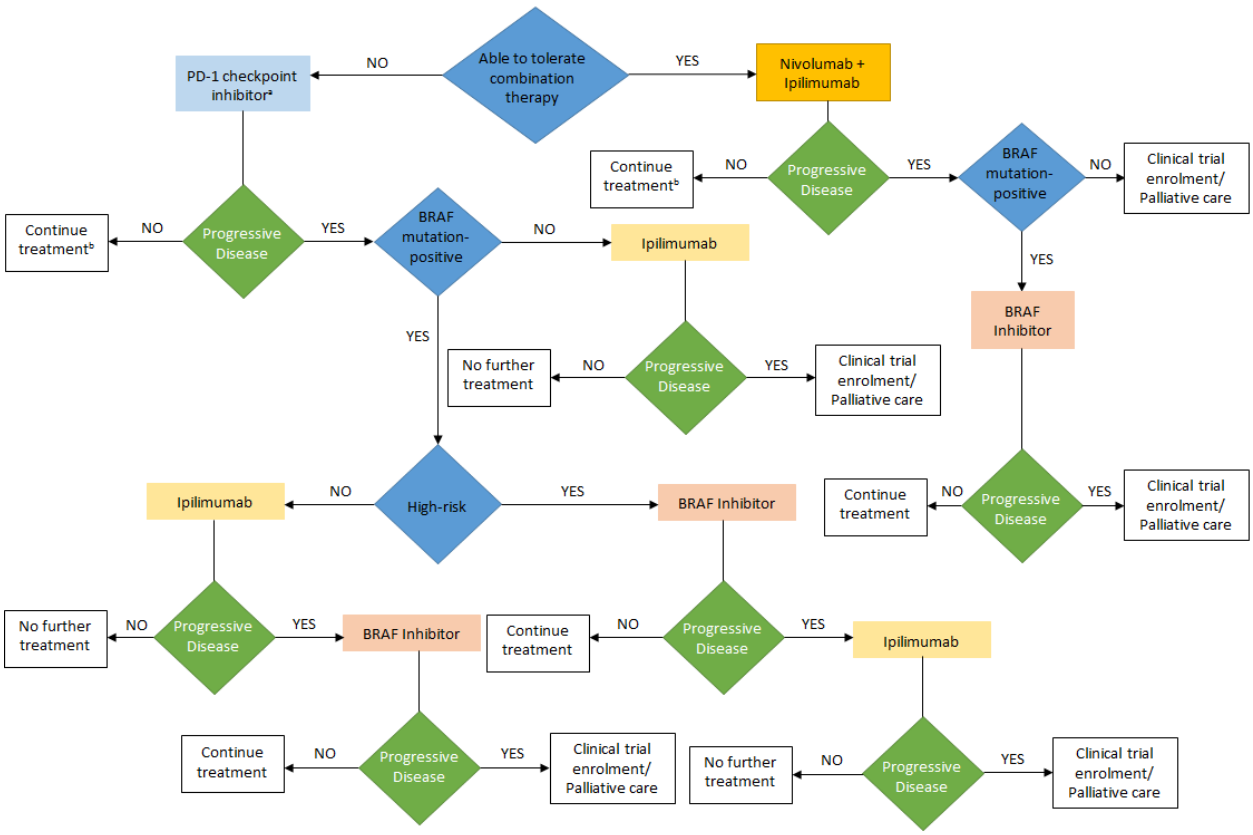


Table 2 Technologies

	Nivolumab plus ipilimumab (Bristol-Myers Squibb)	**BRAF inhibitors**		**Ipilimumab** (Bristol-Myers Squibb)
		Dabrafenib (Novartis)	**Vemurafenib** (Roche)	
Marketing authorisation	Combination immunotherapy therapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.	monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	for the treatment of advanced (unresectable or metastatic) melanoma in adults.
Administration method	Nivolumab 1mg/kg plus ipilimumab 3mg/kg every 3 weeks for 4 doses followed by nivolumab 3mg/kg every 2 weeks by intravenous infusion Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient The maximum duration of treatment is anticipated to be 2 years.	150 mg twice daily–a total daily dose of 300 mg until the patient no longer derives benefit or the development of unacceptable toxicity The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily.	960 mg twice daily–a total daily dose of 1,920 mg. Treatment should continue until disease progression or the development of unacceptable toxicity.	3 mg/kg every 3 weeks by intravenous infusion over a 90-minute period for a total of 4 doses. Liver function tests and thyroid function tests should be evaluated at baseline and before each dose.
Cost	£439 for 40mg (4ml) and	£933 for 28 tablets of 50 mg and £1400 for 28 tablets of	£1,750 for 56 tablets of 240 mg	£3750 for 50 mg (10ml) and £15,000 for 200 mg (40ml)

	£1,097 for 100mg (10 ml) Ipilimumab £3,750 for 50mg at list price £15,000 for 200mg at list price [redacted] for 50mg with PAS [redacted] for 200mg with PAS Source; the company's submission, table 5 page 24-25	75 mg Source: MIMS March 2016	Source: MIMS March 2016	Source MIMS March 2016

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 Ipilimumab and pembrolizumab can be used for all types of metastatic melanoma (including BRAF mutation negative and positive) but ipilimumab has serious autoimmune side effects. Systemic therapy of advanced melanoma involves the use of ipilimumab and pembrolizumab given sequentially as single agents. Generally, clinicians prefer pembrolizumab for first line therapy over ipilimumab as it is more effective and less toxic. Clinicians will only consider ipilimumab for patients who are fit enough to tolerate its side effects.

3.2 Approximately 50% of patients with BRAF mutation positive disease are considered for immunotherapy (pembrolizumab or ipilimumab) as a first line treatment, followed by second-line treatment with BRAF inhibitors, such as vemurafenib and dabrafenib. The other 50% of patients with BRAF mutation positive melanoma whose disease is rapidly progressive, who have short life expectancy and poor prognostic features (high disease burden, raised serum lactate dehydrogenase, poor performance status and multiple, symptomatic brain metastases) are treated with dabrafenib and vemurafenib. .

3.3 Nivolumab monotherapy was being still being appraised by NICE when submissions were received for this appraisal. Expert consensus is that nivolumab and pembrolizumab when administered as single agents have very similar efficacy and safety characteristics and both are anti-PD1 monoclonal antibodies.

3.4 The combination of nivolumab plus ipilimumab is a potential alternative to the sequential use of pembrolizumab and ipilimumab in the first line treatment of advanced melanoma. Nivolumab plus ipilimumab has a high rate of serious side effects, particularly colitis, and would only be considered for patients fit enough to tolerate these side effects. Furthermore the 067 trial is not yet mature for overall survival and some clinicians may wish not to use the combination regimen in the absence of

such data. Nevertheless in clinical situations where the maximum chance of a rapid and potentially durable response to treatment is needed, nivolumab plus ipilimumab may be chosen by a number of melanoma clinicians in discussion with patients. This treatment will be administered in centres specialised in the systemic therapy of advanced melanoma.

3.5 Nivolumab plus ipilimumab is more effective than either ipilimumab on its own or nivolumab on its own according to the CheckMate 067 trial (Larkin et al, NEJM). There is no direct comparison between nivolumab plus ipilimumab and the BRAF inhibitors (dabrafenib and vemurafenib).

3.6 NHS staff routinely administer ipilimumab and pembrolizumab, so no further training is needed for administration of nivolumab plus ipilimumab. Ipilimumab is given as a 90 minute infusion every 3 weeks for 4 cycles only. Nivolumab is given as an infusion every 2 weeks until progression or unacceptable toxicity, while pembrolizumab is given every 3 weeks until progression or unacceptable toxicity. Therefore, more treatment visits will be needed for the administration of nivolumab plus ipilimumab than pembrolizumab.

3.7 Patients who use nivolumab plus ipilimumab tend to experience more severe side effects than with ipilimumab monotherapy which could result in more admissions to hospital to manage toxicity, particularly for patients experiencing colitis. However, because patients taking nivolumab plus ipilimumab discontinue therapy permanently soon after experiencing side effects, the average duration of therapy with nivolumab plus ipilimumab may be less than for nivolumab or pembrolizumab monotherapy, which may limit the impact its introduction would have on outpatient resources for delivery of intravenous therapy for advanced melanoma. In Checkmate 067, fewer than half of the patients started on the combination regimen continued treatment beyond the initial 12 weeks.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review of clinical effectiveness identified 2 relevant randomised controlled trials (RCTs) for nivolumab plus ipilimumab. In the studies, nivolumab (1mg/kg) plus ipilimumab (3mg/kg) was administered every 3 weeks for 4 doses followed by nivolumab alone (3mg/kg) every 2 weeks by intravenous infusion.

- CheckMate 067 trial was a multicenter, international (7 UK centres), double-blind RCT that compared nivolumab plus ipilimumab (n=314 [n=30 from UK]) with nivolumab monotherapy (n=316) or ipilimumab monotherapy 3mg/kg IV every 3 weeks (n=315 [n=36 from UK]) in people with untreated advanced melanoma with and without the BRAF mutation. The primary outcomes of the trial were overall survival and progression-free survival.

- CheckMate 069 trial was a multicentre, international (no UK centres), double-blind RCT that compared nivolumab plus ipilimumab (n=95 [BRAF-mutation negative, n=72; BRAF-mutation positive, n=23]) with ipilimumab monotherapy (n=47 [BRAF-mutation negative, n=37; BRAF-mutation positive, n=10]), in people who had not received treatment previously. The primary outcome of the trial was overall response rate as defined by the best overall response (either complete or partial response) and tumour response rate assessed according to RECIST criteria.

For details of the trials' designs see company's submission Table 10 (page 44)

4.2 The company stated that in the trials, baseline demographics and disease characteristics were generally well balanced. The company pointed out that in both trials a lower proportion (32%-22%) of patients had BRAF

mutation-positive melanoma than is observed in the general population (~50%). The company explained that this is likely to reflect current clinical practice where BRAF mutation positive patients with significant disease burden and highly symptomatic disease may be deemed less suitable for immunotherapy and instead offered targeted therapies as first-line treatment. For details of baseline patients characteristics in trials see table 13 of the company's submission (page 60 to 61).

ERG comments

4.1 The Evidence Review Group (ERG) commented that the company's systematic review was good quality and identified all relevant RCTs, although the company could have included additional comparators, like nivolumab although outside the scope, to facilitate indirect comparisons through an NMA or the approach presented by the company (covariate adjusted method). The ERG commented that some studies which were not identified through the systematic search were included and used in the company's indirect comparisons and therefore it was unclear whether the selection of these trials (such as the CheckMate 066 trial) may have introduced bias affecting the results. The ERG also commented that some of the trials used in the indirect comparisons were not described in detail, the methods for data extraction were not specified and the quality assessments for some trials were not provided by the company.

4.2 The ERG commented that the CheckMate 067 and 069 RCTs were well-designed and well-conducted and provide appropriate evidence for clinical-effectiveness of nivolumab plus ipilimumab compared with ipilimuab alone. The ERG commented that no head-to-head data were identified comparing nivolumab plus ipilimumab against vemurafenib or dabrafenib.

Clinical trial results

4.3 Progression-free survival (PFS) is reported for both trials and was defined as time interval between the randomisation and disease progression or

death. The company stated that the PFS analysis was conducted using RECIST criteria that do not allow for consideration of "pseudo-progression" as a result of the immuno-oncology mechanism of action of nivolumab where in some instance tumour may temporarily appear to progress (see the company's submission, section 2.1, Figure 3 page 23). For this reason in both trials, patients treated with nivolumab plus ipilimumab could continue treatment beyond initial Response Evaluation Criteria in Solid Tumours (RECIST)-defined progression (where progression is assessed based on tumour size and/or the appearance of new lesions) if they were considered by the investigator to be experiencing clinical benefit and tolerating the study drug. Many of these patients had a response (developed or maintained a target lesion reduction of >30% compared to baseline) after initial RECIST defined progression (see table 7).

4.4 Objective response rate (ORR) was the primary outcome in CheckMate 69 and a secondary outcome in CheckMate 067. ORR was defined as the proportion of patients with complete or partial response. Tumour response was assessed according to RECIST by trial investigators or an independent radiological review committee (IRRC). In CheckMate 067, tumour response was assessed by the investigators and included all patients randomised (ITT population).

4.5 Health-related quality of life was measured by mean changes from baseline in health status by the company who used EQ-5D for both CheckMate 067 and 069 and by changes in work and activity impairment, assessed using the WPAI:GH tool for CheckMate 067 only.

CheckMate 067

4.6 The CheckMate 067 trial began in June 2013, and is currently ongoing. The data presented by the company are based on a clinical database lock which took place in February 2015. For each OS comparison, at least 460 events in the nivolumab plus ipilimumab and nivolumab arms are required

to provide at least 90% power to detect a HR of 0.72 with a type I error of 0.025 (2 sided). The HR of 0.72 corresponds to a 39% increase in the median OS assuming a median OS of 14 months for ipilimumab and 19.4 months for each of the experimental treatment arms. The company stated that CheckMate 067 was not designed for a formal statistical comparison between the nivolumab plus ipilimumab and nivolumab alone groups.

Overall survival

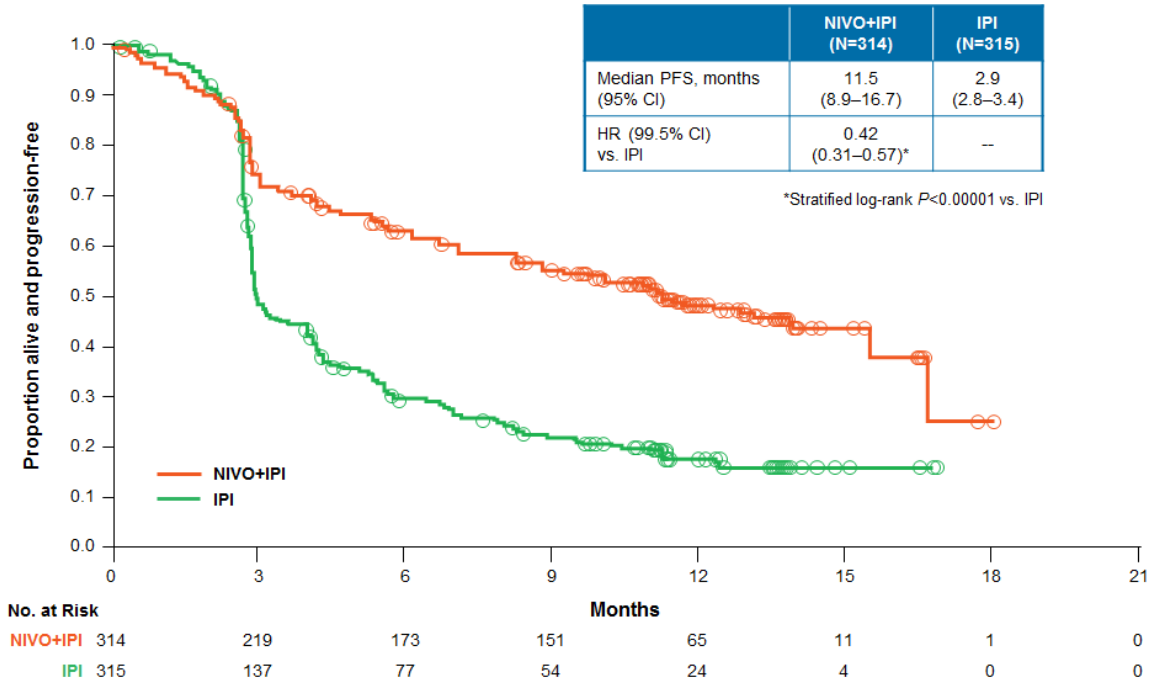
4.7 Results for overall survival were not available as the required minimum follow-up for analysis has not yet been reached (22 months) or an insufficient number of events (deaths) had occurred at the time of company's analyses.

Progression free survival

4.8 For the comparison of PFS, the company estimated that the number of events projected to be observed at a follow-up of at least 9 months would give the study approximately 83% power to detect an average HR of 0.71 at a type I error rate of 0.005 (two-sided) for all comparisons.

4.9 Treatment with nivolumab plus ipilimumab resulted in a significant extension in progression-free survival (PFS) compared with ipilimumab monotherapy (hazard ratio 0.42 [99.5% CI 0.31 to 0.57]); p<0.001) for the ITT population. The median PFS was 11.5 months (95% CI: 8.9 to 16.7) for nivolumab plus ipilimumab and 2.9 months (95% CI: 2.8 to 3.4) with ipilimumab. The Kaplan-Meier (KM) curve for PFS is presented below for the ITT analysis set.

Figure 3 Kaplan-Meier curve for PFS in CheckMate 067 (ITT) (CS, figure 10, page 65)



Objective response rate

4.10 Treatment with nivolumab plus ipilimumab resulted in an unweighted objective response rate difference of 38.4% compared with ipilimumab monotherapy (odds ratio 6.11 [95% CI 3.59 to 10.38]; p<0.001) for the ITT population.

Change in tumour burden

4.11 There was a median change in tumour burden of -51.9% in the population treated with nivolumab plus ipilimumab compared with +5.9% in the ipilimumab monotherapy group. At the time of the company's analysis (median follow-up of approximately 12 months) approximately 76.2% of patients continued to demonstrate a response despite many discontinuing study treatment (ITT population).

Subgroup analyses

4.12 Subgroup analyses assessing the impact of age, gender, race, region, baseline ECOG PS, PD-L1 expression status, BRAF mutation status, M

stage at study entry, history of brain metastases, smoking status, baseline LDH and AJCC stage on clinical efficacy outcomes were pre-planned. The statistical significance of benefit of treatment with nivolumab plus ipilimumab was demonstrated in all subgroups including elevated LDH which is particularly associated with poor prognosis.

CheckMate 069

4.13 The primary datasets used in CheckMate 069 were the all randomised BRAF mutation-negative population for primary efficacy analysis and the all treated population for the safety analyses. The company also conducted efficacy analyses in the all randomised population (ITT population) and in the cohort of patients with BRAF mutation-positive tumours, though these analyses were only intended to be descriptive and BRAF mutation-positive patients were not part of the sample size consideration.

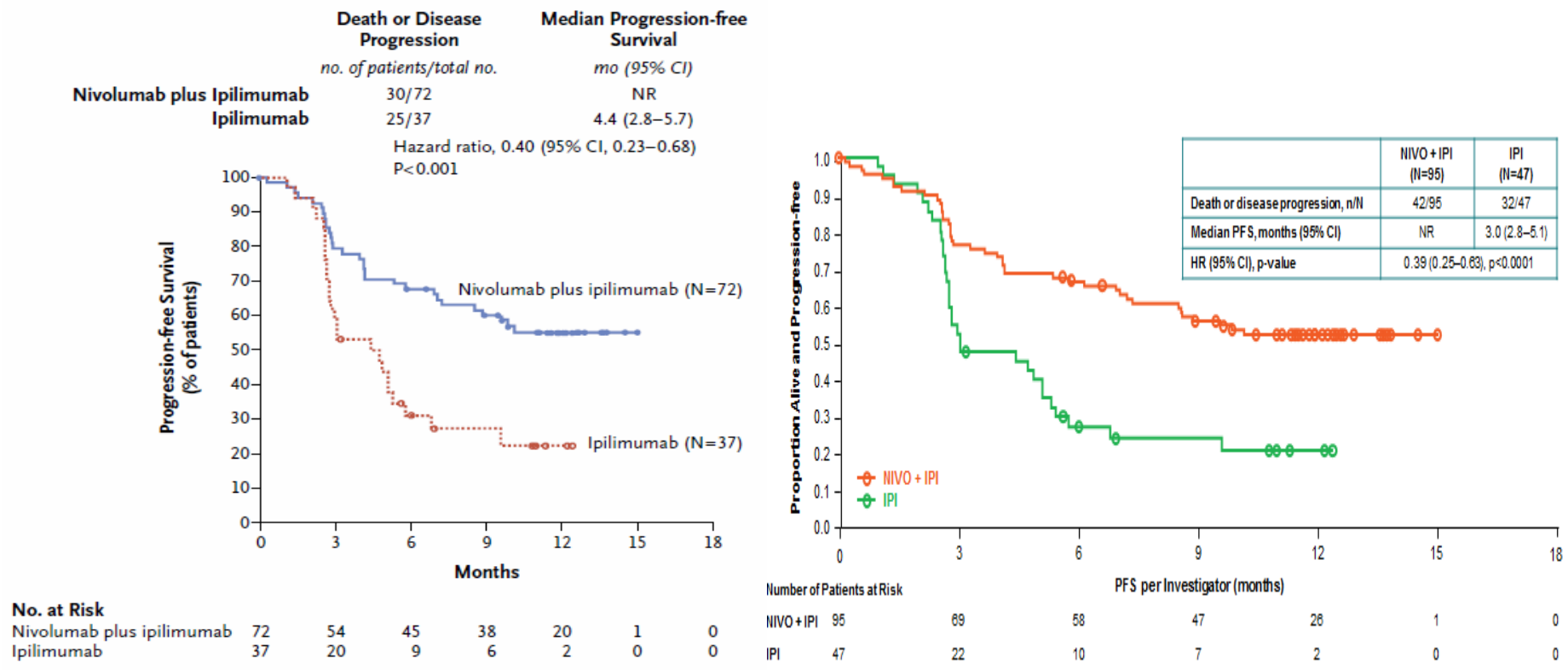
Overall survival

4.14 Early exploratory overall survival data from CheckMate 069 reports an 18-month OS rate of 69% in patients with advanced melanoma, irrespective of BRAF status (ITT population), approximately double the 18-month OS rate of 35%associated with ipilimumab monotherapy in pooled analyses of key historical trials. In exploratory OS analyses conducted by the company on a database lock from August 2015, median OS was yet to be reached in either group. The 75% OS rate (in other words, when a quarter of the patients have died) was reached in both arms and shows an additional 4 months survival associated with the nivolumab plus ipilimumab compared with ipilimumab monotherapy (341 days for nivolumab plus ipilimumab compared with 220 days for ipilimumab) despite a substantial crossover rate (56.5% at the time of analysis) of patients from the ipilimumab group to nivolumab monotherapy (as per protocol).

Progression free survival

4.15 For patients with BRAF mutation negative melanoma (the primary efficacy analysis set) in CheckMate 069, treatment with nivolumab plus ipilimumab resulted in a significant extension in progression-free survival (PFS) compared with ipilimumab monotherapy (hazard ratio 0.40, 95% CI 0.23 to 0.68, p<0.001). The median progression-free survival (PFS) for patients with BRAF mutation negative melanoma (primary efficacy analysis set) was not reached for nivolumab plus ipilimumab arm, whereas the median PFS for ipilimumab alone was 4.4 months (95% CI, 2.8 to 5.7). In ITT population (all randomised patients), treatment with nivolumab plus ipilimumab resulted in a significant extension in progression-free survival (PFS) compared with ipilimumab monotherapy (hazard ratio 0.39, 95% CI, 0.25 to 0.63, p<0.0001). The median PFS for the ITT population was also not reached in nivolumab plus ipilimumab arm and was 3.0 months (95% CI, 2.8 to 5.1) in the ipilimumab alone group. Similarly, among patients with BRAF mutation-positive melanoma, treatment with nivolumab plus ipilimumab resulted in a significant extension in progression-free survival (PFS) compared with ipilimumab monotherapy (hazard ratio 0.38, 95% CI, 0.15 to 1.00, p value not reported). The median PFS for patients with BRAF mutation-positive melanoma was 8.5 months (95% CI, 2.8 to not estimable) in the nivolumab plus ipilimumab group compared with 2.7 months (95% CI 1.0 to 5.4) in the ipilimumab group. The Kaplan-Meier curves for PFS for the primary efficacy analysis set (BRAF mutation negative population) and the ITT analysis set (all randomised patients) from CheckMate 069 are shown below.

Figure 4 Kaplan-Meier curve for PFS in CheckMate 069 Primary efficacy set (left) and Intention-to-treat set (right), (CS, figure 11, page 66 and CS Appendix 7, Figure 3)



Objective response rate

4.16 In CheckMate 069, there was a statistically significant difference in investigator-assessed objective response rate (ORR) of 61% (95% CI, 49 to 72) in the group receiving nivolumab plus ipilimumab compared with 11% (95% CI, 3 to 25) in the ipilimumab alone group in people with BRAF mutation negative melanoma (the primary efficacy analysis set) (OR for response 12.96 [95% CI 3.91 to 54.49]; p<0.001). Among patients with BRAF mutation positive melanoma, the investigator-assessed ORR was 52% in the nivolumab plus ipilimumab group compared with 10% in the ipilimumab group. Across all randomised patients (ITT population), regardless of BRAF mutation status, investigator-assessed ORR was 59% in the nivolumab plus ipilimumab group compared with 11% in the ipilimumab group (OR for response, 12.19 [95% CI: 4.41, 33.68]; p<0.).

Change in tumour burden

4.17 In CheckMate 069 patients with BRAF mutation-negative melanoma (the primary efficacy analysis set), the median change in tumour burden was -68.1% in the nivolumab plus ipilimumab group compared with +5.5% in the ipilimumab group. Similarly, in all randomised patients (ITT population), the median change in tumour burden was -63.5% in the nivolumab plus ipilimumab group compared with +7.8% in the ipilimumab group. The median change in tumour burden for the BRAF mutation positive patients was not calculated.

Subgroup analyses

4.18 Subgroup analyses assessing the impact of metastasis stage at study entry, AJCC stage, age, gender, race, region, baseline ECOG performance status, history of brain metastases, smoking status, and baseline LDH on clinical efficacy outcomes were pre-planned for patients with BRAF mutation-negative and BRAF mutation-positive tumours. The statistical significance of PFS and ORR with nivolumab plus ipilimumab was demonstrated in all subgroups including elevated LDH which is particularly associated with poor prognosis.

4.19 A post-hoc, pooled analysis of patients with mucosal melanoma was conducted due to small numbers of patients with CheckMate 067 and 069. Statistically significant clinical benefit of nivolumab plus ipilimumab compared to ipilimumab monotherapy was demonstrated. Treatment with nivolumab plus ipilimumab resulted in a median PFS 5.9 months (95% CI 2. to not estimable) in patients treated with nivolumab plus ipilimumab compared to 2.7 months (95% CI 2.6 to 2.8) in patients receiving ipilimumab (HR 0.42 [95% CI, 0.23 to 0.72]; p=0.003)

4.20 The company presented changes in tumour burden as 'waterfall plots' (see company's submission figures 13, 16 and 39, pages 69, 72 and 110, respectively). The waterfall plots showed that more patients in the nivolumab plus ipilimumab arm experienced a reduction in tumour size, and achieved at least a partial response, compared with the patients in the comparator groups.

Table 3 Response rates for the Intention to Treat population (CS Table 33, Section 4.11)

Outcome	CheckMate 067		CheckMate 069	
	Nivolumab + ipilimumab (n= 314)	Ipilimumab (n=208)	Nivolumab (n= 95)	Ipilimumab (n= 47)
Objective response rate (ORR)				
Responders, n (%) (95% CI)	181 (57.6) (52.0-63.2)	60 (19.0) (14.9-23.8)	56 (59) (48-69)	5 (11) (4-23)
Complete response, n (%)	36 (11.5)	7 (2.2)	21 (22)	0
Partial response, n (%)	145 (46.2)	53 (16.8)	35 (37)	
Unweighted ORR difference, % (95% CI)	38.4		(not reported)	
Estimated odds ratio (95% CI) p-value	6.11 (3.59, 10.38) <0.001		12.19 (4.41, 33.68)	
Duration of response				
Median (range), months	Not reached	5.98 (1.1, 10.0)	Not reached	Not reached
Time to treatment response				
Median (range), months	2.8 (1.1, 11.6)	2.8 (2.5, 12.4)	2.8 (2.3, 12.5)	2.8 (2.5, 12.4)
CI = confidence interval; CR = complete response; DTIC = dacarbazine; ORR = Objective response rate; PR; partial response rate., Response rates assessed by investigators and included all randomised patients (ITT)				

4.21 Health-related quality of life was assessed using EORTC QLQ-C30, which is specifically developed to assess the quality of life of cancer patients, and EQ-5D and EQ-5D VAS (visual analogue scale). The company presented data from CheckMate 067 up to 67 weeks of follow-up and a minimum follow-up of 25 weeks for CheckMate 069.. The proportion of patients from CheckMate 067 and CheckMate 069 with at least 1 baseline and post baseline EORTC QLQ-C30 assessment was 87.3% and 65%, respectively, for the nivolumab plus ipilimumab arm and 82.2% and 77%, respectively, for the ipilimumab alone arm. The company reported similar completion rates for EQ-5D and EQ-5D VAS. For each of the utility measures, no clinically meaningful changes (defined as a minimally important difference of ≥10 points for EORTC QLQ-C30, ≥0.08 points for EQ-5D utility and ≥0.7 points for EQ-5D VAS) was seen in either treatment arm, at any timepoint for the time periods presented.

ERG comments

4.22 The ERG considers CheckMate 069 and CheckMate 067 to be 2 good quality, double blind, phase II and III randomised controlled trials. The ERG expressed concern at the lack of data to support the company's claim that the response is similar for nivolumab plus ipilimumab and the BRAF inhibitors, and therefore the use of nivolumab plus ipilimumab as first line therapy for all patients, including patients with BRAF positive mutation melanoma.

Indirect comparison/MTC

4.23 The company did not do a network meta-analysis for the following reasons:

- proportional hazards assumption could not be made between the BRAF inhibitors, immunotherapies and chemotherapy due to differences in mechanism of action between treatments

- there were high levels of patient crossovers from chemotherapy to BRAF inhibitor therapy in the relevant trials
- differences in design and baseline characteristics between trials.

Instead, the company presented 2 indirect comparisons: 1 for nivolumab plus ipilimumab compared with ipilimumab alone; and 1 for nivolumab plus ipilimumab compared with BRAF inhibitors (dabrafenib and vemurafenib). The company selected trial arms (see table below) which were compared using a covariate-adjusted model, rather than using indirect comparison via a common comparator.

Table 4 Company's selected evidence base for indirect comparisons (CS, table 18, page 83)

Trial	Treatments	BRAF status	Previously treated?	Patient level data available?	Subsequent therapy / crossover
CheckMate 067	• Nivolumab plus Ipilimumab • Nivolumab • Ipilimumab	Mixed	No	Yes (only for PFS)	No subsequent therapy pre-progression Post progression subsequent therapies included anti-PD1s, ipilimumab and BRAF inhibitors
CheckMate 069	• Nivolumab plus Ipilimumab • Ipilimumab	Mixed	No	Yes (small sample size)	Crossover from ipilimumab to nivolumab on progression
CheckMate 066	• Nivolumab • Dacarbazine	BRAF mutation negative	No	Yes	Crossover (from dacarbazine) & subsequent ipilimumab
MDX010-20	• Ipilimumab 3mg/kg • gp-100 • Ipilimumab 3mg/kg + gp-100	Unknown	Yes	Yes	No subsequent ipilimumab or BRAF inhibitors
BRIM-3	• Vemurafenib • Dacarbazine	BRAF mutation positive	No	No	Crossover (from dacarbazine) & subsequent ipilimumab
BREAK-3	• Dabrafenib • Dacarbazine	BRAF mutation positive	No	No	Crossover (from dacarbazine) & subsequent ipilimumab
Key: PFS, progression free survival					

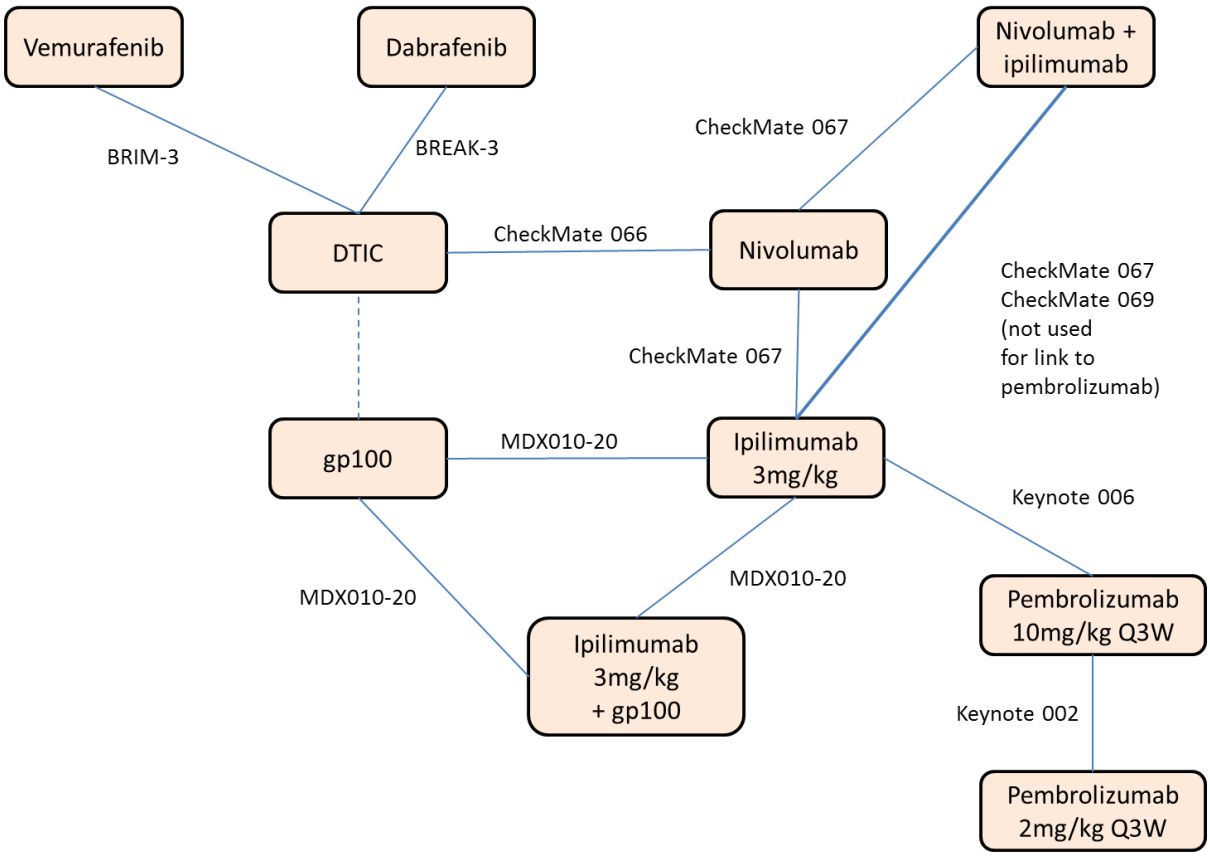
Indirect comparison of nivolumab plus ipilimumab versus ipilimumab

4.24 Both OS and PFS data from CheckMate 069 was not used due to lack of maturity at the time of submission. The company used PFS data for nivolumab plus versus ipilimumab from CheckMate 067. Because the OS data from CheckMate 067 were not mature, the company assumed equivalence of the nivolumab and ipilimumab regimen with for nivolumab monotherapy (using the OS data from CheckMate 066) and for ipilimumab (using data from MDX010-20). The company acknowledged that CheckMate 066 only enrolled BRAF mutation-negative patients who had not been treated previously, but stated that previous treatment and BRAF mutation status should not have an impact on outcomes.

Indirect comparison of nivolumab plus ipilimumab versus BRAF inhibitors (dabrafenib and vemurafenib)

4.25 Because PFS and OS data were not available for the comparison of nivolumab plus ipilimumab with dabrafenib or vemurafenib, the company did an indirect comparison. The company used patient level data from CheckMate 067, CheckMate 066, and MDX010-20, and aggregate/summary data from BRIM-3 (basecase)/ BREAK-3 (scenario analysis) using digitalised pseudo patient level data to form an indirect comparison (see figure below). The individual patient data from CheckMate 067, CheckMate 066 and MDX010-20 were adjusted for the key prognostic patient characteristics identified by a meta-analysis of phase II trials by Korn et al. 2014 which had identified variables affecting OS and FS in patients with advanced melanoma. The company stated that the analyses were consistent with the approach used in NICE TA 319 and were also validated by its advisory which included UK clinicians.

Figure 5 Network diagram (CS figure 24, page 81 and Company's clarification response, Figure 1, page 5)



Key: DTIC, dacarbazine; gp-100, gp-100 melanoma peptide vaccine.

Notes: The dotted line between DTIC and gp-100 does not indicate a trial, but rather indicates that if DTIC and gp-100 are considered equivalent, it allows for MDX010-20 to be linked within this network of treatments.

4.26 The company defined time-to-progression in the same way as PFS, except that patients which progress due to death are censored at death. PrePS is defined the same way as PFS, except that patients which progress due to death are counted as events, and all other patients are censored at their PFS time. PPS only includes patients that have progressed and follows time to death, or censoring, from the point of progression. TTP and PrePS are used to inform the long-term extrapolation of PFS. TTP, PrePS and PPS are used to inform the long-term extrapolation of OS.

4.27 The company fitted parametric curves to TTP, PrePS and PPS separately using the exponential, Weibull, log-normal, log-logistic, gamma and Gompertz models.

4.28 For the indirect comparison of nivolumab plus ipilimumab with ipilimumab alone, the company made the following assumptions:

- the OS data from CheckMate 066 and MDX010-20 could be used as a proxy assuming equal efficacy between ipilimumab, nivolumab and nivolumab plus ipilimumab.
- only post-progression survival (PPS) relies on OS data, therefore data for nivolumab and ipilimumab monotherapy were used to inform PPS for nivolumab plus ipilimumab (the company considered this assumption of equal efficacy is to be conservative)
- BRAF mutation status does not affect the treatment effect of immunotherapies
- line of treatment does not independently impact treatment effectiveness. This assumption was needed as MDX010-20 enrolled previously treated patients whereas the other trials in the indirect comparisons, CheckMate 067 and CheckMate 066, enrolled treatment naive patients.
- ipilimumab plus gp100 and ipilimumab monotherapy were assumed to have equal efficacy in MDX010-20. This assumption was required to maximise the data used by including data from both these trial arms in MDX010-20 to estimate PPS of combination immunotherapy and ipilimumab. In MDX010-20 there was no marked difference in OS or PFS for ipilimumab plus gp100 and ipilimumab monotherapy.

4.29 The company provided a comparison of the results from their model with unadjusted, partially adjusted (study and treatment), and fully adjusted (all covariates) results, and results from CheckMate 067 (see table below).

Table 5 Indirect comparisons using patient level data for nivolumab plus ipilimumab versus ipilimumab (Company's clarification response, table 6, pages 8-9 and ERG report table 35, page 104)

Outcome	Hazard ratio (95% CI) for Cox model with covariates for study and treatment	Hazard ratio (95% CI) for Cox model with covariates for study, treatment, ECOG, M-stage, age group, gender, brain metastases and elevated LDH
OS	0.607 (0.402, 0.916)	0.596 (0.395, 0.901)
PFS	0.536 (0.391, 0.735)	0.544 (0.396, 0.746)
PPS	0.991 (0.606, 1.618)	0.900 (0.550, 1.473)
OS- overall survival, PFS – progression free survival, PPS – post progression survival		

4.30 The company observed a steep drop in the KM curves at day 84 CheckMate 067 for both treatments related to the clustering of progression events around first scheduled tumour assessment occurred was 12 weeks (84 days). Although a large number of patients were seen to progress at or shortly after the 3 month timepoint, some of these patients would be expected to have progressed earlier than 3 months. Therefore, in order to make the fit of the parametric survival curves meaningful to these data near to the start of the curves, the company cut the data at Day 84.

Indirect comparison of nivolumab plus ipilimumab versus BRAF inhibitors (dabrafenib and vemurafenib)

4.31 For the indirect comparison of nivolumab plus ipilimumab versus BRAF inhibitors (dabrafenib and vemurafenib), the company used the same data for nivolumab plus ipilimumab that it used for the indirect comparison with ipilimumab (see paragraph 4.21 above). For the BRAF inhibitors, the company used aggregate data from the vemurafenib arm from BRIM-3. The company assumed equal efficacy between vemurafenib and dabrafenib.

4.32 The company digitised published OS and PFS Kaplan-Meier curves from BRIM-3 for vemurafenib. Using the digitised curves, the company created pseudo patient level data using Guyot et al 2012. The company fitted

parametric survival curves for OS and PFS separately to the single arm pseudo patient level data and these curves were then used directly in the economic model. To compare OS and PFS between nivolumab plus ipilimumab and vemurafenib , the OS and PFS estimates for nivolumab plus ipilimumab (as constructed within the economic model from TTP, PrePS and PPS; see section 5.X below) were re-estimated, adjusted for the observed patient characteristics in the BRIM-3 trial.

4.33 As with the indirect comparison with ipilimumab, the company assumed that the BRAF mutation status does not have an effect on immunotherapies and that the line of treatment is not independently prognostic.

Indirect comparison of nivolumab plus ipilimumab and pembrolizumab

4.34 At the clarification stage in response to a request from the ERG the company performed an adjusted indirect comparison to enable a comparison of nivolumab plus ipilimumab and pembrolizumab by including the trials: CheckMate 067, Keynote 006 (pembrolizumab 10mg/kg Q3W versus ipilimumab) and Keynote 002 (pembrolizumab 10mg/kg Q3W versus pembrolizumab 2mg/kg Q3W).[1]

4.35 [redacted]

4.36 [redacted]

[1] Please note, the marketing authorisation for pembrolizumab is only for the 2mg/kg Q3W dosage.

ERG comments

4.37 The ERG was concerned that the company used the same inclusion criteria for the direct and indirect evidence as other trials which could have linked the network or informed an indirect comparison were not identified in the systematic search. Although CheckMate 066 was not identified in the search for indirect evidence, it was used by the company in its network.

4.38 The ERG's critiqued the company's reasons for not doing a network meta-analysis. The ERG agreed that the proportional hazards assumption was unlikely to apply for the whole survival curve for the BRAF inhibitors compared with dacarbazine (due to the differences in mechanism of action). Nevertheless, the ERG believes that the company could have segmented the survival curves into sections in which the proportional hazards assumptions holds and then used a piecewise constant model. Similarly, the ERG agreed that the differences between the trials in terms of crossover and subsequent therapies could affect the comparability of the trials in the network. However, the ERG commented that the company could have used an appropriate method to adjust for switching or used the ITT method. The ERG stated that a network meta-analysis would have been possible to conduct and that the differences in the baseline characteristics between studies would not have been so great as to make the results from a network meta-analysis unsuitable for decision making. Regarding the Korn meta-analysis which the company used to determine the prognostic factors used in its indirect comparison, the ERG commented that there were differences the definitions of prognostic factors used by the company's analysis compared to the Korn et al study. The ERG notes that no rationale or references were provided to support the assumption.

Table 6 Comparison of prognostic factors in the Korn et al. study and the company's analysis (ERG report, table 85 page 189)

Parameter	Korn *et al.*[19]	Company's analysis

Parameter	Korn *et al.*[19]	Company's analysis
Age	Continuous variable	Dichotomous variable: Above or below 65 years of age
Gender	Dichotomous variable: Male or female	Dichotomous variable: Male or female
Disease	Dichotomous variable: Visceral disease or not	Dichotomous variable: M1c; or M0, M1a or M1b
Performance status	Three-level variable: ECOG PS 0, 1 or 2-3	Dichotomous variable: ECOG PS 0 or ≥1
Brain metastases	**Trial-level variable** Dichotomous variable: Inclusion or exclusion of patients with brain metastases	**Individual-level variable** Dichotomous variable: Brain metastases or not
LDH level	Not included	Dichotomous variable: Above or below ULN

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; ULN, upper limit of normal (range).

4.39 The company stated that [redacted].

4.40 The ERG acknowledges the uncertainty introduced if extrapolating OS and PFS long-term from very immature data, and notes that with this approach the company could use data from MDX010-20, with a follow-up of up to 56 months (4.7 years) for OS, compared to the available data for the direct comparison from CheckMate 069 with a follow up of up to 18 months for OS.

[redacted]

4.41 The ERG expressed concern at the loss of randomisation resulting from the company's covariate-adjusted model approach and questioned whether this approach could adjust for all differences between the trials. The ERG stated that these differences would be minimised in a network meta-analysis.

4.42 The ERG commented on the company's assumption of equal efficacy between dabrafenib and vemurafenib. The ERG noted that while the assumption was accepted in TA321, it was not considered robust by the ERG who appraised the company's submission. The ERG also noted that there were other 3 BRAF inhibitor trials (COMBI-d, COMBI-V and coBRIM) with relatively large sample sizes and median follow up of 10 to 20 months identified by the company apart from BRIM-3 and BREAK-3. Due to time constraints the ERG was unable to determine the impact of trial selection on subsequent analyses.

4.43 The ERG noted that the company approach requires many assumptions and that most importantly it breaks randomisation. Additionally, the ERG commented that the selection of study data was inadequately described and unclear.

4.44 With regard to the comparison to pembrolizumab presented by the company during clarification, the ERG commented that the comparability of the included trials has not been fully assessed, and that the results should be interpreted with caution.

Adverse effects of treatment

4.45 In CheckMate 067, no clinically meaningful changes in EORTC QLQ-C30 or EQ-5D were observed in either treatment group. In patients who experienced a Grade 3-4 AE, deterioration in EORTC QLQ-C30 global health status was similar between treatment groups.

4.46 In CheckMate 069, no clinically meaningful changes in EORTC QLQ-C30 or EQ-5D were observed in either treatment group and no significant

differences in improvement or deterioration in health-related quality of life were observed from baseline compared with ipilimumab monotherapy

4.47 Health-related quality of life was generally shown to deteriorate during the first 12 weeks of treatment with nivolumab plus ipilimumab before returning to baseline levels or similar from week 13 (when patients are no longer receiving ipilimumab alongside nivolumab therapy).

5 Cost-effectiveness evidence

Model structure

5.1 The company presented a new (de novo) semi-Markov survival model of nivolumab plus ipilimumab for 2 subpopulations: people with previously untreated BRAF-mutation-negative disease (compared with ipilimumab) and people with previously untreated BRAF-mutation positive disease (compared with ipilimumab, dabrafenib and vemurafenib. The model adopted a lifetime horizon of 40 years and a cycle length of 1 week. The model perspective was the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.

5.2 The model had 3 health states: pre-progression, progression and death (see Figure 4). The transition from progression-free to progression was derived from time to progression (TTP), and transition from progression-free to death from pre-progression survival (PrePS) outcomes from relevant clinical trials. The mortality rates for patients in the progression state were derived from post-progression survival (PPS) data. Under the modelling approach taken, the company assumes that time-to-progression is a proxy for overall survival over the entire time horizon of the model. The company also assumes that PPS depends on the time of progression only between the time patients enter the model and year 3. Mortality in post-progression after year 3 was assumed to depend on the time within the model, and not on time of disease progression.

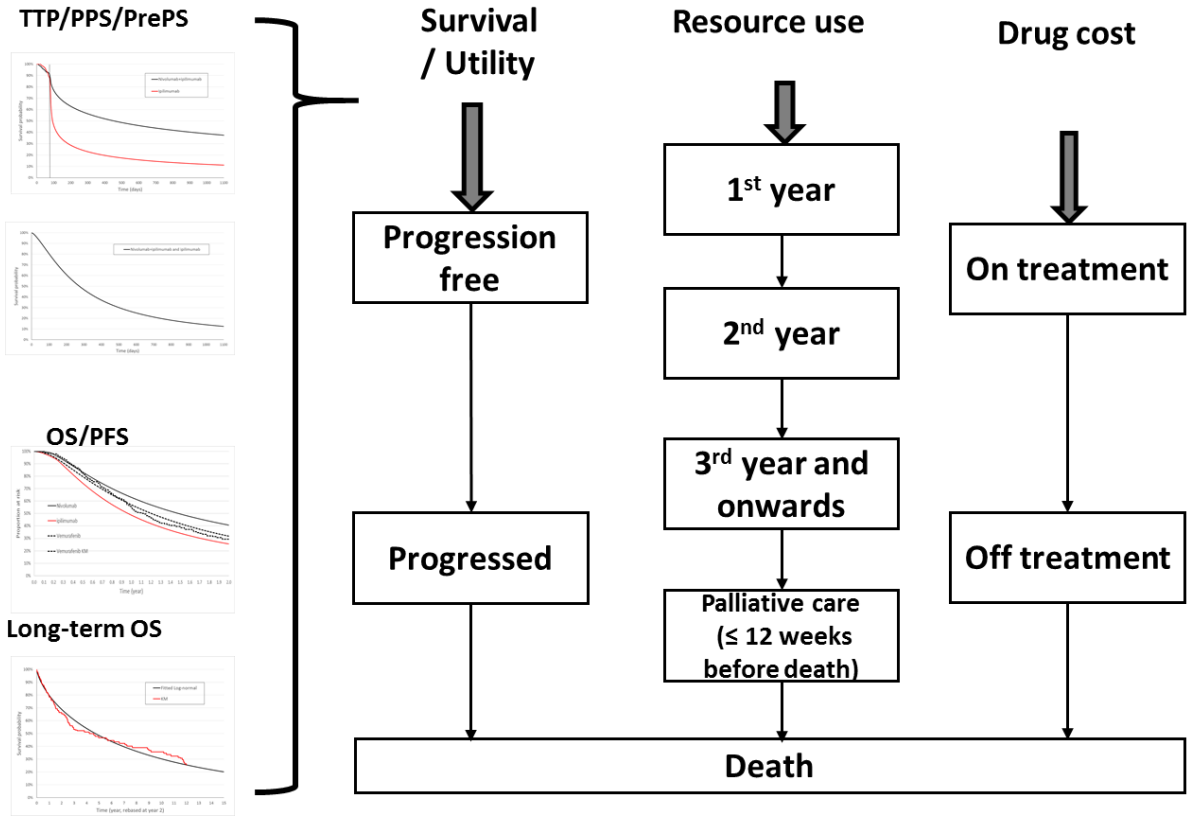
5.3 For BRAF mutation-positive patients, the company modelled survival with dabrafenib and vemurafenib based upon parametric curves fitted to trial-based empirical OS and PFS using digitised data from the BRIM-3 study. This was used to derive the proportions of patients in the progression-free, progressed and death states in each Markov cycle using the area under the curve method. OS and PFS were used by the company because no TTP, PPS and PrePS data was available. In the company's base case model, the same survival efficacies (OS and PFS) are assumed for dabrafenib and vemurafenib.

5.4 Patients receiving nivolumab plus ipilimumab receive treatment for a maximum duration of 2 years in the model. Patients have a maximum of 4 doses of ipilimumab in both the nivolumab plus ipilimumab and ipilimumab monotherapy cohorts. The on treatment period for patients in the BRAF inhibitor treatment arms is defined based on the progression free health state in line with the license.

5.5 For modelling resource use, the model adopted 4 states as follows

- first year after treatment initiation;
- second year after treatment initiation,
- third and subsequent years after treatment initiation,
- 12 weeks before death (palliative care)

Figure 6 Economic model structure (simplified) (CS, page 129, figure 44)



ERG comments

5.6 The ERG commented that the justification presented by the company (including a similar approach used in a previous submission) to support the modelling approach taken was inadequate. .The ERG commented that the company's model was unnecessarily complex and a simpler approach such as partitioned survival modelling could have been taken.

5.7 The ERG did not agree that the company's assumption of equal efficacy between ipilimumab, nivolumab and nivolumab plus ipilimumab for PPS using data from CheckMate 066 and MDX010-20 as a proxy for OS was conservative. The ERG strongly disagrees with the company's assertion, because setting the same PPS for all immunotherapies suggests that TTP could be a proxy for OS (in other words, more time without progression will result in more time alive). The ERG does not believe that the link between TTP and OS has been tested or justified by the company.

Instead the ERG consider that the company's analysis strategy might have favoured the treatment with the longer TTP, i.e. combination therapy.

5.8 The ERG did not agree with the exclusion of pembrolizumab (which was included in the final scope) and requested that a comparison of nivolumab plus ipilimumab and pembrolizumab be presented during clarification (see section 1 of the company's clarification response).

5.9 The ERG commented that other aspects of the model such as the cycle length and time horizon were appropriate.

Model details

Modelling of clinical effectiveness

5.10 The clinical effectiveness estimates of nivolumab plus ipilimumab used in the model were based on the CheckMate 067 trial. TTP and PrePS data from CheckMate 067 was used to extrapolate PFS., and data from MDX010-20 and CheckMate 066 were used to estimate PPS.

5.11 Because the OS data from CheckMate 067 and 069 were not mature, the company assumed equivalence with the OS data for nivolumab monotherapy using data from CheckMate 066 and for ipilimumab using data from MDX010-20.

Survival Curve fitting

Nivolumab plus ipilimumab and ipilimumab (BRAF mutation negative population)

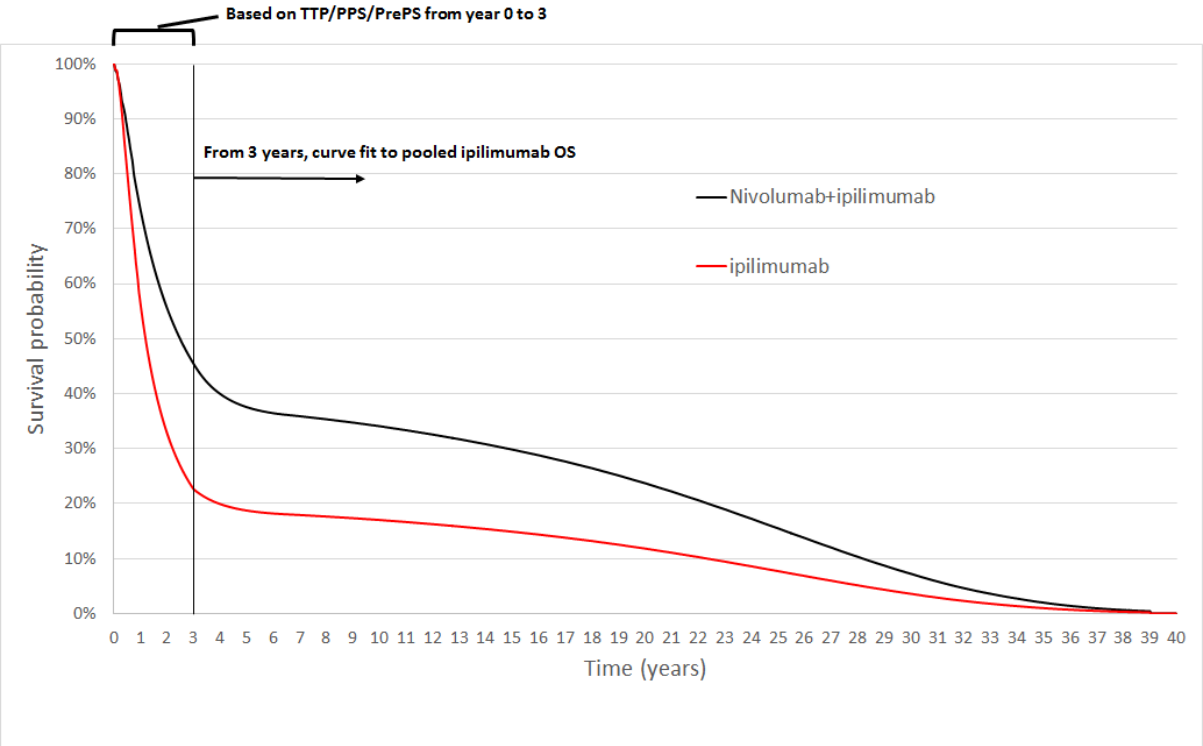
5.12 For TTP, the Kaplan Meier data from CheckMate 067 (nivolumab plus ipilimumab) were used for the first 84 days, adjusted for the patients' baseline characteristics based on the estimates of a Cox proportional hazards model. After 84 days, the company fitted parametric curves to the CheckMate 067 data. The company considered the log-normal distribution

to be the best fit in the base case and tested the impact of using other curves on cost-effectiveness results in scenario analyses.

5.13 The company modelled Pre-PS using Kaplan-Meier data from CheckMate 067 (because of the small number of events) adjusted by covariates for the length of the trial follow-up. After the end of maximum trial follow-up, the company assumed patients die at the same rate as the general population using age-specific mortality for the UK.

5.14 The company modelled PPS based on the nivolumab arm of the CheckMate066 trial and the pooled ipilimumab and ipilimumab plus gp100 arms of the MDX010-20 trial fitting the log-logistic function to the data from the start of the model to year 3. After year 3 to the time horizon, the company used a Gompertz parametric model, based on pooled long term survival data from 12 studies for ipilimumab (Schadendorf et al). The final modelled OS for BRAF mutation-negative patients, combining short-term trial-based estimates, long-term OS from pooled ipilimumab estimates over 40 years

Figure 7 Final overall survival in the base case model for BRAF mutation-negative analysis over life time (40 years) (CS, figure 52, page 146)



BRAF inhibitors (vemurafenib and dabrafenib for BRAF mutation positive population only)

5.15 For the nivolumab plus ipilimumab and ipilimumab, the company used the same method it used for the BRAF mutation-negative analysis to estimate PFS and OS (in other words, covariate-adjusted parametric curves or KM data for TTP, PPS and PrePS for the first 3 years; and long-term pooled ipilimumab OS from year 3 onwards). The only difference was that the company based the patient characteristics on the vemurafenib arm of the BRIM-3 trial to reflect BRAF mutation-positive patients and to maintain comparability with the PFS and OS used for the dabrafenib and vemurafenib arms.

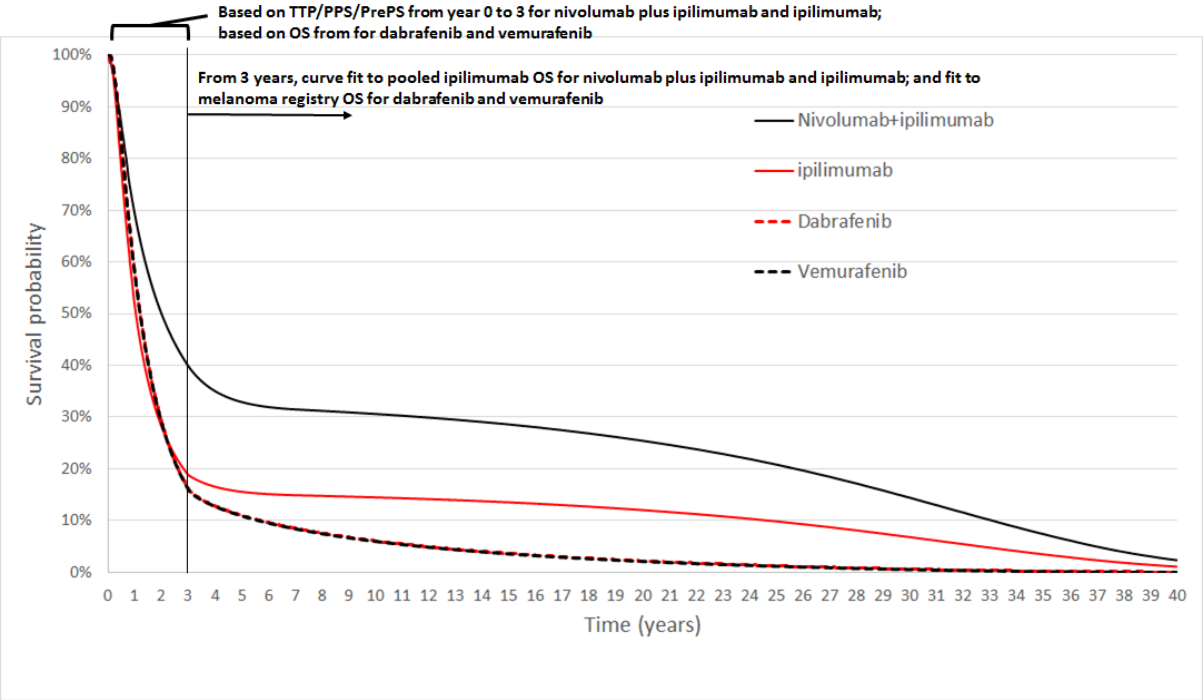
5.16 Individual patient data from the vemurafenib BRIM-3 were not available, so the company generated 'pseudo patient-level data' from published Kaplan-Meier curves of the BRIM-3 trial using digitisation software. A

generalised gamma parametric model was considered to be the best fit. The overall survival curve was set as the upper bound for PFS.

5.17 For the nivolumab plus ipilimumab and ipilimumab monotherapy, the final PFS combines TTP and PrePS based on BRIM-3 trial patient characteristics. For dabrafenib and vemurafenib, it is assumed that the 2 BRAF inhibitors have the same PFS, and the KM data from vemurafenib BRIM-3 trial were used to fit parametric curves generalised gamma curve in the base case.

5.18 The modelled OS for BRAF mutation-positive patients for the first 3 years for the nivolumab plus ipilimumab and ipilimumab combines TTP, PPS, and PrePS using patient characteristics from the vemurafenib arm in the BRIM-3 trial. For dabrafenib and vemurafenib, the company assumed that the 2 BRAF inhibitors have the same OS, and the KM data from vemurafenib BRIM-3 trial were used to fit parametric curves using the log-normal curve in the base case. After year 3 to the end of the time horizon, the company chose a Weibull parametric model fitted to data from the American Joint Committee on Cancer registry for melanoma-specific mortality and age-matched general population mortality for the UK.

Figure 8 Final overall survival in the base case model for BRAF mutation-positive analysis over life time (40 years)(CS, figure 56, page 153)



Population

5.1 The company based the patient characteristics in the model on the CheckMate 067 trial for BRAF mutation-negative disease and from the vemurafenib arm of the BRIM-3 trial for BRAF mutation-positive disease (see table 7).

5.2 The model allowed subsequent treatment with ipilimumab for people receiving nivolumab and other comparator treatments except ipilimumab. In the base case 29.7% and 22.0% people with BRAF mutation-negative and BRAF mutation positive melanoma respectively, received subsequent ipilimumab treatments.

Table 7 Patient characteristics at baseline influencing treatment effectiveness (ERG report, table 59 adapted from CS, pg 138 [table 51] and 147 [table 52])

Characteristics	BRAF-	BRAF+
Mean age	62	59
% male	66.2%	59.0%
% under 65	53.3%	100%

Characteristics	BRAF-	BRAF+
% stage M1c	59.2%	66.0%
ECOG status = 0	70.4%	68.0%
% elevated LDH (>ULN)	38.4%	58.0%
% with brain metastases	3.9%	0%
Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of the normal range.		

Adverse events

5.3 The model included adverse events for endocrine disorder (any grade), diarrhoea (grade 2+) and other adverse events (grade 3 +).The company estimated proportions of patients experiencing these adverse events from trial data. For nivolumab plus ipilimumab and ipilimumab alone, the company used data from CheckMate 067. For dabrafenib and vemurafenib, the company used data from BREAK-3 and BRIM-3 trials respectively (see the company's submission for details, section 4.16). The values used in the model are summarised in table 7.

Tables 8 and 9 Proportion of patients with adverse events and average utility decrement applied for adverse events by treatment in the model (CS, table 53, page 156, and table 56, pg 163)

	Modelled % of patients having AE			
	Nivolumab + ipilimumab	Ipilimumab	Dabrafenib	Vemurafenib
Endocrine disorder (any grade)	30.0%	11.3%[a]	0%[b]	0%[b]
Diarrhoea (Grade 2+)	24.6%	18.6%	0%[b]	5.5%
Other adverse events (Grade 3+)	49.5%	27.0%	32.0%	44.5%

	Utility value	Uncertainty in the model	Reference in submission	Justification
Utility values for health states defined by progression status				
Progression free	0.7954	Sampling using variance-covariance matrices assuming multivariate-normal distribution	Section 5.4	Based on statistical models fitted using EQ-5D data collected in CheckMate 067 trial
Progressed	0.7625			
Utility decrements for adverse events				

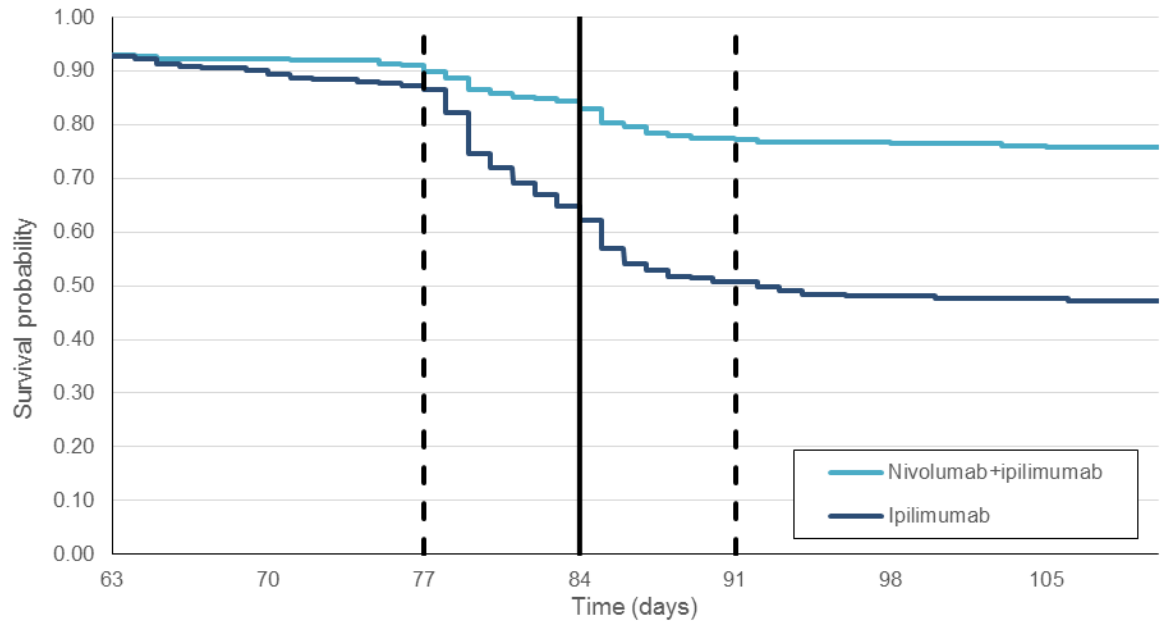
The Regimen	-0.03373	Sampling using variance-covariance matrices assuming multivariate-normal distribution	Section 5.4	Based on statistical models fitted using EQ-5D data collected in CheckMate 067 trial
Ipilimumab	-0.03136			
Dabrafenib	0	Fixed		Conservative assumption
Vemurafenib	0	Fixed		

ERG comments

5.4 The ERG did not agree with the company's methodology for calculating the short- and long-term mortality in the PPS health state as it produced implausible results. The company's approach to the nesting of the two curves resulted in substantial differences in expected survival for patients based on time of progression since treatment initiation. The difference was dictated by how evidence sources are synthesised rather than the data themselves. As the TTP were times different between the immunotherapies, and the PPS was modelled dependent on TTP, the company's stated assumption of equal PPS for nivolumab plus ipilimumab and ipilimumab did not hold due to the modelling approach taken.

5.5 The ERG did not agree with the 84 day cut-off for partitioning the KM curve because the study protocol stated that the first assessment was planned for any time between 11 and 13 weeks. It considered that a cut off time point should have been set either earlier in time (for example at 11 weeks, or 77 days), avoiding the cluster of events observed at 84 days, or after the cluster, e.g. at 13 weeks, or 91 days. The ERG stated that it would expect the choice of cut off would influence the parameter estimation for the post-cut off parametric model and therefore the extrapolation of outcomes over time. The ERG noted that the company did not conduct any sensitivity analysis around this assumption.

Figure 9 Comparison of TTP KM curves from CheckMate 067 at 77, 84 and 91 days (ERG report figure 43, page 209)



Survival estimate at time	Nivolumab plus ipilimumab	Ipilimumab
77 days	0.910	0.873
84 days	0.844	0.648
91 days	0.774	0.506

Note: time to progression Kaplan Meier estimates extracted from the curves reported in the company's electronic model.

Company's base-case results and sensitivity analysis

Deterministic base-case

5.1 The company presented base-case results using the list prices for all drugs (see table 71 and 72 of the company's submission, page 182). Since ipilimumab, vemurafenib and dabrafenib are recommended by NICE with patient access schemes (PASes); the company also presented base-case analyses assuming different discount rates for these comparators (see table 73 and 74 of the company's submission, page 183). The ERG presented the analyses based on the actual PASs in a confidential appendix to its report which will be relevant for the decision making.

5.2 In the company's deterministic base case analyses, nivolumab plus ipilimumab provided a total of 5.09 and 4.85 quality-adjusted life years (QALYs), in the BRAF mutation-negative melanoma and BRAF mutation-positive melanoma respectively. The fully incremental comparisons demonstrated that in the BRAF mutation-negative melanoma population, nivolumab plus ipilimumab was associated with the incremental cost effective ratio (ICER) of £10,433 per QALY gained compared with ipilimumab alone using list prices ([redacted] per QALY gained using the company PASes for ipilimumab and nivolumab). In the BRAF mutation positive melanoma population, nivolumab plus ipilimumab dominated (that is, provided more QALYs at lower cost than) both ipilimumab and vemurafenib). It was more costly and more effective than dabrafenib, with an incremental cost-effectiveness ratio (ICER) of £11,284 per QALY gained using list prices ([redacted] per QALY gained using the company's PASes for ipilimumab and nivolumab and estimated PASes for dabrafenib and vemurafenib). Full details of the base case results, including clinical outcomes and disaggregated costs, can be found in section 5.7 (page 180 to 192) of the company submission; details of the deterministic and probabilistic analyses can be found in section 5.8 (page 192–201).

Probabilistic base-case

5.3 The company also compared the deterministic base-case results with the results generated by running the model probabilistically 1,000 times. The company stated that the base-case results by both the analyses (probabilistic and deterministic) were very similar (see table 8).

Table 9 Company's base case results using PAS prices (CS, pg 183, Table 73)

Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)		Dominance		ICER (£) incremental (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
BRAF mutation negative population										
Ipilimumab	[redacted]									
Nivolumab + ipilimumab	[redacted]									
BRAF mutation positive population										
Ipilimumab	[redacted]									
Dabrafenib	[redacted]									
Vemurafenib	[redacted]									
Nivolumab + ipilimumab	[redacted]									

Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years; PSA – probabilistic sensitivity analyses

Deterministic sensitivity analyses

5.4 36 one-way sensitivity analyses were presented for BRAF mutation-negative melanoma and 42 analyses for BRAF mutation-positive melanoma. For sensitivity analyses, the company varied the parametric curves for each relevant parameter, duration of treatment was varied from 0% to 75% discontinuation at 2 years (the base case was 100% discontinuation at 2 years), and the maximum treatment duration from 3 to no maximum (the base case was a maximum duration of 2 years). In the submission, the company presented results as tornado diagrams (see Figure 71 and 72 of the company's submission page 203 to 204) that included 20 most influential parameters. In every tornado diagram, the company presented pair-wise comparison of nivolumab plus ipilimumab with ipilimumab alone. The tornado diagrams showed that the results were most sensitive to changes in the following parameters:

- the fitted parameter curves for time to progression (post 84 days),
- the pooled ipilimumab long term OS
- post-progression survival

The parameters to which the results were sensitive included

time on treatment, as well as utility parameters and administration cost of nivolumab.

ERG comments

5.5 The ERG identified two minor data entry errors in the model. The company's model was corrected to include the proportion of patients receiving ipilimumab after BRAF inhibitors reported by McArthur et al., i.e. 18% and not 22% as included in the company's model. The ERG found the values associated with the proportion of patients experiencing endocrine treatment-related adverse events (TRAEs) in the ipilimumab arm not to correspond between the CS and the CheckMate 067 CSR, as the value was 11.3% in the former while the second reported a proportion

equal to [redacted]. In all other aspects, the ERG found that company's model to work as intended and described, consistent with the company's assumptions.

5.6 The ERG's corrections did not have any impact on the BRAF mutation negative analysis results (as the variation in patients moving to second-line ipilimumab after BRAF inhibitors did not apply). The ICER for the incremental analysis between nivolumab plus ipilimumab and dabrafenib increased from £11.284 to £12,119 per QALY gained and [redacted] per QALY gained using list and PAS prices, respectively.

Company scenarios

5.7 The company performed a range of scenario analyses to assess the robustness of the model with respect to the following structural assumptions:

- fitting alternative parametric curves to TTP, PPS, long-term survival and time on treatment curve for nivolumab
- alternative approach for indirect comparison for trial evidence (comparing the CheckMate 066 trial with the CA184-024 trial, instead of the MDX010-20 trial) and alternative Post progression survival data (based on combined PPS for nivolumab and ipilimumab).
- alternative treatment discontinuation rule and maximum length of treatment duration
- alternative approach to modelling dosing, drug cost and utilities
- time horizon
- discount rates

5.8 The company presented results of scenario analyses as pair-wise comparisons of nivolumab with all relevant comparators (see the company's submission table 97 (page 233-236) and table 98 (page 237-240). The scenario analyses demonstrated that nivolumab remained cost effective compared to its comparators for the majority of scenarios except in the scenarios where patients were continued to receive nivolumab beyond 2 years.

5.9 The ERG asked the company to provide a comparison of nivolumab plus ipilimumab against pembrolizumab as part of the clarification questions. As a response, the company conducted a meta-analysis of the hazard ratios for OS and PFS based on the CheckMate 067, Keynote 006 and Keynote 002 trials to compare nivolumab plus ipilimumab, ipilimumab and pembrolizumab (at two dosages, i.e. 10 mg/kg q3w and 2 mg/kg q3w).

Table 10: Company's base case results including pembrolizumab – BRAF mutation-negative population (using company's assumptions for PAS drug prices [for pembrolizumab] and the PAS for nivolumab and ipilimumab) (Company's clarification response, table 3, page 4)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									
[redacted]									
[redacted]									

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

Table 11: Company's base case results including pembrolizumab – BRAF mutation positive population (using company's assumptions for PAS drug prices [for pembrolizumab, vemurafenib and dabrafenib] and the PAS for nivolumab and ipilimumab) (Company's clarification response, table 4, page 4)

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									

[redacted]									
[redacted]									
[redacted]									
[redacted]									

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

ERG comments

5.10 The ERG did not consider the comparison of nivolumab plus ipilimumab against the BRAF inhibitors dabrafenib and vemurafenib for the BRAF positive mutation population to be appropriate because the company used 2 different modelling approaches in the comparison:

- a semi-Markov model (modelling transition between the health states) for immunotherapies and
- a partitioned survival model (modelling health state occupancy) for the BRAF inhibitors.

The main differences between the partitioned survival and the semi-Markov approaches are the assumptions on the determinants of the mortality benefit. In the partitioned survival model the OS is assumed independent on PFS (and TTP), while in the semi-Markov approach differences in TTP (and PFS) determine differences in OS. The ERG did not consider the comparison to produce robust results as the effect of using different modelling approaches was not taken into account by the company.

5.11 The ERG did not consider the comparison of nivolumab plus ipilimumab versus pembrolizumab to be adequate because:

- the model assumed constant proportionality of the hazards over the entire time horizon, while the hazard ratios were estimated based on short-term follow-up with no evidence supporting this assumption.

- assuming HRs for the OS in the model assumed that, in addition to melanoma-specific mortality, pembrolizumab and nivolumab plus ipilimumab would result in mortality rates lower than the general public.
- the assumption of a different OS derives was based on a naive comparison of the HRs between ipilimumab, nivolumab plus ipilimumab and pembrolizumab [redacted] difference in the NMA presented by the company.

ERG exploratory analyses (using company's assumptions for PAS discounts)

5.12 The ERG explored the impact of selected company's assumptions to assess the impact they produced on the model results and assess the plausibility of the model intermediate and final outputs. The key areas of uncertainty identified by the ERG granting exploration through scenario analyses were:

- Dependency on time of progression of post-progression mortality rates for immunotherapies
  - The ERG increased the time point at which the long-term mortality rates nesting was implemented in the model to more than 40 years, so that the entire PPS was determined by extrapolation of data from the Checkmate 066 and MDX010-20 RCTs. This resulted in ICERs for nivolumab plus ipilimumab £18,324 per QALY gained compared with ipilimumab of in the BRAF mutation negative population and £42,539 per QALY gained compared with dabrafenib in the BRAF mutation positive based on list prices ([redacted]).
- Treatment effect on pre-progression mortality for immunotherapies
  - The ERG averaged together the Kaplan Meier curves observed in the two trial arms. Half of the general population mortality rates were applied between day 511 and 553 (as they were applied in the ipilimumab Kaplan Meier curve), and applied fully from the end of the

longest follow-up time between the two arms (i.e. 553 days in the nivolumab plus ipilimumab arm) until the end of the time horizon, as no other robust alternative data sources were identified.

  - In the BRAF mutation negative analysis, the ICERs for nivolumab plus ipilimumab compared with ipilimumab was £11,260 per QALY gained using the list price and [redacted] per QALY gained in PAS scenarios. The ICERs for the BRAF mutation positive subpopulation for nivolumab plus ipilimumab compared with dabrafenib were £12,627 per QALY gained in the list price scenario [redacted].

- Treatment dosage assumptions for nivolumab plus ipilimumab
  - The company had assumed a flat dose reduction and assumed that only 90.16% of the total quantity of the planned does would be received during the entire time horizon (with 2 years maximum treatment time in the base case). The ERG removed this dose reduction which resulted in an ICER of £12,302 and £13,241 per QALY gained in the BRAF mutation negative and BRAF mutation positive subpopulations using list prices, respectively and [redacted].
- Second-line treatments received in post progression
  - The ERG conducted a scenario analysis to assess the robustness of the model results to the proportion of patients receiving subsequent therapies. As the ERG did not have access to the same data for the BRIM-3 trial, the analysis only compares nivolumab plus ipilimumab and ipilimumab.
  - The resulting ICER was considerably lower than the base case estimate for list price scenario, when compared to the BRAF mutation negative analysis results. [redacted].

ERG preferred base case scenario (using actual PAS discounts for comparators)

5.13 The ERG presented a single preferred base case scenario including both BRAF mutation negative and positive patients using the same case mix observed in CheckMate 067. This is because according to the company's assumptions, BRAF mutation status does not influence the outcomes associated with immunotherapy treatment (either nivolumab plus ipilimumab or ipilimumab monotherapy. The ERG base case makes use of the subsequent therapy data observed directly from the CheckMate 067 clinical study report.

5.14 The ERG preferred base case included the following changes:

- Alternative probabilities of receiving subsequent treatments, using data from the CheckMate 067 trial which allowed a comparison of nivolumab plus ipilimumab against ipilimumab monotherapy regardless of BRAF mutation status
- Removal of nested long-term PPS mortality to avoid the implausible survival conditional on time of progression
- Averaging of the PrePS Kaplan Meier curves for combination immunotherapy and ipilimumab from the CheckMate 067 RCT as no significant difference was observed
- Removal of the constant flat dose reduction for nivolumab.

The results of the ERG's preferred base case scenario are presented in the table below **using the actual patient access scheme discounts** for each of the treatments.

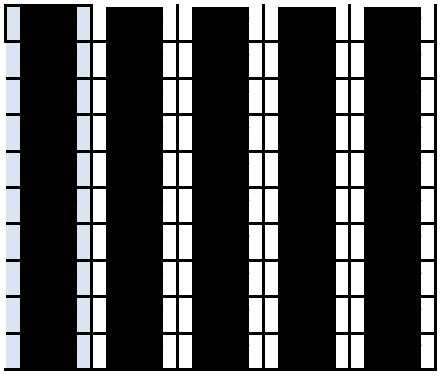
Table 12 ERG preferred base case ICERs using actual PAS discounts (Table 133, page 9 of ERG PAS confidential appendix)

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
[redacted]			[redacted]
[redacted]			

5.15 As an exploratory analysis, the ERG did an analysis in the BRAF positive population using a 5 year time horizon to reduce the uncertainty associated with the long-term extrapolations of the 2 approaches used by the company (see section 5.10). The results of this analysis is shown in the table below.

Table 13 ERG's exploratory analysis for the BRAF positive population for a 5-year time horizon using actual PAS discounts (ERG's PAS confidential appendix, table 135, page 13)



Innovation

5.16 Justifications for considering nivolumab plus ipilimumab to be innovative:

- Advanced melanoma disproportionately affects younger patients and thus has a significant impact on the working age. Negative implications of this include loss of economic productivity, which is not included in the quality-adjusted life year (QALY) calculation, but should be considered as benefits to wider society.

- Based on conservative assumptions of equal post-progression survival for all immuno-oncology treatments suggest that the Regimen will more than double the long-term survival rate compared with ipilimumab monotherapy (46% vs 23% and 38% vs 18% for BRAF mutation-negative and BRAF mutation-positive patients respectively at Year 3. The depth of response to the Regimen is also unprecedented with76.2% of patients continuing to demonstrate response at the time of analysis (median follow-up approximately 12 months), despite many discontinuing study treatment within the Phase III trial.

- Melanoma experts in the UK believe the introduction of the Regimen will change the way in which treatment decisions are made in clinical

practice (see Section 3.2); this represents a noteworthy step-change in the management of this condition.

6 End-of-life considerations [if relevant, otherwise delete this section]

6.1 The company stated that advanced melanoma is associated with a short life expectancy, with median life expectancy between 9.5 and 13.5 months and the survival analyses of CheckMate 069 trial data indicate that nivolumab plus ipilimumab offers an extension to life of at least 3 months compared to ipilimumab alone. The company reported estimated the number of new cases and relapsed cases of advanced melanoma in England in 2016 to be 1,577.

6.2 The ERG commented that the survival benefit compared to ipilimumab is not yet fully established, pending follow-up survival data from CheckMate 067.

Table 14 End-of-life considerations (CS, table 44, page 123)

Criterion	**Data available**
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median life expectancy: up to 13.5 months with established standard of care (9.5 to 13.5 months depending on data source, treatment history and dosing) Source: pooled analyses of key clinical trials and real world evidence
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	75% survival times: Nivolumab plus ipilimumab: 341 days Ipilimumab: 220 days Between group difference: 121 days (4 months) Source: CheckMate 069 patient level data
The treatment is licensed or otherwise indicated for small patient populations	Advanced melanoma population for 2016: 1,577 (anticipated new cases and relapsed cases) Source: ONS population estimates for 2013 and melanoma incidence estimates for 2012 extrapolated using increased incidence rate of 3.5% previously

Criterion	**Data available**
	used in melanoma submissions Advanced melanoma proportion based on reported epidemiology data (10%) Patients requiring second- or subsequent-line therapy based on previous precedence in melanoma submissions (21%)

7 Equality issues

7.1 None.

8 Authors

Richard Diaz

Technical Lead(s)

Eleanor Donegan

Technical Adviser

with input from the Lead Team (Jane Adam, Jeremy Braybrooke, Pam Rees and Brian Shine).

Appendix A: Clinical efficacy section of the draft European public assessment report

The draft EPAR was not supplied by the company.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma

Final scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab in combination with ipilimumab within its marketing authorisation for treating advanced, unresectable melanoma.

Background

Melanoma is a cancer of the skin. In its early stages, melanoma is normally asymptomatic and can be cured by surgery (resection). However, at presentation, approximately 10% of melanomas will have spread to nearby lymph nodes (stage III) or to other parts of the body (stage IV). It occurs more commonly in fair-skinned people and there is strong evidence that ultra violet exposure is causal. People with an above-average mole count, sun-sensitive skin, or a strong family history of melanoma are at increased risk.

There were 11,281 new diagnoses of melanoma and 1781 deaths registered in England in 2012. In the UK, more than one-third of people diagnosed with melanoma are aged less than 55 years. Approximately 20-73% of people with stage III melanoma (including 20-34% of people with stage IIIc) and 5-22% of those with stage IV melanoma will live longer than 5 years, with survival rates being slightly higher in women than in men.

Approximately 50% of melanomas harbour activating BRAF mutations, and over 90% of these are BRAF V600 mutations. Diagnostic tests can be used to detect the BRAF mutation, including the cobas test, generic PCR sequencing tests and other validated BRAF mutation tests.

The management of advanced melanoma is rapidly evolving, with several ongoing clinical trials, and there is uncertainty about how these treatments will be sequenced in future. Treatment for advanced, unresectable melanoma is often based upon the person's BRAF mutation status.

NICE Technology Appraisal (TA) 319 recommends ipilimumab as a treatment option for adults with previously untreated unresectable or metastatic melanoma and TA268 recommends ipilimumab as a treatment option for previously treated disease. For people with a BRAF V600 mutation, TA's 269 and 321 recommend vemurafenib and dabrafenib as treatment options. NICE TA 357 recommends pembrolizumab as a treatment option after disease has progressed with a BRAF V600 or MEK inhibitor (for people with the BRAF V600 mutation) or ipilimumab (for people without the BRAF V600 mutation). Ipilimumab, vemurafenib , dabrafenib and pembrolizumab are only

recommended if the respective companies provide the drugs at the discount agreed in the patient access schemes. Dacarbazine and supportive care may also be considered when ipilimumab or BRAF inhibitors are unsuitable or have already been tried.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). This may activate T-cell responses and promote an anti-tumour immune response. Nivolumab is administered intravenously.

Nivolumab in combination with ipilimumab does not currently have a marketing authorisation in the UK for treating advanced or unresectable melanoma.

Nivolumab has a marketing authorisation in the UK, as a monotherapy, for treating advanced (unresectable or metastatic) melanoma in adults.

Nivolumab is being studied in combination with ipilimumab compared with nivolumab monotherapy or ipilimumab monotherapy for people with previously untreated advanced, unresectable melanoma.

Intervention(s)	Nivolumab in combination with ipilimumab
Population(s)	Adults with advanced (unresectable or metastatic) melanoma
Comparators	• Ipilimumab • Pembrolizumab • BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal 321, Oct 2014, 'Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma.' Review proposal date Oct 2017. Technology Appraisal 319, Jul 2014, 'Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma'. Review proposal date Jun 2017. Technology Appraisal 269, Dec 2012, 'Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma'. Static list. Technology Appraisal 268, 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'. Review proposal date Jun 2017. Technology Appraisal 357, Oct 2015. 'Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab'. Review proposal date Oct 2018. Ongoing appraisals: Technology Appraisal in preparation, ID661 'Dabrafenib and trametinib for treating advanced unresectable or metastatic BRAFV600 mutation-positive melanoma. Earliest anticipated date of publication June 2016.

	Technology Appraisal in preparation, ID801. 'Pembrolizumab for treating advanced melanoma not previously treated with ipilimumab'. Earliest anticipated date of publication Nov 2015. Related Guidelines: Clinical Guideline in Preparation Melanoma: assessment and management of melanoma. Clinical Guideline. Earliest anticipated date of publication July 2015 Related Interventional Procedures: Interventional Procedure Guidance 446, Mar 2013 'Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma'. Review proposal date TBC. Interventional Procedure Guidance in preparation, 'Electrochemotherapy for the treatment of malignant melanoma (GID-IP1041)'. Earliest anticipated date of publication TBC. Related Public Health Guidance/Guidelines: Public Health Guidance 32, Jan 2011, 'Skin cancer prevention: information, resources and environmental changes
Related National Policy	NHS England, 2013/14, NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a. NHS England, 2013/14, NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a. National Cancer Peer Review Programme, 2013, Manual for Cancer Services: Skin Measures. National Service Frameworks, Cancer Department of Health, 2013, NHS Outcomes Framework 2014-2015. Domains 1, 2, 4 and 5. Department of Health, 2011, Improving outcomes: a strategy for cancer Department of Health, 2009, Cancer commissioning guidance Department of Health, 2007, Cancer reform strategy

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Bristol-Myers Squibb (nivolumab) Patient/carer groups • Black Health Agency • British Skin Foundation • Cancer Black Care • Cancer Equality • Cancer 52 • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Melanoma UK • Muslim Council of Britain • OcuMel UK • Rarer Cancers Foundation • Skcin - Karen Clifford Skin Cancer Charity • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Anaesthetists • Association of Cancer Physicians • Association of Surgeons of Great Britain and Ireland • British Association of Dermatologists • British Association of Skin Cancer Specialist Nurses • British Association of Surgical Oncology • British Dermatological Nursing Group	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Bayer (dacarbazine) • Bristol-Myers Squibb (ipilimumab) • Merck Sharp & Dohme (Pembrolizumab) • Novartis Pharmaceuticals (dabrafenib) • Roche Products (vemurafenib) Relevant research groups • British Society for Dermatological Surgery • Cochrane Skin Group • Institute of Cancer Research • MRC Clinical Trials Unit • Myfanwy Townsend Melanoma Research Fund • National Cancer Research Institute • National Cancer Research Network

Consultees	**Commentators (no right to submit or appeal)**
• British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • Cancer Research UK • Melanoma Focus • Primary Care Dermatology Society • Royal College of Anaesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS Bury CCG • NHS Calderdale CCG • NHS England • Welsh Government	• National Institute for Health Research • Skin Cancer Research Fund • Skin Research Centre • Skin Treatment & Research Trust <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that manufacture comparator technologies; Healthcare Improvement Scotland ; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Melanoma (advanced, unresectable) - nivolumab (with ipilimumab) [ID848]

Company evidence submission

Bristol Myers Squibb Pharmaceuticals Ltd.

January 2016

File name	Version	Contains confidential information	Date
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Contents

Tables and Figures

Abbreviations

Abbreviation	Definition
AE	Adverse events
AIC	Akaike information criteria
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
BIC	Bayesian information criteria
BOR	Best overall response
CD28	Cluster of differentiation 28
CD137	Cluster of differentiation 137
CDSR	Cochrane Database of Systematic Reviews
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
CL	Confidence limit
CMH	Cochran–Mantel–Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CSR	Clinical study report
CT	Computerised tomography
CTLA-4	Cytotoxic T-lymphocyte antigen-4
D	Dominant
Dab	Dabrafenib
DARE	Database of Abstracts of Reviews of Effects
DC	Discontinuation
DMC	Data monitoring committee
DOR	Duration of response
DR	Distant recurrence
DSU	Decision Support Unit
DTIC	Dacarbazine
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	EuroQol-five dimension
ESMO	European Society for Medical Oncology
ERG	Evidence Review Group
FACT-M	Functional Assessment of Cancer Therapy - Melanoma

Abbreviation	Definition
gp-100	Glycoprotein-100
HR	Hazard ratio
HRQL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IMM	Immune modulating medication
Inc	Incremental
IPI	Ipilimumab
irRC	Immune-related response criteria
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
KM	Kaplan–Meier
LDH	Lactate dehydrogenase
LR	Local recurrence
LY	Life year
LYG	Life years gained
M	Metastatic
MHC	Major histocompatibility complex
MID	Minimally important difference
MRI	Magnetic resonance imagery
MTD	Maximum tolerated dose
mWHO	Modified World Health Organization
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NED	No evidence of disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIVO	Nivolumab
NR	Not reached/reported
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analyses
PAS	Patient access scheme
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1

Abbreviation	Definition
PD-L2	Programmed death-ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PLD	Participant level data
PPS	Post-progression survival
PR	Partial response
PrePS	Pre-progression survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance score
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
q2w	Every 2 weeks
q3w	Every 3 weeks
q12w	Every 12 weeks
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of product characteristics
SMR	Society for Melanoma Research
STA	Single technology appraisal
TCR	T-cell receptor
TOT	Time on treatment
TRAE	Treatment related adverse event
TRSAE	Treatment related serious adverse event
TSD	Technical support document
TTP	Time to progression
TTR	Time to treatment response
ULN	Upper limit of normal range
UV	Ultraviolet
VAS	Visual analogue scale
Vem	Vemurafenib
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health
WTP	Willingness to pay

1 Executive summary

Nivolumab and ipilimumab therapy is a new combination regimen that offers the potential for long-term overall survival (OS), a superior objective response rate (ORR) and progression free survival (PFS) compared to the currently available standard of care for advanced (unresectable/metastatic) melanoma in adults, thereby meeting a current unmet medical need in the management of this aggressive, life-threatening disease.

Disease overview

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. Although less common than other skin cancers, melanoma is by far the most serious, accounting for 90% of all skin cancer-related deaths (see Section 3.1).

Rates of melanoma have been steadily rising over the last 50 years. Malignant melanoma increased by 78% in males and 48% in females from 2003 to 2012, making it the fifth most common cancer in England. This increasing incidence is widely attributed to changing lifestyle factors such as an increase in holidays taken in the sun and greater use of ultraviolet (UV) sunbeds, both increasing people's exposure to UV light. In 2010, 89.8% of melanoma cases were thought to be caused by UV radiation (see Section 3.1).

Burden of disease

Melanoma is the most frequently diagnosed cancer in people aged 25 to 29. With a mean age at diagnosis of 50 years and up to 20% of cases occurring in young adults aged 40 or under, this condition has a significant impact on the working age population (see Section 3.1).

The number of new cases of melanoma in England in 2013 was 11,763. Of all patients diagnosed with malignant melanoma, up to 10% present with advanced disease (unresectable stage IIIc and stage IV in the American Joint Committee on Cancer [AJCC] staging system). Assuming the incidence of melanoma is still increasing at 3.5% per year, the expected number of new cases of advanced melanoma in England for 2016 is 1,304, all of whom would be expected to receive some kind of treatment in a first-line setting (see Section 3.3).

Current management and unmet need

Standard of care for advanced melanoma in England currently consists of ipilimumab or BRAF inhibitor (dabrafenib or vemurafenib) monotherapy at first-line (see Section 3.2). These treatments have all demonstrated significant clinical benefit over traditional chemotherapy (which has no proven effect on survival times) but unfortunately still have limitations such that durable response and long-term survival remains elusive for many patients with advanced melanoma (see Section 3.6). This has a significant, negative impact on patients, carers and wider society. Within the last few weeks, pembrolizumab was recommended by the National Institute for Health and Care Excellence (NICE) as a treatment option for advanced melanoma in both pre-treated and previously untreated patients, but is not in routine use in clinical practice. Current standard of care for patients with advanced melanoma is ipilimumab and/or - for patients with BRAF mutation-positive disease - the BRAF inhibitors.

There is, therefore, a clear and substantial unmet medical need for additional treatment options that can provide durable response and long-term survival for the broad range of advanced melanoma patients presenting in clinical practice; improving upon the clinical benefit associated with currently available treatments. Nivolumab plus ipilimumab therapy (herewith referred to as 'the Regimen') meets this need.

The Regimen offers a durable clinical response and the potential for long-term survival benefit

The Regimen is the first immuno-oncology combination treatment to demonstrate long-term clinical benefit, including the potential for long-term overall survival (OS), in a trial setting.

The clinical evidence for the Regimen is derived from two randomised controlled trials (RCT), together involving more than 1,000 patients with advanced melanoma: CheckMate 067 (Phase III) and CheckMate 069 (Phase II). In these trials, the Regimen demonstrated significantly superior ($p<0.001$) objective response rates (ORR) and progression-free survival (PFS) compared with ipilimumab monotherapy (see Section 4.7).

Median OS has not yet been reached in either Checkmate 067 or Checkmate 069 because the number of events (deaths) pre-specified in the statistical analysis plan has not yet been reached in either study. Early OS data from CheckMate 069 reports an 18-month OS rate of 69% (see Section 4.7); and Phase I data (CheckMate 004) demonstrates a 3-year OS of 68% in patients treated with concurrent nivolumab and ipilimumab therapy (1-year OS of 75% at what is expected to be the licensed dose - see Section 4.11). These survival rates are unprecedented in advanced melanoma with immuno-oncology therapy (ipilimumab) previously associated with an 18-month OS rate of 35% and a 3-year OS rate of 22% (pooled analyses of key trials). Modelled estimates based on conservative assumptions of equal post-progression survival for all immuno-oncology treatments suggest that the Regimen will more than double the long-term survival rate compared with ipilimumab monotherapy (see Section 5.3).

The Regimen offers a step-change in the management of advanced melanoma

The Regimen represents the next generation in immuno-oncology treatment; combining the distinct yet complementary mechanism of actions associated with PD-1 (nivolumab) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) (ipilimumab) checkpoint inhibitors (see Section 2.1).

Clinical efficacy and survival data for the Regimen are compelling (see Section 4.7). Modelled survival estimates suggest the Regimen could provide long-term survival to more than twice the amount of patients who achieve remission with ipilimumab monotherapy (see Section 5.3). This curative potential and the possible return to normal living that the Regimen offers to a broad range of patients with advanced melanoma is a remarkable improvement compared with the limited efficacy available from chemotherapy.

Due to the unprecedented clinical benefit the Regimen offers, melanoma experts in the UK believe the introduction of this regimen would change the way in which treatment decisions are made in clinical practice (see Section 3.2); this represents a noteworthy step-change in the management of this condition. Indeed, the adoption of the Regimen for the treatment of advanced (unresectable or metastatic) melanoma in the National Health Service (NHS) in England would represent a further, significant advance in the management of this life-threatening condition.

Nivolumab was designated a Promising Innovative Medicine by the Medicines and Healthcare products Regulatory Agency and it was given a positive scientific opinion under the Early Access to Medicines Scheme for use as monotherapy for the treatment of advanced melanoma. Ipilimumab is the current standard of care in the NHS in England for BRAF mutation-negative patients first-line and has the largest market share of all of the products currently licensed to treat advanced melanoma in the UK.

1.1 Statement of the decision problem

The decision problem addressed in this submission matches that described in the final scope, as summarised in Table 1, with one exception. Pembrolizumab was included in the final scope as a comparator to the Regimen without prior consultation or discussion. Pembrolizumab was not recommended by NICE for pre-treated and previously untreated patients until October and November 2015, respectively. The most recent (December 2015) prescribing data indicate that pembrolizumab is not established in routine use in clinical practice and cannot be considered standard of care in the NHS in England. It is not, therefore, considered a relevant comparator for the purposes of this appraisal.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced (unresectable or metastatic) melanoma	Adults with advanced (unresectable or metastatic) melanoma	-
Intervention	Nivolumab in combination with ipilimumab	Nivolumab in combination with ipilimumab	-
Comparator(s)	• Ipilimumab • Pembrolizumab • BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma	• Ipilimumab • BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma	The current standard of care is ipilimumab and/or the BRAF inhibitors (for those with BRAF mutation-positive disease only). Pembrolizumab is not included in the current clinical pathway of care having only been recommended by NICE for use in NHS England after disease progression with ipilimumab in October 2015; and for use in patients not previously treated with ipilimumab in November 2015. Recent prescribing data indicate that there is virtually no pembrolizumab usage in a first-line setting and it is not in routine use in clinical practice. Pembrolizumab is not therefore established standard of care for advanced melanoma in NHS England and thus is not a relevant comparator to the Regimen.
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	-

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	A cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year is presented. A lifetime time horizon of 40 years is used in the base case analysis. Costs are considered from a National Health Service and Personal Social Services perspective. The availability of patient access schemes for the comparator technologies has been taken into account in a confidential appendix, list prices are used within the submission document as requested by NICE.	-
Subgroups to be considered	None specified.	None specified.	-
Special considerations including issues related to equity or equality	None specified.	None specified.	-

1.2 Description of the technology being appraised

CTLA-4 and programmed death-1 (PD-1) are immune checkpoints involved in T-cell differentiation and function that can be exploited by cancer cells to avoid immune responses and promote tumour growth. Nivolumab and ipilimumab are both fully human, monoclonal antibodies that act as checkpoint inhibitors of PD-1 and CTLA-4 respectively, at their distinct (yet complementary) positions within the T-cell response pathway so that the immune response to tumour growth is potentiated rather than inhibited (see Section 2.1).

The Regimen is anticipated to be indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults; marketing authorisation pending.

Details of the technology being appraised in this submission are summarised in Table 2.

Table 2: Technology being appraised

UK approved name	The Regimen
Brand name	Opdivo® plus Yervoy®
Marketing authorisation status	Type II application filed to the EMA in July 2015 CHMP opinion anticipated January/February 2016 Marketing authorisation anticipated March/April 2016
Indications and any restriction(s) as described in the summary of product characteristics	Licence application is for the Regimen for the treatment of advanced (unresectable or metastatic) melanoma in adults
Method of administration and dosage	Nivolumab 1mg/kg plus ipilimumab 3mg/kg every 3 weeks for 4 doses followed by nivolumab 3mg/kg every 2 weeks by intravenous infusion (draft SPC). Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (draft SPC). Note: In practice, it is anticipated that the maximum duration of treatment will not exceed 2 years.
Key: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; kg, kilogram; mg, milligram.	

1.3 Summary of the clinical effectiveness analysis

An extensive clinical trial programme supports the use of the Regimen for the treatment of advanced (unresectable or metastatic) melanoma in adults.

This clinical trial programme includes two RCTs that provide direct evidence of the potential clinical effectiveness of the Regimen compared with current standard of care, ipilimumab monotherapy (see Section 4.7). A summary of these trials is provided below:

CheckMate 067

- Phase III, multicentre, double-blind RCT comparing the clinical efficacy and safety of the Regimen with ipilimumab 3mg/kg monotherapy in previously untreated patients who have advanced melanoma with or without a BRAF mutation.
- Significant benefit with respect to the co-primary endpoint of PFS was observed in the Regimen group (median PFS, 11.5 months), compared with the ipilimumab group (median PFS, 2.9 months): hazard ratio (HR) for death or disease progression, 0.42 (95% confidence interval [CI]: 0.31, 0.57); p<0.001.

- Significant benefit with respect to the secondary endpoint of ORR was observed in the Regimen group (57.6%), compared with the ipilimumab group (19.0%): odds ratio (OR) for response, 6.11 (95% CI: 3.59, 10.38); p<0.001.
- Deep and durable responses in the Regimen group were represented by a median change in tumour burden of -51.9% and median duration of response not yet reached, compared with a median change in tumour burden of +5.9% in the ipilimumab group (median duration of response not reached).
- Results for the co-primary endpoint of OS are not available at this time as patients are still surviving and the required minimum follow-up for analysis has not yet been reached (22 months, see Section 4.4).

CheckMate 069

- Phase II, multicentre, double-blind RCT comparing the clinical efficacy and safety of the Regimen with ipilimumab 3mg/kg monotherapy in previously untreated patients who have advanced melanoma with or without a BRAF mutation.
- Significant benefit with respect to the primary endpoint of ORR in patients with BRAF mutation-negative tumours was observed in the Regimen group (61%), compared with the ipilimumab group (11%): OR for response, 12.96 (95% CI: 3.91, 54.49); p<0.001.
- Significant benefit with respect to secondary analysis of ORR in all randomised patients was observed in the Regimen group (59%), compared with the ipilimumab group (11%): OR for response, 12.19 (95% CI: 4.41, 33.68); p<0.0001.
- Significant benefit with response to the secondary endpoint of PFS was observed in the Regimen group (median PFS not reached), compared with the ipilimumab group (median PFS, 3.0 months): HR for death or disease progression, 0.39 (95% CI: 0.25, 0.63); p<0.0001.
- 18-month OS rate of 69% associated with the Regimen, irrespective of BRAF mutation status; approximately double the 18-month OS rate of 35% associated with ipilimumab monotherapy in pooled analyses of key trials.

Median OS has yet to be reached in RCTs because patients are surviving and the number of pre-specified events (deaths) has not yet occurred. However, modelled estimates based on Phase III data suggest that the Regimen will more than double the long-term survival rate compared with ipilimumab monotherapy (see Section 5.3). The potential long-term survival benefit is supported by Phase I data from the CheckMate 004 trial that demonstrate an unprecedented 3-year survival rate of 68% in patients treated with concurrent nivolumab and ipilimumab therapy (both previously treated and previously untreated patients and patients with or without a BRAF mutation); this is a 46% improvement on pooled analyses of the 3-year survival rate associated with ipilimumab monotherapy (see Section 4.11).

The Regimen was associated with increased toxicity compared with ipilimumab monotherapy, as expected *a priori*, but demonstrated a predictable safety profile, manageable in line with well-established safety algorithms already familiar to clinicians (see Section 4.12). As a result, the median duration of the majority of Select Adverse Events (AEs) (those with a potential immunological cause) was short, rarely exceeding 10 weeks, and deaths due to study drug toxicity were rare across clinical trials. Study drug toxicity was often best managed through discontinuation of study drug; importantly this did not appear to impact clinical benefit. Furthermore, in patients who experienced a Grade 3-4 adverse event, deterioration in health-related quality of life (HRQL) was not markedly different between treatment groups.

Taken together, the clinical data from these trials present a compelling case that the Regimen represents a significant advance in the treatment of advanced melanoma, improving durable response and long-term survival without jeopardising patient safety and HRQL.

1.4 Summary of the cost-effectiveness analysis

A de novo economic model was developed based upon the previously-accepted economic models for the nivolumab monotherapy (NICE ID845) and ipilimumab monotherapy (NICE TA268 and TA319). The model structure captures the unique characteristics of immuno-oncology therapy, including the Regimen, for the treatment of advanced melanoma and facilitates the use of the best available efficacy, safety, health-related quality of life HRQL and resource use data. The model established the comparative efficacy of the Regimen and the comparators using covariate-adjusted patient level data analyses, the results from trial-based utility and safety analyses and the most relevant resource use inputs based upon current UK clinical practice. In line with expected UK clinical practice, treatment with nivolumab within the Regimen is modelled to continue until no further clinical benefit is observed – until loss of clinical benefit, unacceptable toxicity or 2 years of continuous treatment – long enough to have observed at least two consecutive scans to confirm response (see Section 5.2.3).

The structure and key assumptions of the decision model were validated by health economics experts, the model estimations of OS and PFS were comparable to clinical data and broadly in line with clinician expectation with the exception of post progression survival which is conservatively assumed the same for the Regimen as ipilimumab monotherapy. The cost-effectiveness results for comparators are in line with published cost-effectiveness literature.

The base case analyses (at list price for all treatments) show the Regimen is a cost effective option for all patients with advanced (unresectable or metastatic) melanoma versus all comparators at a cost-effectiveness threshold of £30,000, with incremental cost-effectiveness ratios (ICERs) of £10,433 and £11,284, in BRAF mutation-negative and BRAF mutation-positive patients, respectively (see Table 3 and Table 4 below).

At the threshold of £30,000, the probabilities of the Regimen being most cost effective are 100% for both BRAF mutation-negative and BRAF mutation-positive patients. Extensive sensitivity and scenario analyses demonstrated that the base case results are robust to uncertainties of key model parameters and assumptions.

Concluding statement

The Regimen represents the next generation in immuno-oncology treatment; uniting the distinct yet complementary mechanism of actions associated with PD-1 and CTLA-4 checkpoint inhibitors. The clinical trial programme that supports the Regimen provides direct evidence of its potential clinical effectiveness compared with current standard of care, ipilimumab monotherapy. Modelled estimates based on Phase III data suggests that the Regimen will more than double the long-term survival rate compared with ipilimumab monotherapy. This potential long-term survival benefit is supported by Phase I data from Checkmate 004 that demonstrate an unprecedented 3-year survival rate of 68%, as well as early OS data from CheckMate 069 that report an 18-month OS rate of 69%, in patients treated with the Regimen. This is a 46% improvement on pooled analyses of the 3-year survival rate associated with ipilimumab monotherapy.

The Regimen is a new, innovative, cost-effective and step-changing treatment option which meets an unmet medical need by offering durable clinical response and the potential for improved long-term survival to a broad range of patients with advanced (unresectable or metastatic) melanoma

Table 3: Base case results – BRAF mutation-negative (drug prices based on list price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
Ipilimumab	[redacted]	3.77	2.90						
Nivolumab plus ipilimumab	[redacted]	6.55	5.09	£22,826	2.79	2.19	£10,433		£10,433

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

Table 4: Base case results – BRAF mutation-positive (drug prices based on list price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
Dabrafenib	[redacted]	2.24	1.74						
Vemurafenib	[redacted]	2.24	1.74	£19,070	0.00	0.00	Same QALYs	Dominated	Excluded due to dominance
Ipilimumab	[redacted]	3.38	2.59	£25,161	1.13	0.85	£29,597	Extended dominated	Excluded due to dominance
Nivolumab plus Ipilimumab	[redacted]	6.26	4.85	£35,085	4.02	3.11	£11,284		£11,284

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

2 The technology

2.1 Description of the technology

Brand name: Opdivo® plus Yervoy®

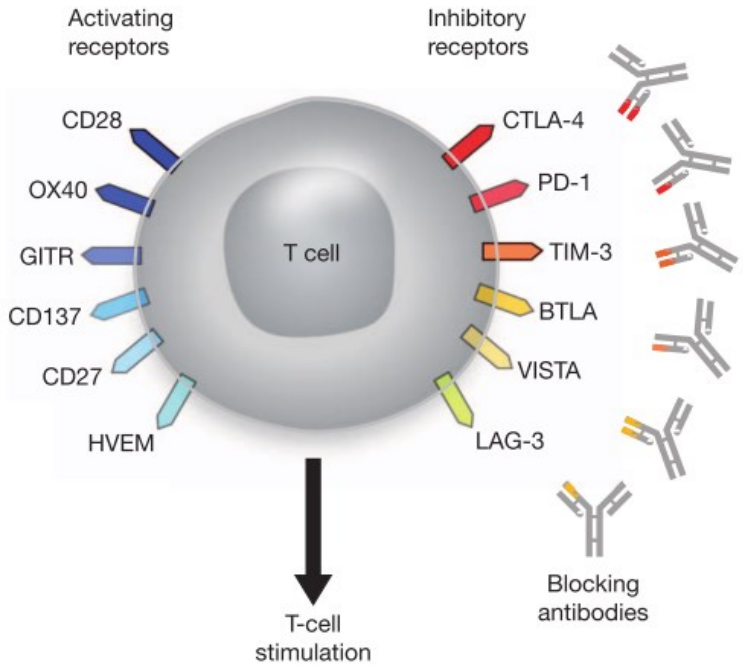
UK approved name: Nivolumab plus ipilimumab (hereafter referred to as the Regimen)

Therapeutic class: monoclonal antibodies

Brief overview of the mechanism of action:

Immunotherapy has been at the forefront of therapeutic development in oncology since the discovery that cancer cells evade destruction by exploiting the signalling pathways that control the immune system. The typical immune response to foreign cells or antigens in the body is the activation of T-cells that can then destroy those foreign cells or antigens. T-cells proliferate and differentiate through various pathways, with T-cell activation regulated through a complex balance of positive and negative signals provided by co-stimulatory receptors on the T-cell surface (Figure 1). Healthy, non-foreign cells ('self'-cells) avoid T-cell destruction by stimulating inhibitory receptors known as checkpoints to suppress the T-cell response; cancer cells can use these same inhibitory receptors to escape immune responses. Blocking antibodies designed to bind to these checkpoints (so called 'checkpoint-inhibitors') can prevent tumour driven T-cell suppression, as depicted in Figure 1, and increase immune activity against cancer cells.

Figure 1: Receptors involved in regulation of the T-cell immune response



Source: Mellman et al., 2011[1]

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) are immune checkpoints involved in T-cell differentiation and function:

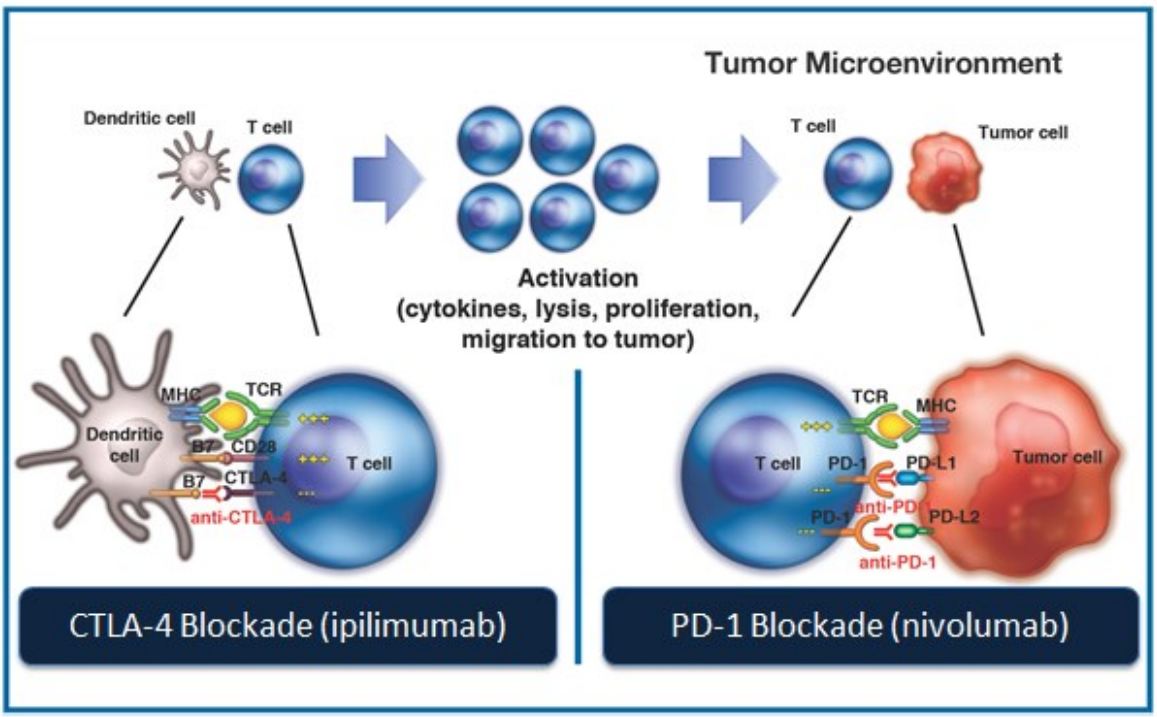
- CTLA-4 is specifically involved in inhibiting constant T-cell production to avoid 'self-damage' in the priming and activation (early) stage of the immune response
  - This pathway 'switches off' the immune response to tumour antigens stopping production of activated T-cells in human malignancy.
- PD-1 is specifically involved in inhibiting T-cell destruction of healthy, 'self-cells' at the effector (later) stage of the immune response
  - Tumour cells can exploit this pathway by up-regulating proteins that engage PD1 to limit the activity of T-cells at the tumour site.

Ipilimumab and nivolumab are both fully human, monoclonal immunoglobulin antibodies (IgG1k and IgG4 HuMab, respectively) that act as checkpoint inhibitors of CTLA-4 and PD-1 at their distinct, yet complementary, positions within the T-cell response pathway:

- Ipilimumab stops the immune response from being 'switched off' which allows the production of active T-cells to continue, increasing the number of activated T-cells surrounding the tumour.
- Nivolumab stops the inactivation of T-cells at the tumour site, allowing the active T-cells to infiltrate and destroy the tumour.

The Regimen therefore potentiates immune-mediated tumour destruction; stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes, as depicted in Figure 2.

Figure 2: Nivolumab and ipilimumab stimulation of immune-mediated tumour destruction



Key: CD28, cluster of differentiation 28; CTLA-4; cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; TCR, T-cell receptor.

It is important to recognise the key differences of immuno-oncology therapies, when compared to standard anti-cancer therapies which arise from their novel mechanism of action.

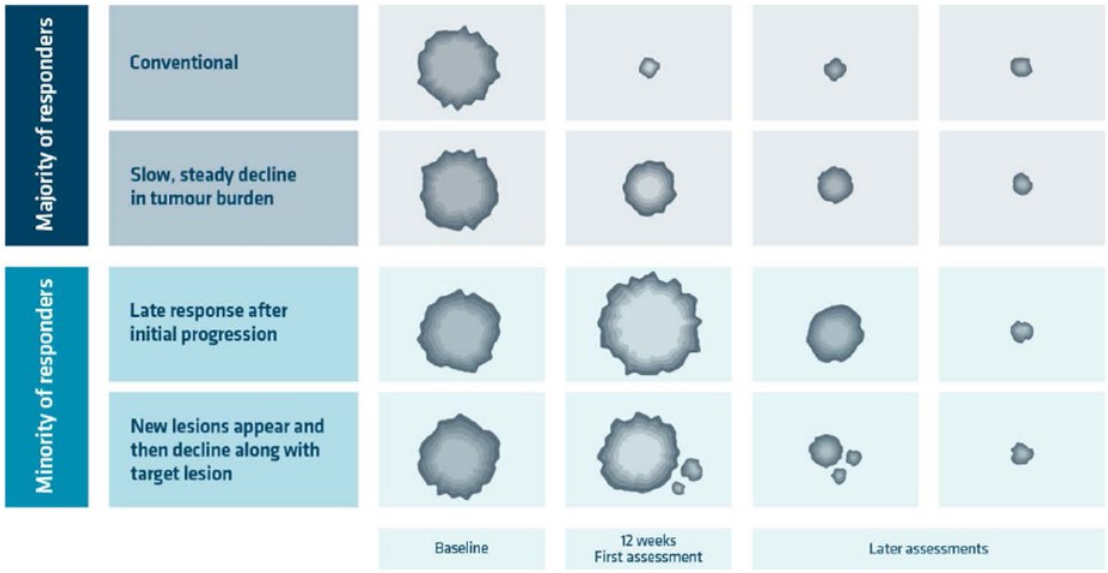
Firstly, varying patterns of response can be observed with immuno-oncology therapies such that patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment. This is due to increased T-cell activity making the tumour appear bigger ('pseudo-progression') as presented in Figure 3.

Secondly, immuno-oncology therapies should not be considered targeted therapies. Whilst they target specific pathways in the immune system, this is not the same as targeting a mutation on the tumour itself. Tumour expression testing is not considered to be clinically relevant as a means of guiding treatment decisions in current practice (see Section 3.2). In the case of programmed death-ligand 1 (PD-L1), there are a number of reasons why tumour expression is not considered clinically valid[2-5]:

- PD-L1 tumour expression is an inducible marker with a transient/dynamic nature such that biopsy at baseline may not be reflective of PD-L1 tumour expression at response or progression;
- There is no standard by which PD-L1 tumour expression is measured; various assays available use different antibodies, different staining protocols, different target cell assessment, different biopsies (fresh or archival), different scoring methods and different thresholds for defining a positive test result;
- Other cell types that express PD-L1 may be present in the tumour microenvironment or tumours may express programmed death-ligand 2 (PD-L2) that have clinical activity with PD-1 inhibitor therapy;
- Response to PD-1 inhibitor therapy is observed irrespective of PD-L1 tumour expression across a number of tumour types including melanoma (see Section 4.7).

This is consistent with advice received from UK clinicians at previous National Institute for Health and Care Excellence (NICE) appraisal committee meetings for PD-L1 monotherapies.[6]

Figure 3: Typical patterns of response observed with immuno-oncology



Ipilimumab is widely acknowledged to elicit an immune memory (with the CTLA-4 pathway attenuating the early activation of naïve and memory T-cells) such that patients only require

short-term, fixed dose treatment for continued response. Such immune memory is less commonly associated with nivolumab (with the PD-1 pathway attenuating the later activation of effector T-cells) and nivolumab monotherapy is licensed to be administered on a continuous dosing schedule. However, it remains unclear as to whether this continuous dosing is necessary with many patients shown to have continued response despite discontinuation of nivolumab therapy. Duration of treatment is considered further in Section 4.

2.2 Marketing authorisation and health technology assessment

Nivolumab (Opdivo®) has marketing authorisation in the UK, Europe, the US and elsewhere as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. Nivolumab is also approved for the treatment of squamous non-small cell lung cancer after previous chemotherapy in adults, but this indication falls outside of the scope of this appraisal. Ipilimumab (Yervoy®) also has a marketing authorisation in the UK, Europe, the US and elsewhere as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.

A Type II application was filed in July 2015 to the European Medicines Agency (EMA) to vary the existing marketing authorisations, to allow both nivolumab and ipilimumab to be used in combination with each other for the treatment of advanced melanoma. The EMA's Committee for Human Medicinal Products (CHMP) is expected to give its opinion on the Regimen in January/February 2016, with a European marketing authorisation expected in late Q1/early Q2 2016.

The draft summary of product characteristics (SmPC) is provided in Appendix 1. The draft European public assessment report is not yet available.

The Regimen was licensed for use in the US for BRAF mutation-negative advanced (unresectable or metastatic) melanoma in October 2015, the first and only combination of two immuno-oncology agents approved by the US Food and Drug Administration. This licence was granted on the basis of early data from the CheckMate 069 trial in which patients with BRAF mutation-negative melanoma were the primary efficacy analysis set (see Section 4.3)

It is anticipated that BMS will submit the Regimen for health technology assessment to the Scottish Medicines Consortium, the All Wales Medicines Strategy Group and the National Centre for Pharmacoeconomics in the Republic of Ireland following receipt of a positive CHMP opinion.

2.3 Administration and costs of the technology

Table 5: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate).	Draft SmPC
Acquisition cost (excluding VAT)	Nivolumab £439 for 40mg £1,097 for 100mg Ipilimumab £3,750 for 50mg at list price	List price for nivolumab; ipilimumab price quoted with and without PAS

	Cost	Source
	£15,000 for 200mg at list price [redacted] for 50mg with PAS [redacted] for 200mg with PAS	
Method of administration	Intravenous infusion	Draft SmPC
Doses and dosing frequency	Nivolumab 1mg/kg plus ipilimumab 3mg/kg q3w for 4 doses followed by nivolumab 3mg/kg q2w	Draft SmPC
Average length of a course of treatment	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Maximum duration of treatment is anticipated to be 2 years. The recommended induction regimen of ipilimumab is 3 mg/kg administered every 3 weeks for a total of 4 doses.	Draft SmPC Clinical consensus[2, 8, 9]
Average cost of a course of treatment	There is no defined course length for the Regimen therefore estimates are presented here in an illustrative manner using median doses from the CheckMate 067 trial, a more detailed estimation of treatment costs can be found in the economic analysis by BRAF status. Median 4 doses of nivolumab and 4 doses of ipilimumab per patient. Mean 5 x 50mg vials per dose for ipilimumab and 2 x 40mg vials per dose for nivolumab for the first 4 doses and 6 x 40mg vials per dose for nivolumab after the first 4 doses. Average cost on the basis of the median doses received within the CheckMate 067 trial is £78,512 at list price for ipilimumab [redacted]	Doses from CheckMate 067 trial[10] Mean vial requirements calculated based upon individual patient weight data as presented in Section 5.5.2
Anticipated average interval between courses of treatments	Retreatment is not anticipated	-
Anticipated number of repeat courses of treatments	Retreatment is not anticipated	-
Dose adjustments	Dose escalation or reduction is not recommended.	Draft SmPC
Anticipated care setting	Hospital or clinic.	Draft SmPC
Key: kg, kilogram; mg, milligram; PAS, patient access scheme; q2w, every 2 weeks; q3w, every 3 weeks; SmPC, Summary of Product Characteristics.		

2.4 Changes in service provision and management

The Regimen requires no additional tests or investigations outside of those required for the diagnosis of advanced melanoma.

The Regimen must be initiated and supervised by physicians experienced in the treatment of cancer. Hospital oncology units already have the staffing and infrastructure needed for the administration of cancer treatments. It is anticipated that the administration of the Regimen would utilise this existing National Health Service (NHS) infrastructure.

The main additional resource use to the NHS is associated with the administration schedule of the Regimen. The 2-weekly dosing schedule of nivolumab after week 12 represents a more frequent administration schedule than current therapies (see Section 3.2). This is fully accounted for in the economic modelling presented in Section 5. As with other immuno-oncology-therapies, patients should also be continuously monitored for signs or symptoms of Select adverse events (AEs) with a potential immunological cause (at least up to 5 months after the last dose), as early identification of AEs and intervention are an important part of the safe use of both nivolumab and ipilimumab. Clinicians will be familiar with monitoring patients for Select AEs as such monitoring is already recommended for patients receiving ipilimumab monotherapy. However, the additive toxicity of administering nivolumab and ipilimumab concurrently (see Section 4.12) may increase monitoring requirements, particularly in the early stages of treatment. This is again fully accounted for in the economic modelling presented in Section 5.

No concomitant therapies are expected to be specified in the marketing authorisation for the Regimen, other than those used to manage AEs. Common AEs are well characterised and, in the majority of cases, can be quickly resolved with appropriate management, including initiation of corticosteroids and treatment modifications, as recommended in established safety algorithms and summarised in the draft SmPC (Appendix 1).

2.5 Innovation

The Regimen represents the next generation in immuno-oncology treatment; uniting the distinct yet complementary mechanism of actions associated with PD-1 and CTLA-4 checkpoint inhibitors (see Section 2.1).

Despite continued therapeutic advances, durable response and long-term survival remain elusive for many patients with advanced melanoma (see Section 3).

The Regimen significantly improved clinical response and progression-free survival (PFS) compared with ipilimumab monotherapy in head-to-head clinical trials (see Section 4.7). Early survival analyses of Phase II data demonstrates an 18-month overall survival (OS) rate of 69% associated with the Regimen (see Section 4.7); the potential OS benefit of combination treatment is supported with Phase I trial data that shows a 3-year OS rate of 68% associated with concurrent nivolumab and ipilimumab therapy (see Section 4.11). Such survival rates have never been seen before in advanced melanoma[5] with immuno-oncology therapy (ipilimumab) previously associated with an 18-month OS rate of 35% and a 3-year OS rate of 22% (pooled analyses of key trials).[11]

Whilst this survival benefit will be captured in the quality-adjusted life year (QALY) calculation, the significant clinical improvement associated with the Regimen should be viewed as innovative and represents a step-change in the management of this condition. Modelled estimates based on conservative assumptions of equal post-progression survival for all immuno-oncology treatments suggest that the Regimen will more than double the long-term survival rate compared with ipilimumab monotherapy (46% vs 23% and 38% vs 18% for BRAF mutation-negative and BRAF mutation-positive patients respectively at Year 3; see Section 5.3).

The depth of response to the Regimen is also unprecedented with76.2% of patients continuing to demonstrate response at the time of analysis (median follow-up approximately 12 months), despite many discontinuing study treatment within the Phase III trial.

Advanced melanoma disproportionately affects younger patients and thus has a significant impact on the working age population (see Section 3.1). There are a number of negative consequences of this, one being loss of economic productivity (see Section 3.1), which is not included in the QALY calculation presented in Section 5, but should be considered when assessing health-related benefits to wider society.

Furthermore, whilst the clinical benefit described above will be captured in the QALY calculation, the curative potential associated with the Regimen, and the possible return to normal living that this offers patients is a remarkable advance from that achieved in the past with chemotherapy that should be viewed as innovative. Melanoma experts in the UK believe the introduction of the Regimen will change the way in which treatment decisions are made in clinical practice (see Section 3.2); this represents a noteworthy step-change in the management of this condition.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease background

Disease background

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.[12, 13] Melanoma is less common than other skin cancers, representing only 4% of all skin cancers in the UK, but is by far the most serious, accounting for 90% of all skin cancer-related deaths.[12, 14]

Often the first visible indication of melanoma is typically a mole that has changed in shape, colour, size or feel (cutaneous melanoma). Melanoma can also originate from other sources, e.g. ocular and mucosal. In these cases the initial signs and symptoms may be less obvious. Initially, melanoma is normally asymptomatic and, if detected early, can be cured by surgical removal. If it goes undetected, melanoma can invade and destroy nearby tissue, and thereafter may metastasise. When this occurs, symptoms become more severe.[15] Specific symptoms will depend on the sites to which melanoma has spread, but patients may typically experience pain and fatigue that affect their physical and mental well-being, weight loss, loss of appetite, nausea and shortness of breath.[15, 16]

As with other forms of cancer, melanoma is divided into stages that describe how widespread the disease has become. The commonly used American Joint Committee on Cancer (AJCC) staging system is summarised in Appendix 2.[15] The Regimen is expected to be indicated for the treatment of advanced (unresectable or metastatic) melanoma. Such patients would be classified as Stage III or Stage IV in this staging system.

Genetically, melanoma can be characterised by a mutation of BRAF: a serine/threonine protein kinase, encoded on chromosome 7q34, that activates the MAP kinase/ERK-signalling pathway.[17] Approximately 50% of all melanomas are estimated to harbour activating BRAF mutations with BRAF mutations more commonly observed in younger patients (<60 years).[17-23]

Course and prognosis

There are a number of factors that can increase the risk of developing melanoma. These include exposure to ultraviolet (UV) rays, having fair skin, having red or blonde hair, having a genetic predisposition to the condition and the presence of atypical or numerous moles (more than 50).[13, 16, 24-26] There are also a number of prognostic factors in melanoma, the

most significant of which include speed of diagnosis, staging and location of metastasis, lactate dehydrogenase (LDH) levels, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale at diagnosis and age.[16, 27-32] Stage IV (metastatic) disease and poor performance status at diagnosis have the poorest prognosis, particularly when brain metastases are present.[16, 27-29, 31, 33]

Incidence and prevalence

Rates of melanoma have been steadily rising over the last 50 years.[34] Malignant melanoma increased by 78% among males and 48% among females from 2003 to 2012, making it the fifth most common cancer in England.[35]

This increasing incidence is widely attributed to changing lifestyle factors such as an increase in holidays taken in the sun and greater use of UV-sunbeds, both increasing people's exposure to UV light. In 2010, 89.8% of melanoma cases were thought to be caused by UV radiation.[34, 36] Potentially as a reflection of lifestyle factors, melanoma is the most frequently diagnosed cancer in people aged 25 to 29.[37] With a mean age at diagnosis of 50 years and up to 20% of cases occurring in young adults (<40 years), this condition has a significant impact on the working age population.[14, 26, 38]

Burden of illness

Studies have shown that alongside physical symptoms, melanoma impacts psychological functioning, with approximately one-third of melanoma patients experiencing considerable levels of distress, mostly at the time of diagnosis and following treatment.[39, 40] At a recent technology appraisal, patient experts confirmed that metastatic melanoma is associated with severe emotional stress and anxiety about the future (both for the patient and their family) and a reduced quality and length of life.[6]

Systemic therapy can decrease patients' health-related quality of life (HRQL) during treatment, but the overall gain in HRQL appears to be favourable, especially in patients with a poor prognosis, i.e. advanced disease at diagnosis.[41] With immuno-oncology therapy, this may be attributable to the resultant extension of life, given that HRQL is seen to decline in the final months of life in advanced melanoma.[42]

The impact of melanoma on patients' HRQL is thought to be comparable to that of other cancers[39], but the prevalence in the working age population can inevitably have wider negative implications for society. For example, due to the fact that advanced melanoma disproportionately affects younger people in their most productive economic years, an individual who dies from advanced melanoma loses 20.4 years of potential life on average, compared with 16.6 years for all malignant cancer types.[43] As a result, melanoma has the highest loss of economic productivity cost in Europe (estimated at €312,798/death in 2008) compared with other cancers.[44]

The direct costs of melanoma are also substantial, increasing in the later stages of the disease.[45-49] Direct cost drivers include out-patient care, and hospitalisation/hospice stays, which increase during palliative care.[47, 50, 51]

The total cost of all skin cancer in England in 2002 was estimated at approximately £240 million with NHS costs accounting for 42% of the total value.[52] Since 2002 although the introduction of new therapies (see Section 3.2) will have resulted in an increase in direct costs to the NHS, these will also have had a positive impact on indirect morbidity and mortality costs. In addition, these costs will have increased in line with increased prevalence and inflation.

Clinical unmet need

Despite significant and continued advances in melanoma therapeutics (see Section 3.2), limitations with current treatments (see Section 3.5) mean durable response and poor long-term survival remains elusive for a majority of melanoma patients. This has a significant, negative impact on patients, carers and wider society.

3.2 Clinical pathway of care

Systemic therapy options for the management of advanced melanoma have continuously progressed in recent years, with a number of treatments demonstrating significant clinical benefit over traditional chemotherapy (which has no proven effect on survival times).[29, 31, 53, 54] Treatment options currently recommended or under consideration for use in NHS England are summarised in Table 6.

The most recent therapies to receive marketing authorisation for the treatment of advanced melanoma are the PD-1 checkpoint inhibitors, nivolumab and pembrolizumab, and the BRAF/MEK inhibitor combination regimens of dabrafenib plus trametinib and vemurafenib plus cobimetinib. None of these treatments is established care in routine clinical practice. However, because pembrolizumab has recently been recommended as a treatment option by NICE, PD-1 checkpoint inhibitors are included in the future clinical pathway of care algorithm (Figure 5) but not the current clinical pathway of care algorithm (Figure 4) presented in this section.

Table 6: Systemic treatment options for advanced melanoma in England

Product (brand)	Treatment class	Dosing regimen	Marketing authorisation	NICE recommendation	Current use estimates
Ipilimumab (Yervoy®)	CTLA-4 checkpoint inhibitor	3mg/kg IV every 3 weeks for a total of 4 doses[9]	Indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults[9]	TA319: recommended as a possible treatment for adults with advanced (unresectable or metastatic) melanoma that has not been treated before. [55] TA268: recommended as a possible treatment for people with previously treated advanced (unresectable or metastatic) melanoma. [56]	BRAF-mutation positive patients: First-line: 50-75%[2, 3] Second-line: 50-80% of patients that progress on BRAF inhibitor therapy[2] BRAF mutation-negative patients: First-line: ≥75%[2, 3]
Vemurafenib (Zelboraf®)	BRAF inhibitor	960mg (4 × 240mg tablets) twice daily until disease progression or toxicity[57]	Indicated as a monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma[57]	TA269: recommended as a possible treatment for unresectable or metastatic melanoma with the BRAF V600 mutation[58]	BRAF-mutation positive patients: First-line: ≤10%[2] Second-line: ≤30% of patients that progress on or after ipilimumab therapy[2]
Dabrafenib (Tafinlar®)	BRAF inhibitor	150mg (2 x 75mg capsules) twice daily until disease progression or toxicity[59]	Indicated as a monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma [59]	TA321: recommended as a possible treatment for people with melanoma that has spread, cannot be removed by surgery and is BRAF V600 mutation-positive[60]	BRAF-mutation positive patients: First-line: 15-45%[2] Second-line: 70-90% of patients that progress on or after ipilimumab therapy [2]
Pembrolizumab (Keytruda®)	PD-1 checkpoint inhibitor	2mg/kg IV every 3 weeks[61]	Indicated as a monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults[61]	TA357: recommended as a possible treatment for adults with melanoma that has been treated with ipilimumab (melanoma that is BRAF V600 mutation-positive must also have had treatment	First-line: No current use as a first-line treatment under routine NHS funding. Second-line: Limited use.

Product (brand)	Treatment class	Dosing regimen	Marketing authorisation	NICE recommendation	Current use estimates
				with vemurafenib, dabrafenib or trametinib)[6] TA366: recommended as a possible treatment for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab[62]	
Nivolumab (Opdivo®)	PD-1 checkpoint inhibitor	3mg/kg IV every 2 weeks[63]	Indicated as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults[63]	Single Technology Appraisal ongoing (ID845)	No current use under routine funding.
Key: CTLA-4, cytotoxic T-lymphocyte associated protein 4; IV, intravenous; NICE, National Institute for Health and Care Excellence; PD-1, programmed death-1.					

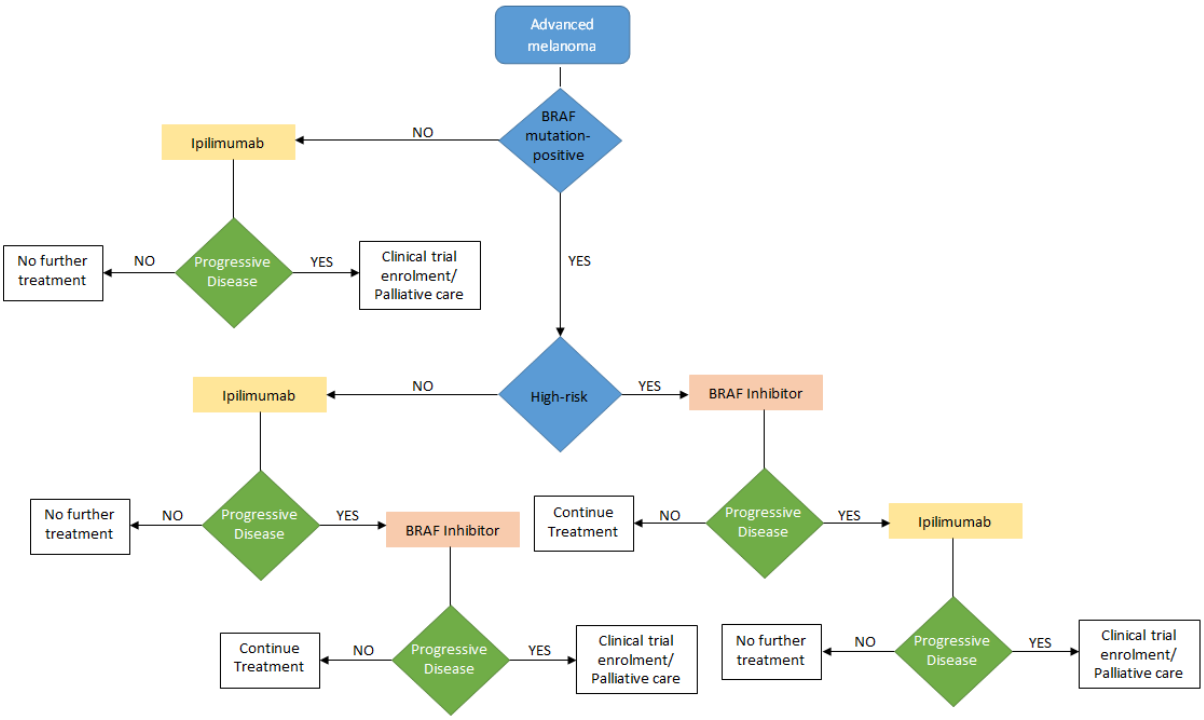
In current clinical practice, the first consideration when making treatment decisions is BRAF mutation status. Patients who are BRAF mutation positive, have a greater number of treatment options available to them, including the BRAF inhibitors (dabrafenib, vemurafenib) and ipilimumab. For patients who are BRAF mutation negative, the BRAF inhibitors are not a treatment option.

For BRAF mutation positive patients, the second consideration is whether patients are considered high-risk, where risk is typically assessed based on tumour burden, performance status (symptom burden), prognosis and disease pace[3, 64]. High risk patients would most likely receive a BRAF inhibitor. Ipilimumab is the only alternative treatment to the BRAF inhibitors in current practice, but is associated with delayed response kinetics (slow response times) compared with BRAF inhibitor therapies.[65-68]

Subsequent-line treatment decisions follow the same considerations, but also take into account first-line therapy in the case of BRAF mutation-positive patients, as those who progress on BRAF inhibitor therapy can subsequently receive ipilimumab therapy and vice versa. In current practice, patients with BRAF mutation-negative melanoma have no second-line treatment options outside of clinical trial enrolment or palliative care, including palliative chemotherapy used to manage disease burden. Current use estimates of established standard of care treatments are included in Table 6.

The current clinical pathway of care for patients with advanced melanoma in NHS England is presented in Figure 4.

Figure 4: Current clinical pathway of care for patients with advanced melanoma in NHS England



Ongoing advances in melanoma treatments are expected to change the first consideration when making treatment decisions. If the Regimen becomes available treatment decisions will be based on whether patients are eligible for immuno-oncology combination treatment, with eligibility primarily based on whether patients are considered 'fit' enough to tolerate the Regimen. Fitness is a relative, subjective assessment, albeit based on objective criteria such

as ECOG status or the presence of brain metastases; some clinicians will use performance status alone as an assessment measure, while others believe disease volume is key as 'fitness' concerns are toxicity based (i.e. can the patient tolerate the side effects of treatment) (see Section 4.12). However, clinicians will be familiar with making such assessments in clinical practice.

This change in treatment decision considerations is driven by the potential inclusion of both the Regimen and PD-1 checkpoint inhibitor monotherapy in the future clinical pathway of care. Compared with established standard of care treatments, the Regimen will likely be the preferred first-line treatment option in all patients due to its superior clinical benefit (see Section 4.7 and 5.3).[3]

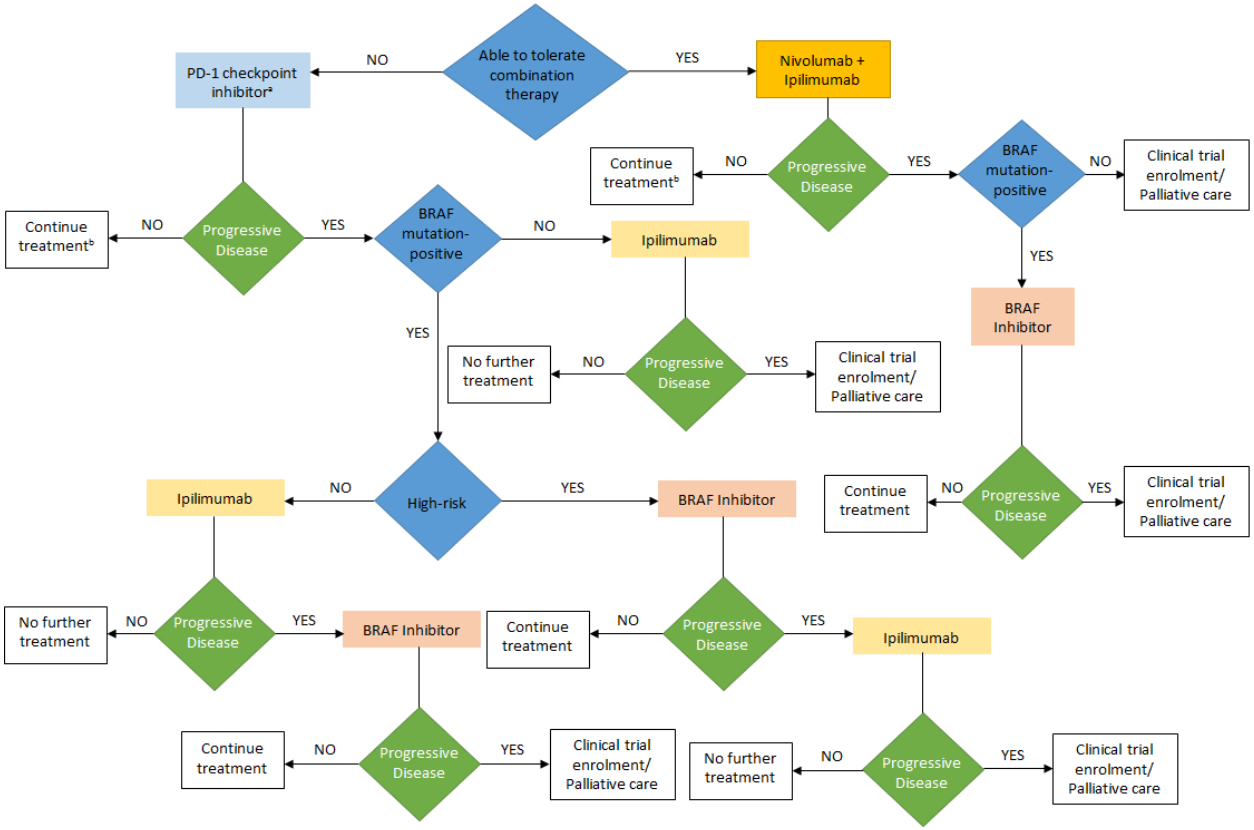
However, in line with recent NICE recommendations and ongoing appraisals, in future, patients who are not considered eligible for the Regimen are likely to receive pembrolizumab or nivolumab monotherapy at first-line, irrespective of BRAF status and risk. This is because PD-1 checkpoint inhibitors offer the potential of long-term survival associated with immuno-oncology therapy without the delayed response kinetics observed with ipilimumab.[2, 3] Thus, BRAF mutation status and patient risk are expected to become secondary considerations, used only to guide treatment decisions in subsequent-line therapy when current treatment options of BRAF inhibitor therapies and ipilimumab monotherapy are more likely to be considered.[3]

Whilst the Regimen and PD-1 checkpoint inhibitors have broad licences (i.e. not restricted to a first-line) it is thought unlikely that one would be used after the other in future clinical practice when considering treatment switching based on disease progression.[3] Similarly, ipilimumab monotherapy is unlikely to be used to treat patients who progress on the Regimen (this is reflected in low rates of ipilimumab use post progression in the CheckMate 067 trial).

It is important to recognise that clinicians and patients want access to a wide range of effective treatment options as possible. Many advanced melanoma patients would benefit from, and indeed are already requesting, the Regimen.[3] In particular, BRAF mutation-negative patients and BRAF mutation-positive patients who fail to respond to BRAF inhibitor therapy at first-line, are the two groups likely to have the greatest need for access to the Regimen.[3]

The future clinical pathway of care for patients with advanced melanoma in NHS England is presented in Figure 5.

Figure 5: Future clinical pathway of care for patients with advanced melanoma in NHS England



Notes: [a], pembrolizumab or nivolumab; [b], continue treatment as long as clinical benefit is observed or until treatment is no longer tolerated.

3.3 Life expectancy, prevalence and incidence of the disease

Population estimates

Based on an incidence rate of 0.0211% in 2012[35] increasing at 3.5% per year[58] and a population size of 53,865,800[69] the number of new cases of melanoma for England in 2013 was 11,763. Of all patients diagnosed with malignant melanoma, up to 10% present at Stage IIIc and Stage IV.[70-72] Assuming the incidence of melanoma is still increasing at 3.5% per year[58], the expected number of new cases of advanced melanoma in England for 2016 is 1,304, all of whom would be expected to receive some kind of treatment in a first-line setting.

Around 21% of these patients are estimated to require second or subsequent-line treatment[56], thus the expected number of relapsed cases of advanced melanoma in England for 2016 is 273.

If it is approved for use, it is difficult to quantify the likely number of patients who would be treated with the Regimen rather than current treatment options considering the patient-specific treatment pathway (see Section 3.2). However, it is expected that the vast majority of patients would be treated at first-line if they are fit enough. Market share estimates are provided in Section 6.

Life expectancy

The life expectancy of advanced melanoma patients is historically poor with median survival estimates of 6-10 months associated with conventional chemotherapy[29, 31, 51, 53, 54]. Whilst these survival statistics are expected to have improved with the introduction of immuno-oncology therapies, it is too early to assess their full impact (ipilimumab and pembrolizumab were only approved for first-line use in England in July 2014 and November 2015, respectively) and a significant impact on median survival estimates is yet to be confirmed; and indeed may fail to emerge with current standard of care, ipilimumab monotherapy (see Section 3.2), given that this treatment results in notable long-term survival in a select proportion of patients with advanced melanoma (approximately 20%[11]). Pooled analyses of clinical trial data and ipilimumab use in an expanded access programme reports median survival estimates of up to 13.5 months associated with ipilimumab monotherapy. [11]

3.4 Clinical guidance and guidelines

NICE guidance

There are a number of NICE guideline and guidance documents and published technology appraisal guidance relating to malignant melanoma:

- NICE Guidelines
  - July 2015. 'Melanoma: assessment and management'[73]
- NICE Guidance on Cancer Services
  - May 2010. 'Improving outcomes for people with skin tumours including melanoma'[74]
  - February 2006. 'Improving outcomes for people with skin tumours including melanoma: the manual'[75]
  - March 2004. 'Improving supportive and palliative care for adults with cancer. The manual'[76]
- NICE Public Health Guidance
  - January 2011.'Skin cancer prevention: information, resources and environmental changes'[77]

- NICE Clinical Guidance
  - April 2011. 'Referral guidelines for suspected cancer'[78]
  - July 2010, 'Metastatic malignant disease of unknown primary origin: diagnosis and management of metastatic malignant disease of unknown primary origin'[79]
- NICE Technology Appraisal Guidance
  - October 2014. 'Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma'. TA321[60]
  - July 2014. 'Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma'. TA319[55]
  - December 2012. 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'. TA268[56]
  - December 2012. 'Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma'. TA269[58]
  - October 2015. 'Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab'. TA357[6]
  - November 2015. 'Pembrolizumab for advanced melanoma not previously treated with ipilimumab'. TA366[62]
  - Ongoing appraisal. 'Melanoma (advanced, unresectable, metastatic) – nivolumab'. ID845[80]

Clinical guidelines

There are also a number of clinical guidelines relating to malignant melanoma that are relevant to current clinical practice in England:

- The National Comprehensive Cancer Network clinical practice guidelines in oncology, melanoma 2015 (v3). National Comprehensive Cancer Network, Inc.[64]
- Cutaneous melanoma: The European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow up (2012)[81]
- Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline – Update 2012[12]

3.5 Issues relating to current clinical practice

There are a number of limitations associated with current established treatment options for the management of advanced melanoma; these are summarised in Table 7. As a result, there are still a significant number of advanced melanoma patients for whom durable response and long-term survival remain elusive. This identifies a clear unmet need in current practice.

Table 7: Key issues with current treatment options for advanced melanoma

Treatment	Summary of key issues
BRAF inhibitor therapy	• Only indicated for the treatment of BRAF mutation-positive melanoma – ~50% of melanoma patients possess the BRAF mutation[17, 19-23] • Long-term survival benefit not demonstrated[82] • Resistance to BRAF inhibitors has been observed[17, 22, 83] – Progression thought to be due to the emergence of resistance often observed between 5-8 months post initiation[67, 68, 84]
Ipilimumab monotherapy	• Many patients fail to respond to treatment [10, 65, 66, 85-87] • Long-term survival observed in only 20% of patients[11] – Strongly correlated with induction completion[88, 89] • Delayed response kinetics with typically slower response times[65, 66] than BRAF inhibitors[67, 68]

3.6 Assessment of equality issues

No equality issues related to the use of the Regimen have been identified or are foreseen.

4 Clinical effectiveness

Summary

- Despite continued advances in melanoma therapeutics, durable response and long-term survival remains elusive for many patients with advanced disease
- Nivolumab plus ipilimumab is the first immuno-oncology combination treatment to offer improved clinical benefit to patients with advanced melanoma
- A comprehensive clinical evidence base supports the use of concurrent nivolumab plus ipilimumab therapy in accordance with UK licence terms (nivolumab 1mg/kg plus ipilimumab 3mg/kg q3w for four doses followed by nivolumab 3mg/kg q2w) (the Regimen):
    - CheckMate 067: pivotal Phase III RCT in previously untreated patients who have advanced melanoma with or without a BRAF mutation that investigates the clinical efficacy of nivolumab plus ipilimumab therapy compared with ipilimumab 3mg/kg monotherapy
    - CheckMate 069: Phase II RCT in previously untreated patients who have advanced melanoma with or without a BRAF mutation that investigates the clinical efficacy of nivolumab plus ipilimumab therapy compared with ipilimumab 3mg/kg monotherapy
    - CheckMate 004: supportive Phase I dose-ranging study in previously untreated or treated patients who have advanced melanoma with or without a BRAF mutation that provides longer-term survival data for nivolumab plus ipilimumab therapy
- The Regimen demonstrates high rates of rapid and durable clinical response despite high rates of discontinuation due to study drug toxicity
- In the pivotal Phase III RCT, patients treated with the Regimen lived without disease progression for nearly 12 months having received treatment for less than 3 months on average
- Phase II RCT data demonstrates an 18-month OS rate of 69% associated with the Regimen; approximately double the 18-month OS rate associated with ipilimumab monotherapy in pooled analyses of key trials
- Modelled survival estimates suggest that the Regimen will more than double the long-term survival rate compared with ipilimumab monotherapy (46% vs 23% and 38% vs 18% for BRAF mutation-negative and BRAF mutation-positive patients respectively at Year 3)
- Long-term survival estimates are supported with Phase I data that demonstrates an unprecedented 3-year survival rate of 68% in advanced melanoma patients treated with concurrent nivolumab plus ipilimumab therapy (compared to a 3-year survival rate of 22% for ipilimumab monotherapy in pooled analyses of key trials)
- The Regimen is associated with a predictable safety profile with immune-related adverse events that are acute and reversible in-line with well-established safety algorithms in the majority of patients
- Contrary to conventional cytotoxic agents, the Regimen was not associated with clinically meaningful changes in health-related quality of life, whilst conferring survival benefit in patients with advanced melanoma
- The Regimen represents the next generation of immuno-oncology treatment and would result in a step-change in the management of advanced melanoma if recommended for routine use in the NHS

4.1 Identification and selection of relevant studies

Search strategy

A systematic literature review designed to identify randomised controlled trials (RCTs) of the Regimen and comparator therapies used in the first-line treatment of advanced melanoma in adults was initiated in September 2015.

Information retrieval methods were based upon the research question "What is the relative clinical efficacy and safety of the Regimen versus competing, approved therapies for the treatment of advanced (unresectable or metastatic) melanoma in the UK and Ireland?"

Searches were performed in global electronic databases:

- MEDLINE and MEDLINE In-Process
- EMBASE
- The Cochrane Library, including the following:
    - The Cochrane Database of Systematic Reviews (CDSR)
    - The Cochrane Central Register of Controlled Trials
    - The Database of Abstracts of Reviews of Effects (DARE)
    - The Health Technology Assessment (HTA) database

In addition, annual proceedings of the following conferences were hand searched in order to identify any relevant, on-going research:

- The American Society of Clinical Oncology (ASCO) (2013-2015)
- ESMO (2013-2015)
- The Society for Immunotherapy of Cancer (2013-2015)
- The Society for Melanoma Research (SMR) (2013-2015)

The search strategies used are provided in Appendix 3.

Reference lists of systematic reviews/meta-analyses, clinical guidelines and previous health technology assessments identified through systematic searches were also hand-searched to highlight any further relevant studies. In addition, unpublished data held by BMS were reviewed for relevance to the research question/decision problem.

Of note, at the time of systematic review initiation, pembrolizumab was not recommended for use in the NHS by NICE and was not included in either the draft or pre-invitation scope for this appraisal; therefore pembrolizumab was not included as an intervention of interest.

Study selection

The full eligibility criteria applied to the identified evidence base is presented in Table 8.

RCTs were included in the final evidence base of relevant studies if they investigated the clinical efficacy and/or safety of the Regimen or interventions currently used in the NHS for the treatment of advanced melanoma in adults. Outcomes of interest were those considered representative of the clinical benefit and safety measures adopted in clinical practice and those named in the decision problem. However, trials were not excluded on the basis of outcome alone. RCTs were included regardless of design (parallel, cross-over, open-label, single- or double-blinded).

Table 8: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients with advanced (Stage III or IV unresectable or metastatic) melanoma Treatment naïve and/or treatment exposed	Patients with Stage I or II melanoma Patients with Stage III resectable melanoma Paediatric melanoma patients Patients with non-melanoma malignancy/disease
Intervention	Nivolumab plus ipilimumab Ipilimumab 3mg/kg Dabrafenib 150mg Vemurafenib 960mg	Any other
Comparators	Active therapy Palliative care Best supportive care Placebo	None
Outcomes	Overall survival Progression-free survival Objective response Safety and tolerability HRQL	None
Study design	Randomised controlled trials Systematic reviews/meta-analyses[a]	Non-randomised controlled trials Single-arm trials Observational studies Database analyses Pooled data analyses Non-systematic reviews In-vitro studies Preclinical studies Case reports/series Commentaries/letters/editorials
Language restrictions	None	None

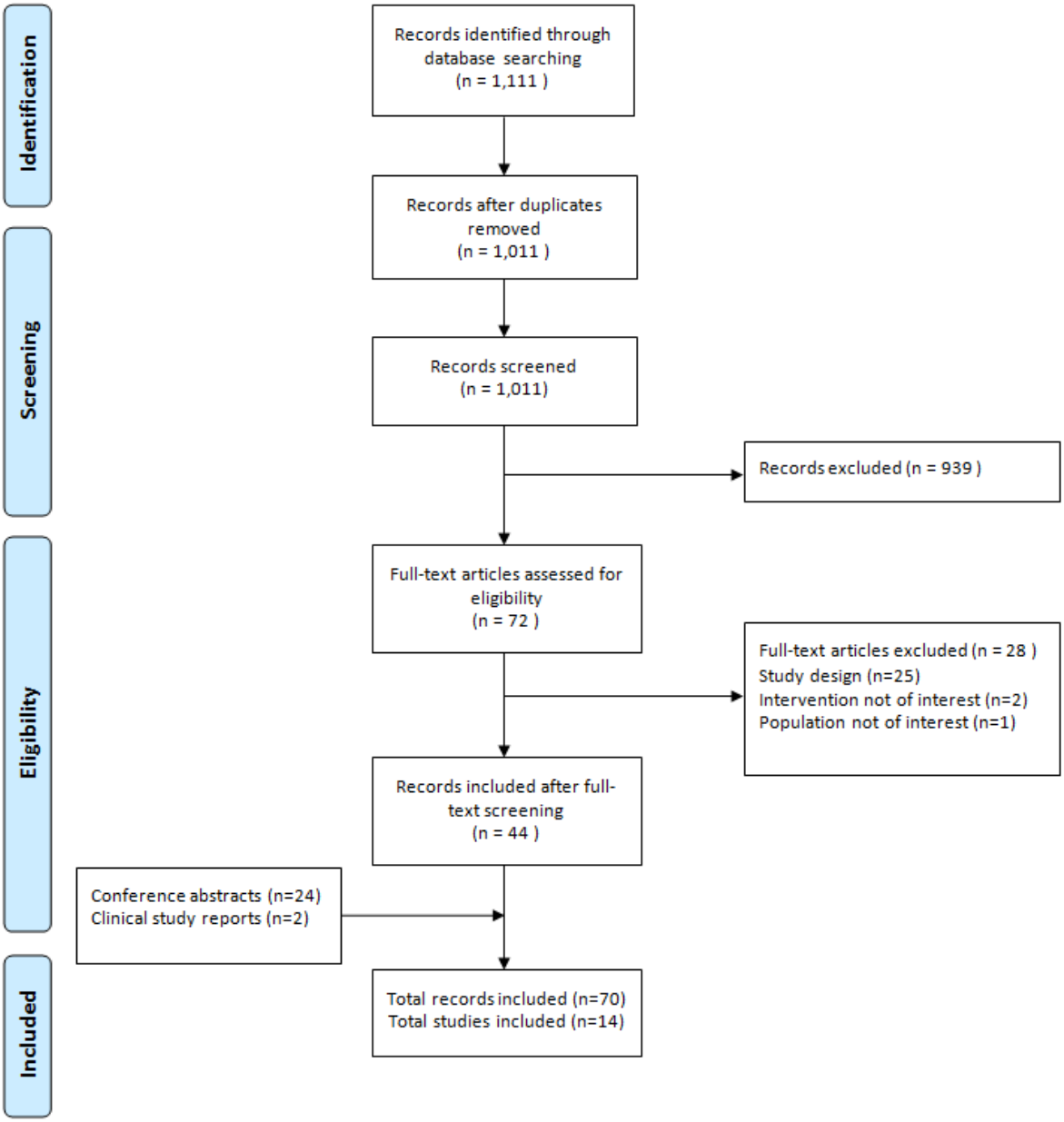
Key: HRQL, health-related quality of life; kg, kilogram; mg, milligram.
Notes: [a], included for reference review only.

Two reviewers independently inspected each reference (title and abstract) identified by the literature searches and applied basic study selection criteria based on the eligibility criteria presented in Table 8 (primary screening). Citations meeting basic study selection criteria (or in cases of disagreement between the two reviewers) were obtained in full and independently assessed against the full eligibility criteria presented in Table 8 (secondary screening). In the event of disagreement between the two reviewers, a third reviewer would have independently assessed the paper and applicability of selection criteria attained by consensus. However, this was not needed as no discrepancies occurred.

If study duplication within publications was suspected, author names, location and setting, specific intervention details, participant numbers, baseline data and date and duration of study were assessed. If uncertainties remained, the authors would have been contacted, but this situation did not occur. Where multiple publications were identified for the same clinical trial, all were included in the final list of articles meeting the eligibility criteria but clearly identified as primary and secondary sources of data for the same trial.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the number of studies included and excluded at each stage of the systematic review is presented in Figure 6.

Figure 6: PRISMA flow diagram of the literature search process



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Original searches of electronic databases identified a total of 1,111 citations of potential relevance to the research question. A total of 100 citations were found to be duplicates therefore primary screening was carried out on 1,011 unique citations.

During primary screening of all citations, a total of 939 citations were excluded as they were clearly not of relevance to the research question. Common reasons for exclusion at this stage included non-RCT trial designs, non-advanced melanoma patient populations and investigations of regimens not of interest to the research question.

A total of 72 citations were accessed in full (where applicable and necessary) for further evaluation. Of these citations, 14 were original publications of trials meeting the eligibility criteria of the review and a further 30 were secondary publications providing additional data sources. In addition, conference proceedings searches identified 24 abstracts that were secondary publications associated with trials identified through electronic database searches. A further 2 secondary sources of unpublished data were also included in the final evidence base in the form of clinical study reports.

A reference list of citations excluded at the secondary screening stage is provided in Appendix 4. All sources of data for each study meeting the eligibility criteria (Table 8) are listed in Table 9.

Table 9: Data sources for included trials

Trial	Comparator(s)	Primary study reference	Secondary study reference(s)
Studies investigating the Regimen			
CheckMate 067 (CA209-067)	Ipilimumab 3mg/kg Nivolumab 3mg/kg	Larkin et al., 2015[10]	Larkin et al. 2015[90] Schadendorf et al. 2015[91] Wolchok et al., 2015[92] CheckMate 067 CSR[93]
CheckMate 069 (CA209-069)	Ipilimumab 3mg/kg	Postow et al. 2015[85]	Abernethy et al., 2015[94] Hodi et al., 2015[95] CheckMate 069 CSR[96]
Studies investigating ipilimumab 3mg/kg monotherapy			
CA184-004	Ipilimumab 10mg/kg	Hamid et al., 2011[86]	Shahabi et al. 2012[97] Ji et al. 2011[98]
CA184-022	Ipilimumab 0.3mg/kg Ipilimumab 10mg/kg	Wolchok et al. 2010[87]	Hamid et al. 2008[99] Lebbe et al. 2008[100]
MDX010-08	Ipilimumab 3mg/kg + DTIC	Hersh et al., 2011[101]	Hersh et al. 2008[102] Hersh et al. 2004[103]
MDX010-20	Ipilimumab 3mg/kg + gp-100 gp-100	Hodi et al., 2010[65]	Koguchi et al. 2015[104] Hatswell et al. 2014[42] Kaufman et al. 2013[105] McDermott et al. 2013[106] Robert et al. 2013[107] Weber et al. 2013[108] Revicki et al. 2012[40] O'Day et al. 2010[109]
Keynote 006	Pembrolizumab 10mg/kg q2w Pembrolizumab 10mg/kg q3w	Robert et al. 2015[110]	Petrella et al. 2015[111] Robert et al. 2015[112]

Trial	Comparator(s)	Primary study reference	Secondary study reference(s)
Studies investigating dabrafenib 150mg monotherapy			
BREAK-3	DTIC	Hauschild et al., 2012[68]	Grob et al., 2014[113] Hauschild et al., 2014[114] Hauschild et al., 2013[115] Latimer et al., 2013[116]
COMBI-d	Dabrafenib + trametinib	Long et al., 2014[117]	Long et al. 2015[118] Long et al., 2015[119] Schadendorf et al., 2015[120] Latimer et al., 2014[121] Long et al., 2014[122] Schadendorf et al., 2014[123]
BRF113220	Dabrafenib + trametinib	Flaherty et al. 2012[124]	Daud et al., 2015[125] Menzies et al., 2015[126] Flaherty et al., 2014[127] Johnson et al., 2014[128] Cebon et al. 2013[129] Schuchter et al. 2013[130]
Studies investigating vemurafenib 960mg monotherapy			
BRIM-3	DTIC	Chapman et al., 2011[67]	Chapman et al. 2015[131] Zabor et al., 2015[132] McArthur et al., 2014[133] Hauschild et al., 2013[82] Chapman et al. 2012[134] Chapman et al. 2011[135] Hauschild et al. 2011[136] McArthur et al. 2011[137]
COMBI-v	Dabrafenib + trametinib	Robert et al., 2015[138]	Ascierto et al. 2015[139] Grob et al. 2015[140] Robert et al. 2015[141] Robert et al., 2014[142]
coBRIM	Vemurafenib + cobimetinib	Larkin et al., 2014[143]	De La Cruz-Merino et al., 2015[144] Dreno et al., 2015[145] Larkin et al., 2015[146] McArthur et al. 2015[147] McArthur et al., 2014[148]
Grippo et al., 2014	Vemurafenib 240mg Vemurafenib 480mg Vemurafenib 720mg	Grippo et al., 2014[149]	-
Key: DTIC, dacarbazine; gp-100, glycoprotein-100; q2w, every 2 weeks; q3w, every 3 weeks.			

4.2 List of relevant randomised controlled trials

One Phase III and one Phase II RCT provide evidence on the clinical benefit of the Regimen within the indication being appraised, as shown in Table 10.

Both of these RCTs directly compare the clinical efficacy and tolerability of the Regimen with ipilimumab 3mg/kg monotherapy; this is the most appropriate comparator of those referenced in the decision problem as (like the Regimen) it can be administered to all advanced melanoma patients, irrespective of BRAF status. At the time of submission, these studies are ongoing.

No head-to-head data are available comparing the Regimen with BRAF inhibitor therapy in patients with BRAF mutation-positive melanoma; their comparative efficacy has therefore been estimated using indirect comparison methods (see Section 4.10 and Section 5.3).

Table 10: List of relevant RCTs

Trial name (NCT number)	Phase	Population	Intervention	Comparator	Primary study reference
CheckMate 067 (NCT01844505)	III	Advanced (unresectable or metastatic) melanoma patients who are treatment naïve.	Nivolumab plus ipilimumab	Ipilimumab 3mg/kg monotherapy Nivolumab 3mg/kg monotherapy[a]	Larkin et al. 2015[10]
CheckMate 069 (NCT01927419)	II	Advanced (unresectable or metastatic) melanoma patients who are treatment naïve.	Nivolumab plus ipilimumab	Ipilimumab 3mg/kg monotherapy[b]	Postow et al. 2015[85]
Notes: [a], results of this treatment arm are not presented as they are not the subject of this submission; [b], patients could receive nivolumab monotherapy upon disease progression and after unblinding.					

In addition to the published primary study references, data are taken from the clinical study reports for each trial. Data have also been presented at the following conferences:

CheckMate 067

- Larkin et al. Efficacy and safety in key patient subgroups of nivolumab alone or combined with ipilimumab versus ipilimumab alone in treatment-naïve patients with advanced melanoma (Checkmate 067). Presented at ECC 2015.[90]
- Schadendorf et al. Patient reported outcomes from a Phase 3 study of nivolumab alone or combined with ipilimumab vs ipilimumab in patients with advanced melanoma: CheckMate 067. Presented at SMR 2015.[91]
- Wolchok et al. Efficacy and safety results from a phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment naïve patients (pts) with advanced melanoma (MEL) (CheckMate 067). Presented at ASCO 2015.[92]

CheckMate 069

- Abernethy et al. Effect of nivolumab (NIVO) in combination with ipilimumab (IPI) versus IPI alone on quality of life (QoL) in patients (pts) with treatment-naive advanced melanoma (MEL): Results of a Phase II study (CheckMate 069). Presented at ASCO 2015.[94]
- Hodi et al. Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study. Presented at ASCO 2015.[95]

4.3 Summary of methodology of the relevant randomised controlled trials

A comparative summary of the methodology of CheckMate 067 and CheckMate 069 is presented below and summarised in Table 11.

CheckMate 067

CheckMate 067 is a Phase III, multicentre, double-blind RCT evaluating the safety and efficacy of nivolumab alone or nivolumab combined with ipilimumab in comparison with ipilimumab alone in patients with previously untreated metastatic melanoma.[10, 93]

CheckMate 067 was initiated on 11th June 2013, and is currently ongoing. Data presented in this submission are based on a clinical database lock of 17th February 2015. Results for the co-primary endpoint of OS are not available at this time as patients are still surviving and the required minimum follow-up for analysis has not yet been reached (22 months, see Section 4.4).

[redacted] Results for progression-free survival (PFS), objective response rate (ORR) and HRQL are available and presented in Section 4.7.

In line with the focus of this submission, results are presented for the Regimen and its direct comparator, ipilimumab monotherapy, in Section 4.7. The results of the nivolumab monotherapy arm are not presented, as they are not the subject of this submission and have been previously presented as part of an ongoing NICE STA [ID845]. Moreover, this study was not designed for a formal statistical comparison between nivolumab monotherapy and the Regimen.

CheckMate 069

CheckMate 069 is a Phase II, multicentre, double-blind RCT comparing the Regimen with standard-of-care ipilimumab monotherapy as a first-line treatment in patients with advanced melanoma.[85, 96] Upon disease progression and after unblinding, patients initially treated with ipilimumab could be given the option to receive nivolumab monotherapy.

CheckMate 069 was initiated on 23rd August 2013, and is currently ongoing. In the majority, data presented in this submission are based on a clinical database lock of 30th January 2015 and include primary endpoint analysis of confirmed ORR in patients with BRAF mutation-negative (wild-type) tumours. The primary endpoint was restricted to this group of patients as at the time of study enrolment, approved treatment options were limited for these patients and only ipilimumab had shown an OS benefit in a RCT setting. Results for PFS and HRQL are also available and are presented in Section 4.7, along with OS rate analyses up to 18 months based on a later database lock of August 2015.

Across both trials, the efficacy endpoints were clinically relevant measures of disease as used in clinical practice. These measures are consistent with other studies of therapeutic

agents in advanced melanoma. As part of the safety and tolerability review, particular attention was paid to the identification and assessment of AEs of specific interest (Select AEs) which were immune-related and potentially associated with the use of nivolumab and ipilimumab.

Of note, patients could continue treatment beyond initial Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression (where progression is assessed based on tumour size and/or the appearance of new lesions) if they were considered by the investigator to be experiencing clinical benefit and tolerating the study drug. This design is based on accumulating clinical evidence indicating that some patients treated with immune system-stimulating agents show disease progression, as defined by conventional RECIST criteria, before demonstrating subsequent clinical objective responses and/or stable disease (see Section 2.1). Patients treated beyond initial RECIST-defined progression discontinued study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumour burden volume from time of initial progression.

In clinical practice, when assessing immuno-oncology therapies, response to therapy will largely be based on clinical judgement, with consideration given to the potential of response despite an initial increase in tumour burden or the presence of new lesions. It is important to note that progression assessments of immuno-oncology therapies against RECIST criteria for tumour progression in clinical trials therefore provide a conservative estimate of benefit from therapy compared to clinical practice assessment of immuno-oncology treatment effect.

Table 11: Comparative summary of RCT methodology

	CheckMate 067	CheckMate 069
Location	Patients were treated across 137 sites in Australia, Europe, Israel, New Zealand and North America, including 7 sites in the United Kingdom	Patients were treated across 21 sites in France and North America.
Trial design	Phase III, randomised, double-blind, active-controlled, multi-centre clinical trial. Patients were randomised in a 1:1:1 ratio through an IVRS. Randomisation was stratified by PD-L1 status, BRAF mutation status and metastatic stage. The sponsor, patients, investigator and site staff were blinded to treatment assignment until progression of disease and treatment discontinuation.	Phase II, randomised, double-blind, active-controlled, multi-centre clinical trial. Patients were randomised in a 2:1 ratio through an IVRS. Randomisation was stratified by BRAF mutation status. The sponsor, patients, investigator and site staff were blinded to treatment assignment until progression of disease and treatment discontinuation.
Eligibility criteria for participants	Men and women aged ≥18 years who signed informed consent and met the following main disease criteria upon screening were enrolled: • Untreated, histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging • PD-L1-positive, PD-L1-negative or PD-L1-intermediate classification according to recent biopsy from an unresectable or metastatic site • Known BRAF mutation status • Prior radiotherapy (non-systemic) completed ≥4 weeks before study drug administration • Measurable disease by RECIST v1.1 criteria • ECOG PS of 0 or 1 Patients who met any of the following key criteria were excluded from study eligibility: • Active brain metastases or leptomeningeal metastases • Ocular melanoma	Men and women aged ≥18 years who signed informed consent and met the following main disease criteria upon screening were enrolled: • Histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging • No prior systemic anticancer therapy for unresectable or metastatic melanoma. Note that prior adjuvant or neoadjuvant melanoma therapy was permitted if it was completed at least 6 weeks prior to first dose and all related AEs have either returned to baseline or stabilised. • Measurable disease by RECIST v1.1 criteria • ECOG PS of 0 or 1 Patients who met any of the following key criteria were excluded from study eligibility: • Active brain metastases or leptomeningeal metastases • Ocular melanoma • Active, known or suspected autoimmune disease

	CheckMate 067	CheckMate 069
	• Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured • Active, known or suspected autoimmune disease • Conditions requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibody or any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways	• Conditions requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration • Prior randomisation in an ipilimumab study trial • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody or any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
Settings and locations where the data were collected	Local laboratory assessments were arranged by site. An independent DMC was established to provide oversight of safety and efficacy considerations and to provide advice regarding necessary actions for the continuing protection of enrolled patients.	Local laboratory assessments were arranged by site. ICON Laboratories were responsible for management of local laboratory results from the site. ICON entered, reviewed, queried, and transferred the results, from the local laboratory reports received from sites to the BMS Oracle Clinical Database. An independent DMC was established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio.
Trial drugs	Nivolumab plus ipilimumab group (n=314): nivolumab 1mg/kg plus ipilimumab 3mg/kg q3w by IV infusion for 4 doses followed by nivolumab 3mg/kg q2w Ipilimumab group (n=315): ipilimumab 3mg/kg q3w by IV infusion for 4 doses (plus nivolumab-matched placebo) Nivolumab group (n=316): nivolumab 3mg/kg q2w by IV infusion (plus ipilimumab-matched placebo) Nivolumab treatment continued until there was disease progression or discontinuation due to toxicity or any other reason. Treatment after disease progression was permitted for patients who had a clinical benefit and were tolerating treatment, as determined by the investigator.	Nivolumab plus ipilimumab group (n=95): nivolumab 1mg/kg plus ipilimumab 3mg/kg q3w by IV infusion for 4 doses followed by nivolumab 3mg/kg q2w Ipilimumab group (n=47): ipilimumab 3mg/kg q3w by IV infusion for 4 doses (plus nivolumab-matched placebo) Nivolumab treatment continued until there was disease progression or discontinuation due to toxicity or any other reason. Treatment after disease progression was permitted for patients who had a clinical benefit and were tolerating treatment, as determined by the investigator.

	CheckMate 067	CheckMate 069
	Drug reductions or dose escalations were not permitted. Dose delays were permitted for all AEs related to trial drugs (regardless of which treatment was attributed to the event).	Patients initially treated with ipilimumab could be given the option to receive nivolumab 3mg/kg q2w upon disease progression and after unblinding. Drug reductions or dose escalations were not permitted. Dose delays were permitted for all AEs related to trial drugs (regardless of which treatment was attributed to the event).
Permitted and disallowed concomitant medication	Immunosuppressive agents, systemic corticosteroids >10mg daily prednisone equivalent or any concurrent antineoplastic therapy were prohibited during the study (unless utilised to treat a drug-related AE). Palliative radiotherapy and surgical resection were permitted if the lesion being considered for such treatment was not a target lesion, the patient was considered to have progressed at the time of palliative therapy, and the case was discussed with the medical monitors. Patients were permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) and a brief course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by contact allergen) was allowed.	Immunosuppressive agents, systemic corticosteroids or any concurrent antineoplastic therapy (including radiotherapy and surgical resection) were prohibited during the study (unless utilised to treat a drug-related AE). Patients were permitted to use inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalent in the absence of active immune disease; or a brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions. Supportive care for disease-related symptoms was also allowed for all patients on the trial.
Primary outcomes	OS: defined as time between the date of randomisation and the date of death. PFS: defined as the time between the date of randomisation and the first date of documented progression or death due to any cause. Investigator-assessed. Assessments for survival were performed continuously during treatment and every 3 months during follow-up.	ORR in patients with BRAF mutation-negative tumours: defined as the number of patients with a BOR of CR or PR divided by the number of randomised patients. Investigator-assessed. Tumour response was assessed according to the RECIST, version 1.1. Tumour assessments began 12 weeks (±1 week) from first dose and continued every 6 weeks (±1 week) for the first 12 months and every 12 weeks (±1 week) thereafter, until disease progression was documented or treatment was discontinued.
Secondary outcomes	ORR: defined as the number of patients with a BOR of CR or PR divided by the number of randomised patients. Investigator-assessed.	DOR: defined as the time between the date of first response to the date of first documented tumour progression or death due to any cause. Investigator-assessed.

	CheckMate 067	CheckMate 069
	Tumour response was assessed according to the RECIST, version 1.1. Tumour assessments began 12 weeks (±1 week) from first dose and continued every 6 weeks (±1 week) for the first 12 months and every 12 weeks (±1 week) thereafter, until disease progression was documented or treatment was discontinued. OS, PFS and ORR difference between the two experimental arms. OS based on PD-L1 expression level: defined as OS based on PD-L1 status using a verified assay with ≥5% tumour cell membrane expression cut-off. HRQL: measured by mean changes from baseline in the EORTC QLQ-C30 scales. HRQL was assessed on Days 1, 15, 22 and 29; 9 weeks from randomisation; every 6 weeks thereafter for the first 12 months; and at follow-up visits 1 and 2.	TTR: defined as the time from randomisation to the date of the first documented CR or PR. Investigator-assessed. PFS in patients with BRAF mutation-negative tumours: defined as the time between the date of randomisation and the first date of documented progression or death due to any cause. Investigator-assessed. ORR in patients with BRAF mutation-positive tumours. PFS in patients with BRAF mutation-positive tumours. HRQL: measured by mean changes from baseline in the EORTC QLQ-C30 scales. HRQL assessment began prior to first dose and continued every 6 weeks for the first 6 months.
Key exploratory outcomes	DOR: defined as the time between the date of first response to the date of first documented tumour progression or death due to any cause. Investigator-assessed. TTR: defined as the time from randomisation to the date of the first documented CR or PR. Investigator-assessed. Percent change in tumour volume: defined as the percent decrease in tumour volume from baseline to nadir, observed up until the date of progression, the date of subsequent anticancer therapy, or death. Safety and tolerability: measured by the incidence of AEs, SAEs, deaths and laboratory abnormalities. Severity of AEs was graded according to the NCI CTCAE, version 4.0. Safety assessments were made continuously during the treatment phase and up to 100 days after the last dose of study drug. HRQL: measured by mean changes from baseline in health status, assessed using the EQ-5D tool and by changes in work and activity impairment, assessed using the WPAI:GH	OS: defined as time between the date of randomisation and the date of death. Assessments for survival were performed continuously during treatment and every 3 months during follow-up. Percent change in tumour volume: defined as the percent decrease in tumour volume from baseline to nadir, observed up until the date of progression, the date of subsequent anticancer therapy, or death. Safety and tolerability: measured by the incidence of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, Select AEs, laboratory abnormalities, and vital sign measurements. AEs were coded using the MedDRA, version 16.1. Severity of AEs was graded according to the NCI CTCAE, version 4.0. Safety assessments were made continuously during the treatment phase. HRQL: measured by mean changes from baseline in health status, assessed using the EQ-5D tool. Biomarker assessment: exploration of the potential association between biomarker (e.g. PD-L1) expression and

	CheckMate 067	CheckMate 069
	tool. EQ-5D assessments were conducted in the on treatment period and during survival follow-up.	efficacy endpoints (response, survival [OS, PFS] and/or safety).
Pre-planned subgroups	Subgroup analyses assessing the impact of age, gender, race, region, baseline ECOG PS, PD-L1 expression status, BRAF mutation status, M stage at study entry, history of brain metastases, smoking status, baseline LDH and AJCC stage on clinical efficacy outcomes were pre-planned.	Subgroup analyses assessing the impact of M stage at study entry, AJCC stage, age, gender, race, region, baseline ECOG performance status, history of brain metastases, smoking status, and baseline LDH on clinical efficacy outcomes were pre-planned for patients with BRAF mutation-negative and BRAF mutation-positive tumours.

Key: AE, adverse event; AJCC, American Joint Committee on Cancer; BOR, best overall response; CD137, cluster of differentiation 137 (a member of the tumour necrosis factor family); CR, complete response; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; DMC, data monitoring committee; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D, EuroQol-five dimension; HRQL, Health-related quality of life; IV, intravenous; IVRS, interactive voice response system; LDH, lactate dehydrogenase; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PR, partial response; q2w, every 2 weeks; q3w, every 3 weeks; PS, performance score; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TTR, time to treatment response; WPAI:GH, Work Productivity and Activity Impairment Questionnaire: General Health.
Source: CheckMate 067 CSR[93]; CheckMate 069 CSR[96]; Larkin et al. 2015[10]; Postow et al. 2015.[85]

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

The hypothesis and associated statistical analysis methods adopted in CheckMate 067 and CheckMate 069 are presented in Table 12.

CheckMate 067

The primary datasets used in CheckMate 067 were the all randomised population (intention-to-treat [ITT] population) for primary efficacy analysis and the all treated population for the safety analyses.[10, 93] Response outcomes were assessed on the response-evaluable population, defined as all randomised patients with at least one on-treatment tumour assessment. Standard censoring methods were used to take account of missing data in primary OS analysis and secondary PFS analysis.

CheckMate 069

The primary datasets used in CheckMate 069 were the all randomised BRAF mutation-negative population for primary efficacy analysis and the all treated population for the safety analyses.[85, 96] Efficacy analyses were also conducted in the all randomised population (ITT population) and in the cohort of patients with BRAF mutation-positive tumours though these were intended to be descriptive only and BRAF mutation-positive patients were not part of the sample size consideration.

In order to preserve an experimental-wise type I error rate of 5%, a hierarchical testing approach was applied to key secondary efficacy endpoints following analysis of the primary endpoint. The hierarchical ordering of key secondary endpoints was as follows: ORR in all randomised patients; PFS in BRAF mutation-negative patients; PFS in all randomised patients.

Table 12: Summary of statistical analyses in the RCTs

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CheckMate 067	Treatment with nivolumab monotherapy or nivolumab combined with ipilimumab will improve overall survival compared to ipilimumab monotherapy in patients with unresectable or metastatic melanoma.	OS analysis was targeted to occur after all subjects had 28 months follow-up per sample size and power considerations. However, the required minimum follow-up for analysis of OS was 22 months and as this has not been reached, results of this endpoint are not available at this time. PFS analysis was conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status and M stage at screening to compare each of the two experimental treatments to the control group. HRs and corresponding two-sided (1-adjusted α) % CIs were estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates were estimated using KM methodology. ORR analyses were conducted using a two-sided CMH test stratified by PD-L1 status, BRAF status and M stage at screening to compare each of the two experimental treatments to the control group. An associated OR and 95% CI were calculated. Additionally, ORRs and corresponding 95% exact CIs were calculated using the Clopper–Pearson method for each of the three treatment arms.	A sample of approximately 915 patients, randomly assigned in a 1:1:1 ratio to the three treatment groups was planned. For the comparison of PFS, it was estimated that the number of events projected to be observed at a follow-up of at least 9 months would give the study approximately 83% power to detect an average HR of 0.71 at a type I error rate of 0.005 (two-sided) for all comparisons. For each OS comparison, at least 460 events in the two respective treatment arms are required to provide at least 90% power to detect a HR of 0.72 with a type I error of 0.025 (two sided). The HR of 0.72 corresponds to a 39% increase in the median OS assuming a median OS of 14 months for ipilimumab and 19.4 months for each of the experimental treatment arms. The study was not designed for a formal statistical comparison between the nivolumab group and the nivolumab plus ipilimumab group.	For patients without documentation of progression or death, PFS was censored on the date of their last evaluable tumour assessment. For patients who did not have any on study tumour assessments and did not die, PFS was censored on their date of randomisation.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CheckMate 069	Treatment with nivolumab combined with ipilimumab will lead to clinical benefit, as demonstrated by an improved clinically meaningful ORR compared to ipilimumab monotherapy, including durable responses with substantial magnitude of tumour reduction.	ORRs and corresponding 95% exact CIs were calculated using the Clopper–Pearson method for each treatment arm. The unweighted difference in ORRs between the two treatment groups and corresponding exact 95% CI were estimated using the method of Newcombe. The weighted difference in ORRs between the two treatment groups along with corresponding two-sided 95% CI were estimated using the CMH method of weighting adjusting for stratification factors. Time to event distributions were estimated using KM techniques. When appropriate, the median along with 95% CI was estimated based on Brookmeyer and Crowley methodology. Rates at fixed timepoints were derived from the KM estimate along with their corresponding log-log transformed 95% CI. Minimum follow-up must be longer than the timepoint to generate rates at fixed timepoints. P-values other than those provided for the ORR primary analysis and the hierarchical analysis of key efficacy endpoints were for descriptive purposes only and not adjusted for multiplicity.	A sample of approximately 100 BRAF mutation-negative patients, randomly assigned in a 2:1 ratio to the two treatment groups was planned. Assuming 66% of subjects were observed to be BRAF mutation-negative, a total of approximately 150 subjects were to be randomised (100 BRAF mutation-negative and 50 BRAF mutation-positive patients). Given a two-sided alpha of 0.05, this number of BRAF mutation-negative patients provided approximately 87% power to show a statistically significant difference in the ORR between the combination group and the monotherapy group, assuming ORRs of 40% and 10%, respectively. For the comparison of PFS, it was estimated that the number of events projected to be observed at a follow-up of at least 9 months would give the study approximately 83% power to detect an average HR of 0.71 at a type I error rate of 0.005 (two-sided) for all comparisons.	For patients without documentation of progression or death, PFS was censored on the date of their last evaluable tumour assessment. For patients who did not have any on study tumour assessments and did not die, PFS was censored on their date of randomisation. For patients without documentation of death, OS was censored on the date the patient was last known to be alive. No adjustments have been made for use of subsequent nivolumab therapy on the ipilimumab arm of the study.

Key: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; HR, hazard ratio; KM, Kaplan–Meier; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Source: CheckMate 067 CSR[93]; CheckMate 069 CSR[96]; Larkin et al. 2015[10]; Postow et al. 2015.[85]

4.5 Participant flow in the relevant randomised controlled trials

Participant flow

CheckMate 067

Participant flow for CheckMate 067 is presented as a Consolidated Standards of Reporting Trials (CONSORT) diagram in Figure 7.

Of the 1,296 patients who enrolled in CheckMate 067, 314 patients were randomised to the Regimen and 315 patients were randomised to ipilimumab.[10, 93] A further 316 patients were randomised to nivolumab monotherapy, but as these are not relevant to this submission, they are not discussed further. One patient randomised to the Regimen and four patients randomised to ipilimumab withdrew from the study before starting treatment.

At the time of the current database lock (17th February 2015), 93 of 313 (29.7%) patients who began treatment with the Regimen were continuing to receive study drug; the most frequent reasons for discontinuation were study drug toxicity (38.3%) and disease progression (22.0%). In the ipilimumab group, 50 of 311 (16.1%) patients who began therapy were continuing in the treatment period of the study. The most frequent reason for discontinuation in this group was disease progression (65.0%).

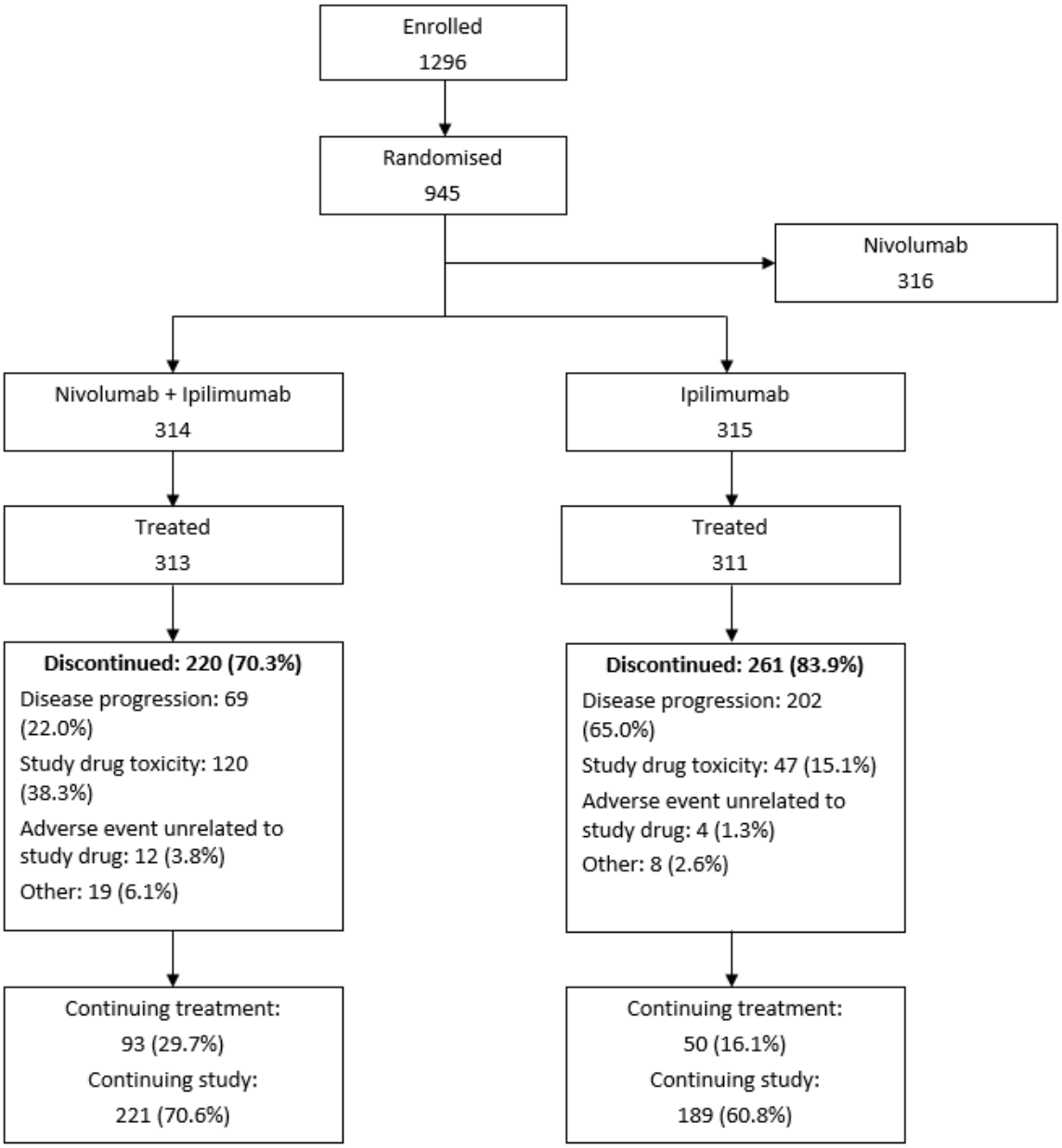
CheckMate 069

Participant flow for all patients and patients with BRAF mutation-negative tumours in CheckMate 069 is presented as a CONSORT diagram in Figure 8.

Of the 179 patients screened in CheckMate 069, 95 patients were randomised to the Regimen and 47 patients were randomised to ipilimumab.[85] One patient in each treatment arm withdrew from the study before starting treatment. Of the treated patients, 108 had BRAF mutation-negative tumours (71 in the Regimen group and 37 in the ipilimumab group).

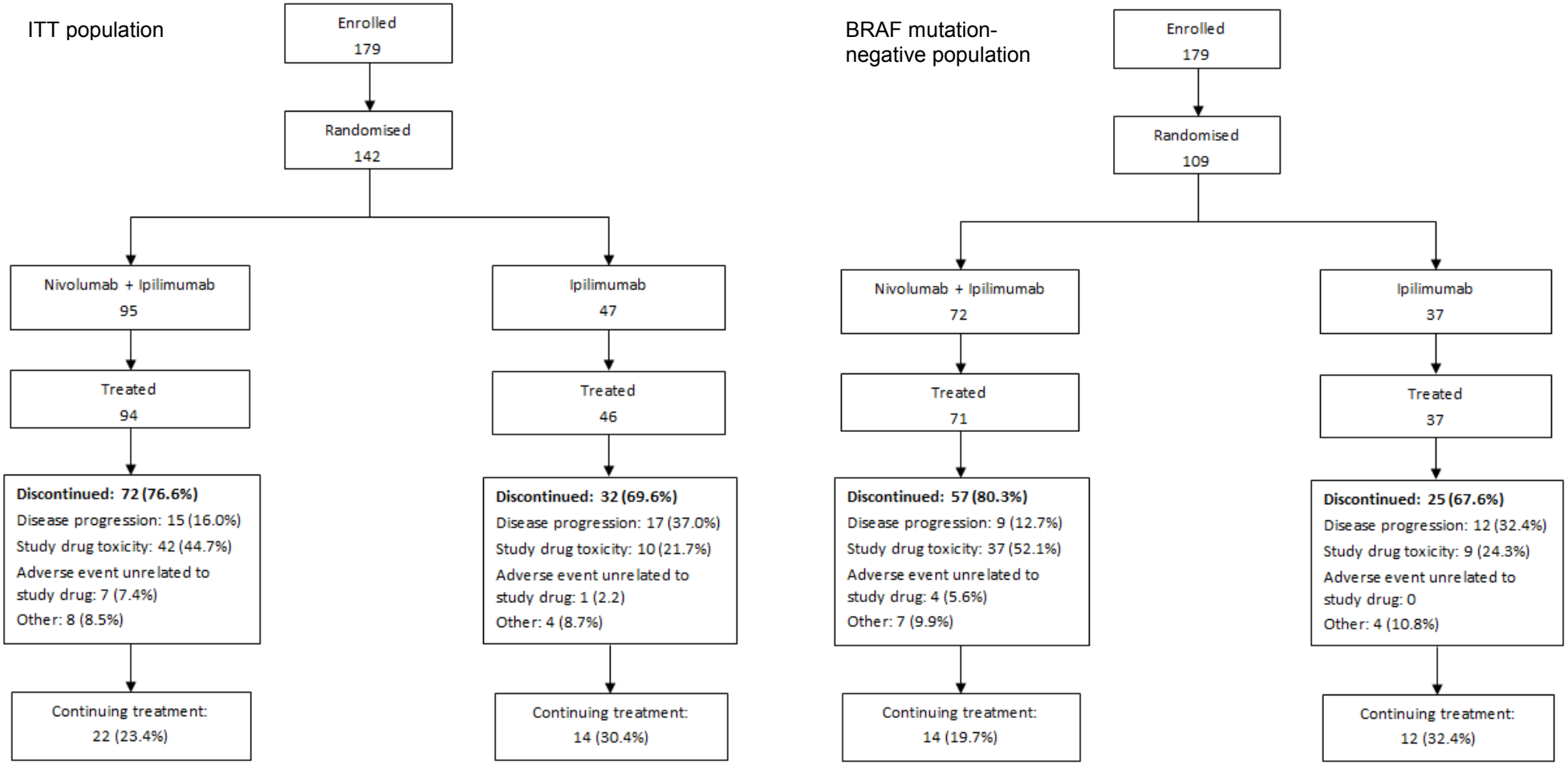
At the time of the primary database lock (30th January 2015), 22 of 94 (23.4%) patients who began treatment with the Regimen were continuing to receive study drug; the most frequent reason for discontinuation was study drug toxicity (44.7%). In the ipilimumab group, 14 of 46 (30.4%) patients who began therapy were continuing in the treatment period of the study. The most frequent reason for discontinuation in this group was disease progression (37.0%). Similar participant flow is observed in the cohort of patients with BRAF mutation-negative tumours.

Figure 7: CONSORT diagram of participant flow at the time of the current database lock in CheckMate 067



Key: CONSORT, Consolidated Standards of Reporting Trials.
Notes: Continuing treatment means patients are continuing to receive study drug; continuing study means patients have discontinued study drug but are still being followed for survival analysis.
Source: CheckMate 067 CSR.[93]

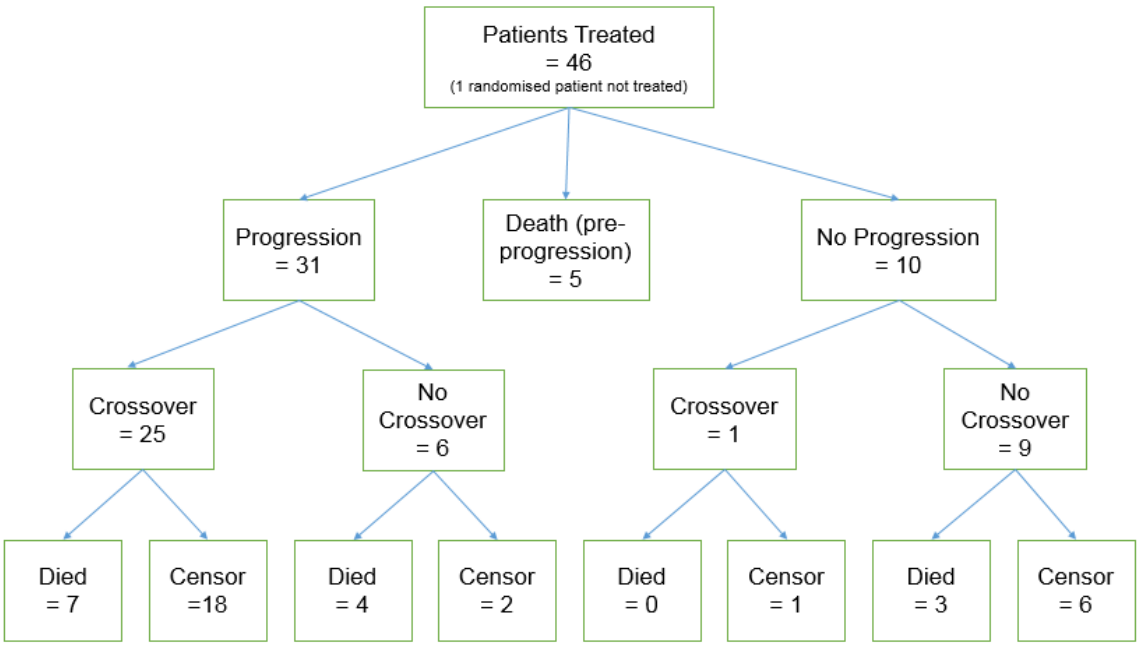
Figure 8: CONSORT diagram of participant flow at the time of the current database lock in CheckMate 069



Key: CONSORT, Consolidated Standards of Reporting Trials.
Source: Postow et al. 2015.[85]

A substantial proportion of patients within the CheckMate 069 trial received nivolumab subsequent to ipilimumab monotherapy as specified within the trial protocol as shown in Figure 9. Only 6 patients eligible for use of nivolumab post progression did not receive treatment within the trial.

Figure 9: Flow diagram for use of nivolumab subsequent to ipilimumab (crossover)



Source: Patient level data from the CheckMate 069 trial

Patient characteristics

Baseline demographic and disease characteristics of patients enrolled in CheckMate 067 and CheckMate 069 are presented in Table 13.

CheckMate 067

Characteristics of patients across treatment groups were well balanced.[10, 93] As specified in the study protocol, all patients enrolled in CheckMate 067 had advanced melanoma and had not received prior systemic therapy. Just over half of all patients enrolled to treatment arms of interest were European (n=347) and this included 66 patients from 7 UK centres that participated in this trial.

Approximately 70% of patients randomised to the Regimen or ipilimumab monotherapy had BRAF mutation-negative melanoma and approximately 75% of patients had negative PD-L1 status (using a 5% cut-off) at baseline. A high percentage of patients had poor prognostic factors at baseline, including M1c disease (58%) and elevated LDH (32%) (Table 13).

CheckMate 069

Baseline demographics and disease characteristics of patients enrolled in CheckMate 069 were similarly well balanced, both in the all randomised (ITT) population and the BRAF mutation-negative population.[85, 96] As specified in the study protocol, all patients had previously untreated advanced melanoma and a higher proportion of patients randomised had BRAF mutation-negative melanoma (76.8%). Two patients assigned to the Regimen presented with an ECOG performance status of 2 at randomisation and were thus identified as a protocol deviation.

Approximately 90% of all patients randomised had Stage IV disease and approximately 75% of patients had negative PD-L1 status (using a 5% cut-off) at baseline. As observed in CheckMate 067, a high percentage of patients had poor prognostic factors at baseline (Table 13).

Of note, in both trials, a lower proportion of patients had BRAF mutation-positive melanoma than is observed in the general population (~50%). This is likely to reflect current clinical practice where BRAF mutation positive patients with significant disease burden and highly symptomatic disease may be deemed less suitable for immunotherapy and instead offered targeted therapies as first-line treatment. This is reflected in the very similar demographics across BRAF mutation-positive and BRAF mutation-negative cohorts (see Appendix 5).

Table 13: Characteristics of participants in the studies across treatment groups

CheckMate 067		
	Nivolumab plus ipilimumab (ITT population, n=314)	**Ipilimumab (ITT population, n=315)**
Age, median years (range) **Age, mean years (SD)**	61 (18-88) 59.3 (13.9)	62 (18-89) 60.8 (13.2)
Gender, male n (%)	206 (65.6)	202 (64.1)
Race, Caucasian n (%)	310 (98.7)	303 (96.2)
Region, n (%)	US: 64 (20.4) EU: 177 (56.4) UK: 30 (9.6) Australia: 40 (12.7) Rest of World: 33 (10.5)	US: 75 (23.8) EU: 170 (54.0) UK: 36 (11.4) Australia: 37 (11.7) Rest of World: 33 (10.5)
ECOG PS, n (%)	0: 230 (73.2) 1: 83 (26.4) 2: 0 Not available: 1 (0.3)	0: 224 (71.1) 1: 91 (28.9) 2: 0
Metastasis stage, n (%)	M0-M1B: 133 (42.4) M1C: 181 (57.6)	M0-M1B: 132 (41.9) M1C: 183 (58.1)
Common metastasis site, n (%)	Lymph node: 174 (55.4) Lung: 184 (58.6) Liver: 93 (29.6)	Lymph node: 196 (62.2) Lung: 184 (58.4) Liver: 92 (29.2)
Elevated LDH, n (%)	88 (28.0)	115 (36.5)
History of brain metastases, yes n (%)	11 (3.5)	15 (4.8)
Disease duration, median years (range)	1.87 (0.1-32.5)	1.95 (0.1, 24.7)
PD-L1-positive[a], n (%)	68 (21.7)	75 (23.8)
BRAF mutation-negative (wild-type), n (%)	213 (67.8)	218 (69.2)

CheckMate 069				
	Nivolumab plus ipilimumab		**Ipilimumab**	
	ITT population (n=95)	BRAF mutation-negative population (n=72)	ITT population (n=47)	BRAF mutation-negative population (n=37)
Age, median years (range) **Age, mean years (SD)**	64 (27-87) 63.3 (11.0)	66 (27-87) 65.4 (10.3)	67 (31-80) 64.5 (10.2)	69 (46-80) 66.5 (8.9)
Gender, male n (%)	63 (66.3)	48 (66.7)	32 (68.1)	23 (62.2)
Race, Caucasian n (%)	92 (96.8)	69 (95.8)	47 (100)	37 (100)
Region, n (%)	France: 12 (12.6) USA: 83 (87.4)	France: 6 (8.3) USA: 66 (91.7)	France: 4 (8.5) USA: 43 (91.5)	France: 4 (10.8) USA: 33 (89.2)
ECOG PS, n (%)	0: 79 (83.2) 1: 14 (14.7) ≥2: 2 (2.1)	0: 62 (86.1) 1: 9 (12.5) ≥2: 1 (1.4)	0: 37 (78.7) 1: 10 (21.3) ≥2: 0	0: 30 (81.1) 1: 7 (18.9) ≥2: 0
Metastasis stage, n (%)	M0: 8 (8.4) M1A: 15 (15.8) M1B: 27 (28.4) M1C: 44 (46.3)	M0: 6 (8.3) M1A: 9 (12.5) M1B: 22 (30.6) M1C: 34 (47.2)	M0: 5 (10.6) M1A: 8 (17.0) M1B: 12 (25.5) M1C: 21 (44.7)	M0: 5 (13.5) M1A: 7 (18.9) M1B: 8 (21.6) M1C: 16 (43.2)
Common metastasis site, n (%)	Lymph node: 43 (45.3) Lung: 57 (60.0) Liver: 24 (25.3)	Lymph node: 30 (41.7) Lung: 44 (61.1) Liver: 17 (23.6)	Lymph node: 25 (53.2) Lung: 27 (57.4) Liver: 18 (38.3)	Lymph node: 17 (45.9) Lung: 20 (54.1) Liver: 14 (37.8)
Elevated LDH, n (%)	24 (25.3)	15 (20.8)	11 (23.4)	7 (18.9)
History of brain metastases, yes n (%)	4 (4.2)	4 (5.6)	0	0
Disease duration, median years (range)	2.34 (0.1-47.4)	1.71 (0.1-23.5)	1.71 (0.1-20.4)	1.40 (0.1-20.4)
PD-L1-positive[b], n (%)	24 (25.3)	Not reported	11 (23.4)	Not reported
BRAF mutation-negative (wild-type), n (%)	72 (75.8)	72 (100)	37 (78.7)	37 (100)

Key: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1; PS, performance status; SD, standard deviation.
Notes: [a], PD-L1 not quantifiable in 36 patients randomised to nivolumab plus ipilimumab and 38 patients randomised to ipilimumab. Validated assay values reported (verified assay values reported in the CSR); [b], PD-L1 not quantifiable in 15 patients randomised to nivolumab plus ipilimumab and 9 patients randomised to ipilimumab.
Source: CheckMate 067 CSR[93]; CheckMate 069 CSR[96]; Larkin et al. 2015[10]; Postow et al. 2015.[85]

4.6 Quality assessment of the relevant randomised controlled trials

CheckMate 067 and CheckMate 069 were conducted in line with Good Clinical Practice (GCP) by qualified investigators using a single protocol to promote consistency across sites and measures taken to reduce the risk of bias.[10, 85, 93, 96]

Baseline demographics and disease characteristics of patients randomised were well balanced, with no key differences between treatment groups of either trial.

Study withdrawal rates (for any reason) were lower in the Regimen arm in both trials, as the main reason for treatment discontinuation was study drug toxicity and the majority of these patients continued to be assessed for efficacy outcomes. These minor imbalances were anticipated *a priori*.

In CheckMate 067, a slightly higher proportion of patients randomised to ipilimumab monotherapy have discontinued study treatment to date, though the majority discontinued due to disease progression, which is accounted for within efficacy assessments. In CheckMate 069, treatment discontinuation rates were higher in the Regimen group.

Outcome assessments were all conducted in accordance with trial validated methodology. However, in recognition of the limitations of validated RECIST criteria for assessing immuno-oncology drugs (see Section 4.3), patients were allowed to receive treatment beyond RECIST-defined progression to better reflect clinical practice. Indeed, both trials are thought to reflect routine clinical practice in England in respect of population, comparator choice, treatment administration and outcomes being assessed. It is also important to note that alongside clinical efficacy outcomes, patient reported outcomes and resource use utilisation (CheckMate 067 only) were also measured as requested by reimbursement agencies.

Quality assessment in accordance with the NICE-recommended checklist for RCT assessment of bias is summarised in Table 14 and presented in full in Appendix 6.

Table 14: Quality assessment results for parallel group RCTs

	CheckMate 067	**CheckMate 069**
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No

	CheckMate 067	CheckMate 069
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
How closely do the RCT(s) reflect routine clinical practice	Population, treatment arms, administration and outcomes all relevant to clinical practice in NHS England.	Population, treatment arms, administration and outcomes all relevant to clinical practice in NHS England.
Key: ITT, intention-to-treat; NHS, National Health Service; RCT, randomised controlled trial. **Source**: CheckMate 067 CSR[93]; CheckMate 069 CSR[96]; Larkin et al. 2015[10]; Postow et al. 2015.[85]		

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Summary

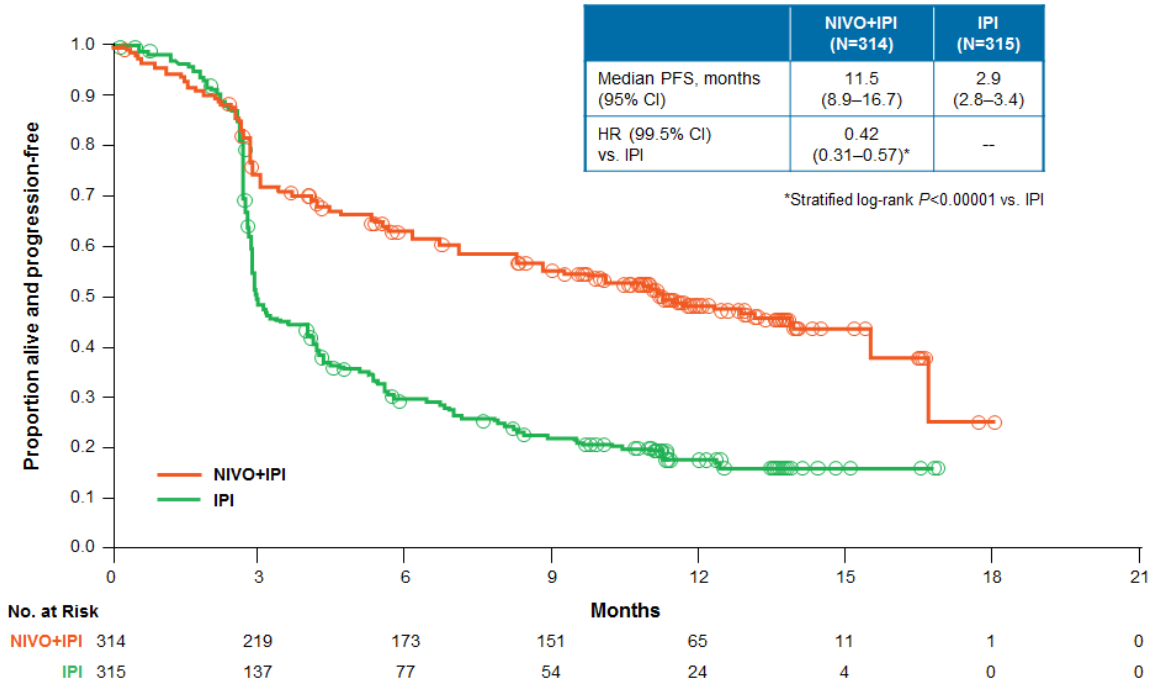
- The Regimen demonstrates consistent survival benefit in advanced melanoma:
  - CheckMate 067: significant extension in PFS compared with ipilimumab monotherapy, HR for death or disease progression: 0.42 (99.5% CI, 0.31 to 0.57); p<0.001 (ITT population)
  - CheckMate 069: significant extension in PFS compared with ipilimumab monotherapy, HR for death or disease progression: BRAF mutation-negative patients, 0.40 (95% CI 0.23 to 0.68); p<0.001 (primary efficacy analysis set); 0.39 (95% CI, 0.25 to 0.63); p<0.0001 (ITT population)
  - CheckMate 069: exploratory OS analysis demonstrates an 18-month survival rate of [redacted] in patients with advanced melanoma, irrespective of BRAF status (ITT population); approximately double the 18-month OS rate associated with ipilimumab monotherapy in pooled analyses of key trials
- The Regimen resulted in rapid and durable clinical response benefit in advanced melanoma:
  - CheckMate 067: unweighted ORR difference of 38.4% compared with ipilimumab monotherapy, OR for response: 6.11 (95% CI 3.59 to 10.38); p<0.001 (ITT population)
  - CheckMate 067: median change in tumour burden of -51.9% compared with +5.9% in the ipilimumab monotherapy group; 76.2% of patients continue to demonstrate response despite many discontinuing study treatment (ITT population)
  - CheckMate 069: 40-50% improvement in ORR irrespective of BRAF status compared with ipilimumab monotherapy, OR for response: BRAF mutation-negative patients, 12.96 (95% CI 3.91 to 54.49); p<0.001; ITT population 12.19 (95% CI 4.41 to 33.68); p<0.0001
  - CheckMate 069: median change in tumour burden of -63.5% compared with +7.8% in the ipilimumab monotherapy group; 82% of patients continue to demonstrate response despite a discontinuation rate of 52% (ITT population)
- The Regimen was not associated with an overall negative impact on patients health-related quality of life:
  - CheckMate 067: no clinically meaningful changes in EORTC QLQ-C30 or EQ-5D observed in either treatment group; in patients who experienced a Grade 3-4 AE, deterioration in EORTC QLQ-C30 global health status was not markedly different between treatment groups
  - CheckMate 069: no clinically meaningful changes in EORTC QLQ-C30 or EQ-5D observed in either treatment group; no significant differences in improvement or deterioration in HRQL from baseline compared with ipilimumab monotherapy
    - HRQL generally shown to deteriorate during the first 12 weeks of combination therapy before returning to baseline levels or similar from Week 13 (when patients are no longer receiving ipilimumab alongside nivolumab therapy)

Survival analysis

CheckMate 067

In ITT analysis, with a median follow-up ranging from 12.2 to 12.5 months across treatment groups, the median PFS was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) in the Regimen group compared with 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group.[10, 93] The corresponding hazard ratio (HR) for death or disease progression confirms a significantly superior PFS benefit with the Regimen: 0.42 (99.5% CI, 0.31 to 0.57); p<0.001. The Kaplan-Meier (KM) curve for PFS is presented in Figure 10.

Figure 10: KM curve for PFS in CheckMate 067, ITT analysis set



Key: CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; ITT, intention-to-treat; KM, Kaplan-Meier; NIVO+IPI, nivolumab plus ipilimumab; PFS, progression-free survival.
Source: Larkin et al. 2015[90]

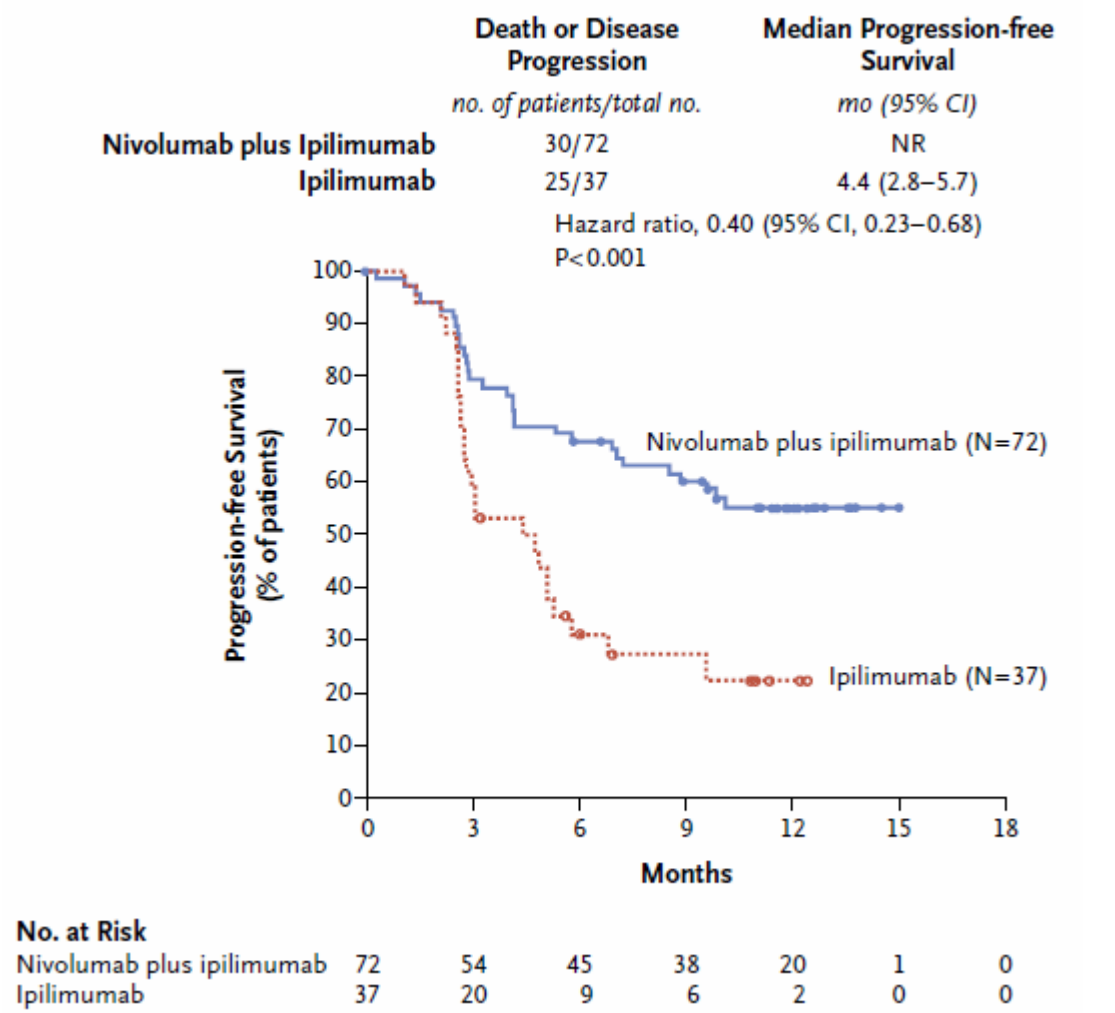
CheckMate 069

In the primary efficacy analysis set (database lock 30th January 2015), the median PFS in patients with BRAF mutation-negative melanoma was not reached in patients treated with the Regimen, but was 4.4 months (95% CI, 2.8 to 5.7) in the ipilimumab group.[85] Not reaching the median PFS can be considered a positive indicator of the potential clinical benefit of the Regimen, relative to ipilimumab monotherapy. The corresponding HR for death or disease progression confirms a significantly superior PFS benefit with the Regimen: 0.40 (95% CI, 0.23 to 0.68); p<0.001.

Among patients with BRAF mutation-positive melanoma, the median PFS was 8.5 months (95% CI, 2.8 to not estimable) in the Regimen group compared with 2.7 months (95% CI, 1.0 to 5.4) in the ipilimumab group (HR: 0.38 [95% CI, 0.15 to 1.00]). In all randomised patients, the median PFS was again not reached in the Regimen group but was 3.0 months (95% CI, 2.8 to 5.1) in the ipilimumab group (HR: 0.39 [95% CI, 0.25 to 0.63];p<0.0001).[95]

The KM curve for PFS in the primary efficacy analysis set is presented in Figure 11. PFS KM curves for patients with BRAF mutation-positive patients and the ITT population are presented in Appendix 7.

Figure 11: KM curve for PFS in CheckMate 069, primary efficacy analysis set



Key: CI, confidence interval; KM, Kaplan-Meier; NR, not reached; PFS, progression-free survival.
Notes: Symbols represent censored observations.
Source: Postow et al. 2015.[85]

In exploratory OS analyses conducted on a recent database lock (August 2015), median OS is yet to be reached in either group. The 75% OS (i.e. when a quarter of the patients have died) has been reached in both arms and shows an additional 4 months survival associated with the Regimen compared with ipilimumab monotherapy (341 days for the Regimen vs 220 days for ipilimumab). This survival benefit is particularly striking considering the substantial crossover rate (56.5% at the time of analysis) of patients from the ipilimumab group to nivolumab monotherapy (as per protocol). Indeed, comparative analyses of OS across treatment groups of CheckMate 069 are not a valid representation of the Regimen versus ipilimumab monotherapy; rather, they would reflect the Regimen versus ipilimumab monotherapy followed by nivolumab therapy (though it should be noted this trial was not designed to evaluate sequencing). The impact of crossover can be clearly observed when assessing survival rates in patients who received nivolumab therapy post progression on ipilimumab monotherapy and those who did not: of patients who did not crossover, 66.7% (4/6) had died at the time of analysis, compared with 28% (7/25) of patients who did crossover to nivolumab therapy on progression post ipilimumab.

Due to the low number of patients eligible for crossover who did not receive subsequent nivolumab (n=6) it was not possible to produce more reliable estimates of comparative OS based upon this trial using statistical methods to adjust for crossover.

Survival rates at 6, 12 and 18 months in all patients treated with the Regimen (ITT population) were 82%, 73% and [redacted], respectively.[96] These are markedly higher than historical survival rates associated with ipilimumab monotherapy with an 18-month OS rate of approximately 35% reported from pooled analyses of key trials.

Response analysis

CheckMate 067

In ITT analysis, investigator-assessed ORR was 57.6% (95% CI, 52.0 to 63.2) in the Regimen group compared with 19.0% (95% CI, 14.9 to 23.8) in the ipilimumab group.[10, 93] The percentage of patients with a complete response (CR) was also higher in the Regimen group (11.5% compared to 2.2% in the ipilimumab group).

Time to objective response was similar in both treatment groups and, to date, median duration of response has not been reached in either treatment group. At the time of analysis (median follow-up of approximately 12 months), 76.2% of patients continued to demonstrate response to the Regimen and 66.7% of patients continued to demonstrate response to ipilimumab.

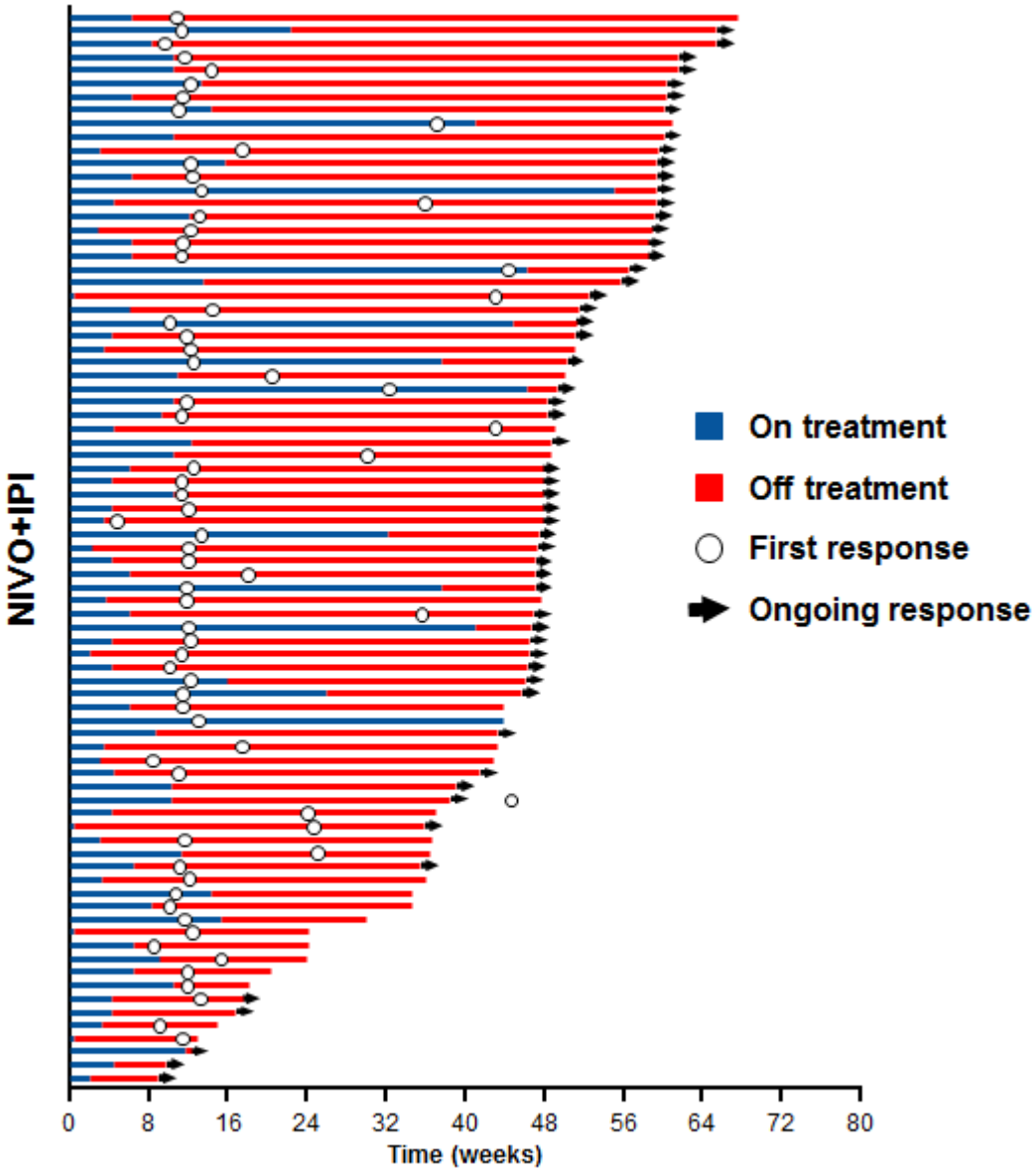
The response analysis from CheckMate 067 is summarised in Table 15.

Table 15: Summary of response in CheckMate 067

	Nivolumab plus ipilimumab (n=314)	**Ipilimumab (n=315)**
Objective response rate[a]		
Responders, n (%) (95% CI)	181 (57.6) (52.0-63.2)	60 (19.0) (14.9-23.8)
Best overall response CR, n (%) PR, n (%)	 36 (11.5) 145 (46.2)	 7 (2.2) 53 (16.8)
Unweighted ORR difference, %	38.4	
Estimated odds ratio (95% CI)	6.11 (3.59, 10.38)	
p-value	<0.001	
Duration of response		
Median months (range)	Not reached	Not reached
Time to treatment response		
Median months (range)	2.8 (1.1, 11.6)	2.8 (2.5, 12.4)
Key: CI, confidence interval; CR, complete response; PR, partial response. **Notes**: [a], confirmed response (CR + PR) as per RECIST v1.1 criteria. **Source**: Larkin et al. 2015.[10]		

Importantly, response to treatment was often continued despite discontinuation of study drug in patients treated with the Regimen, as presented in Figure 12.

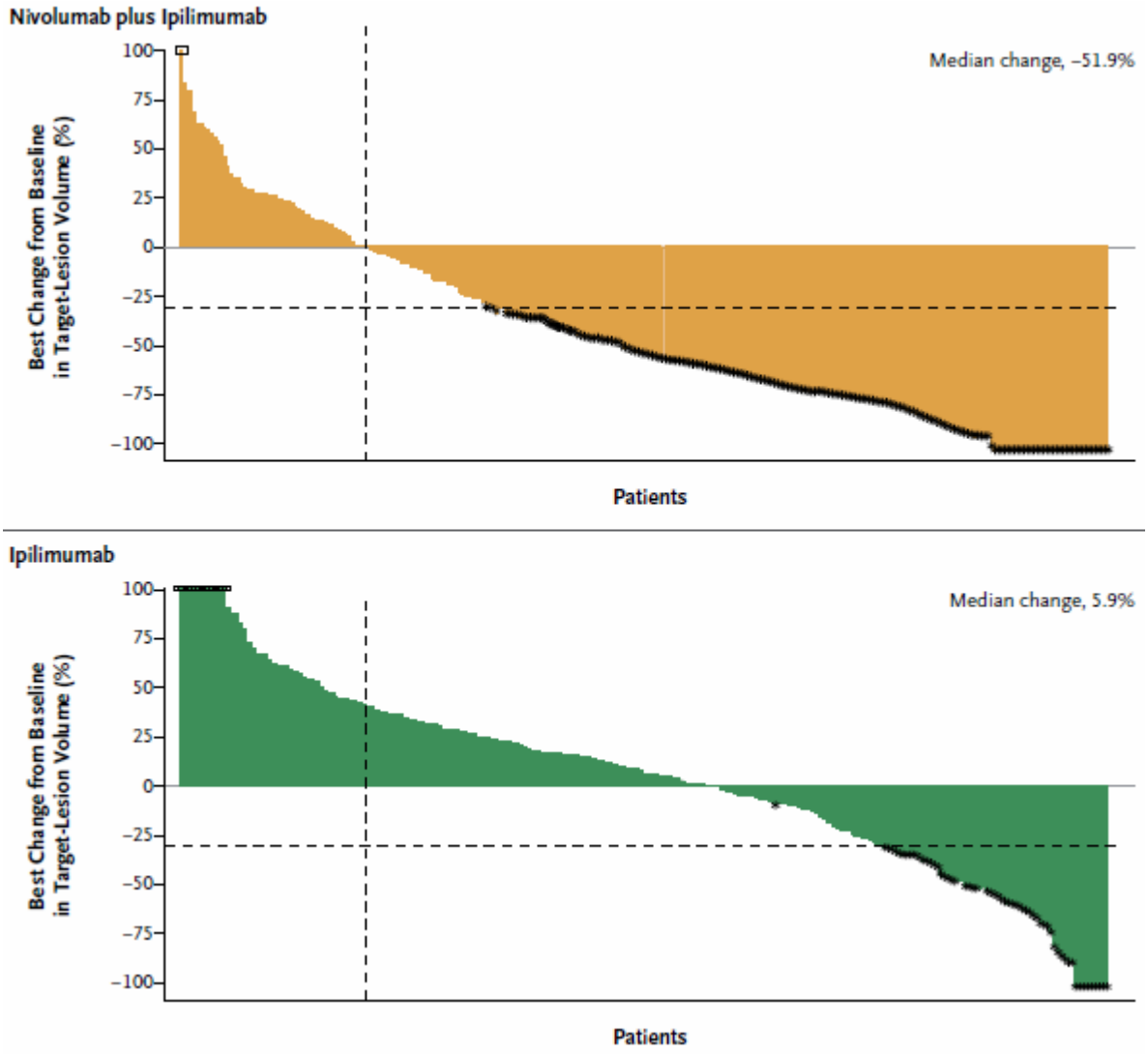
Figure 12: Swimmer plot of time to first response and duration of response in CheckMate 067, patients who discontinued due to study drug toxicity analysis set



Key: NIVO+IPI, nivolumab plus ipilimumab.
Source: Larkin et al. 2015.[90]

The waterfall plot of response presented in Figure 13 shows the percentage change in tumour burden (assessed as the median change from baseline in the sum of the longest diameters of the target tumour lesions) from baseline for each patient. This plot clearly demonstrates the clinical benefit of the Regimen with more patients in this group experiencing a reduction in tumour size and achieving at least a partial response to therapy, compared with patients in the ipilimumab group. The median change in tumour burden was -51.9% (interquartile range, -75.8 to -10.2) in the Regimen group compared with +5.9% (interquartile range, -28.0 to +33.3) in the ipilimumab group.

Figure 13: Waterfall plot of best reduction from baseline in sum of diameters of target lesions in CheckMate 067, response-evaluable analysis set

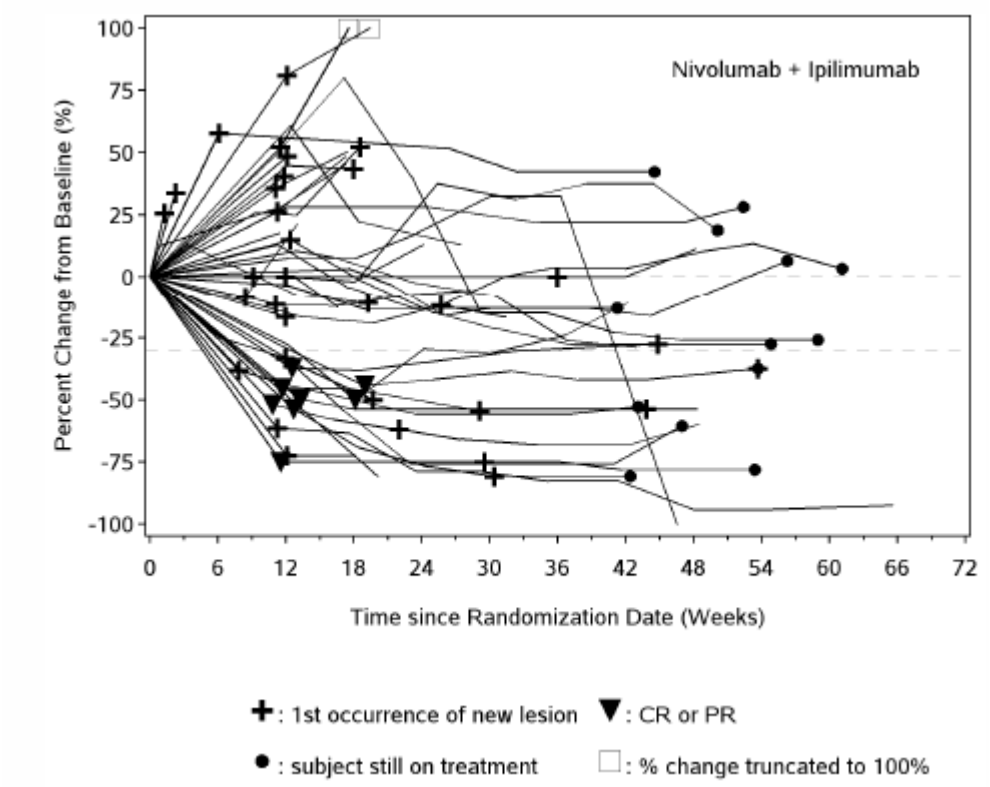


Notes: Asterisk represents responders as per RECIST criteria; rectangles represents % change truncated to 100%; horizontal dashed line represents a PR according to RECIST criteria (≥30% reduction in tumour size); vertical dashed line indicates the inflection point for the nivolumab plus ipilimumab group (representing the proportion of patients achieving a reduction in tumour size).
Source: Larkin et al. 2015.[10]

Of patients with a best overall response of progressive disease, 50 patients in the Regimen group and 99 patients in the ipilimumab group were treated beyond RECIST defined progression as per the study protocol (see Section 4.3). Of these patients, many developed or maintained a target lesion reduction of >30% compared to baseline after initial (RECIST defined) progression, consistent with an unconventional, immune-related response.

Response patterns for response evaluable patients treated with the Regimen beyond RECIST criteria defined progression (n=46) are presented in Figure 14.

Figure 14: Response patterns in patients treated with the Regimen beyond RECIST defined progression in CheckMate 067



Key: CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
Source: CheckMate 067 CSR.[93]

CheckMate 069

In primary efficacy analysis (database lock 30th January 2015), investigator-assessed ORR was 61% (95% CI, 49 to 72) in the Regimen group compared with 11% (95% CI, 3 to 25) in the ipilimumab group.[85] The percentage of patients with a CR was also higher in the Regimen group (22% compared to 0% in the ipilimumab group).

Among patients with BRAF mutation-positive melanoma, investigator-assessed ORR was 52% in the Regimen group compared with 10% in the ipilimumab group. In all randomised patients, investigator-assessed ORR was 59% in the Regimen group compared with 11% in the ipilimumab group ($p<0.0001$).[95] The proportion of patients with a CR in both these patient cohorts was the same as that in patients with BRAF mutation-negative melanoma at 22%.

Objective response analysis from CheckMate 069 is summarised in Table 16.

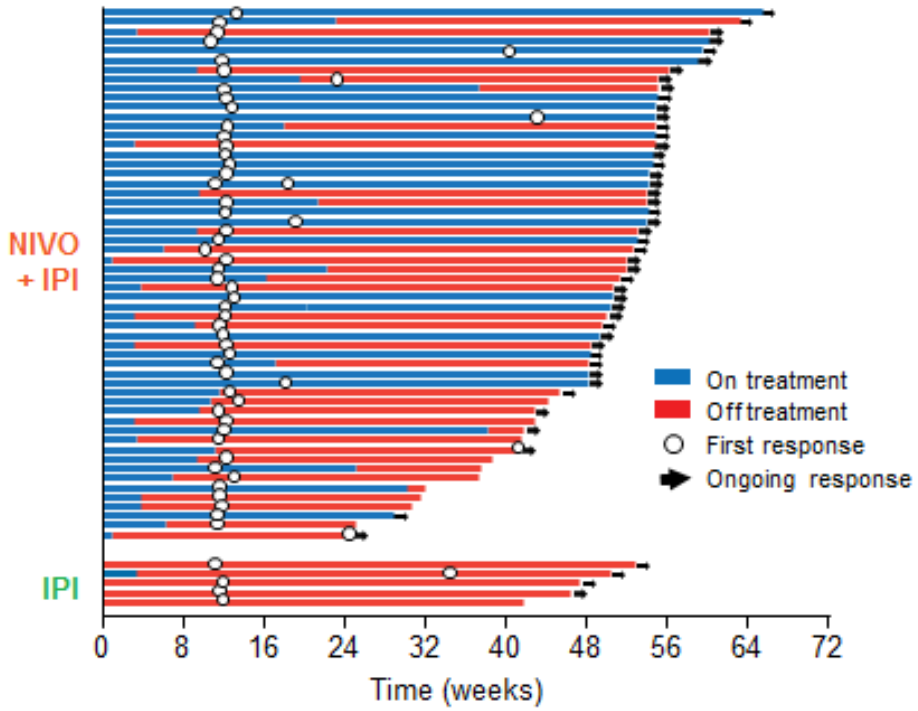
Time to objective response did not differ significantly between treatment groups with the majority of all responses observed at the time of first scan. To date, median duration of response has not been reached in either treatment group; at the time of analysis (minimum follow-up of 11 months), 82% and 75% of patients in the primary efficacy analysis set continued to demonstrate response to the Regimen and ipilimumab, respectively. Similar rates of ongoing response are observed in the ITT population (82% and 80% of responders in the Regimen and the ipilimumab groups, respectively). This durability of response is represented as a swimmer plot in Figure 15.

Table 16: Summary of objective response in CheckMate 069, primary analysis set

	BRAF mutation-negative patients		BRAF mutation-positive patients		All randomised patients	
	Nivolumab plus ipilimumab (n=72)	Ipilimumab (n=37)	Nivolumab plus ipilimumab (n=23)	Ipilimumab (n=10)	Nivolumab plus ipilimumab (n=95)	Ipilimumab (n=47)
Responders, n (%) (95% CI)	44 (61) (49-72)	4 (11) (3-25)	12 (52) (31-73)	1 (10) (0-45)	56 (59) (48-69)	5 (11) (4-23)
BOR CR, n (%) PR, n (%)	 16 (22) 28 (39)	 0 4 (11)	 5 (22) 7 (30)	 0 1 (10)	 21 (22) 35 (37)	 0 5 (11)
Estimated odds ratio (95% CI)	12.96 (3.91, 54.49)		-		12.19 (4.41, 33.68)	
p-value	<0.001		Not calculated		<0.0001	

Key: BOR, best overall response; CI, confidence interval; CR, complete response; PR, partial response.
Source: CheckMate 069 CSR[96]; Hodi et al. 2015[95]; Postow et al. 2015.[85]

Figure 15: Swimmer plot of time to first response and duration of response in CheckMate 069, all responders analysis set

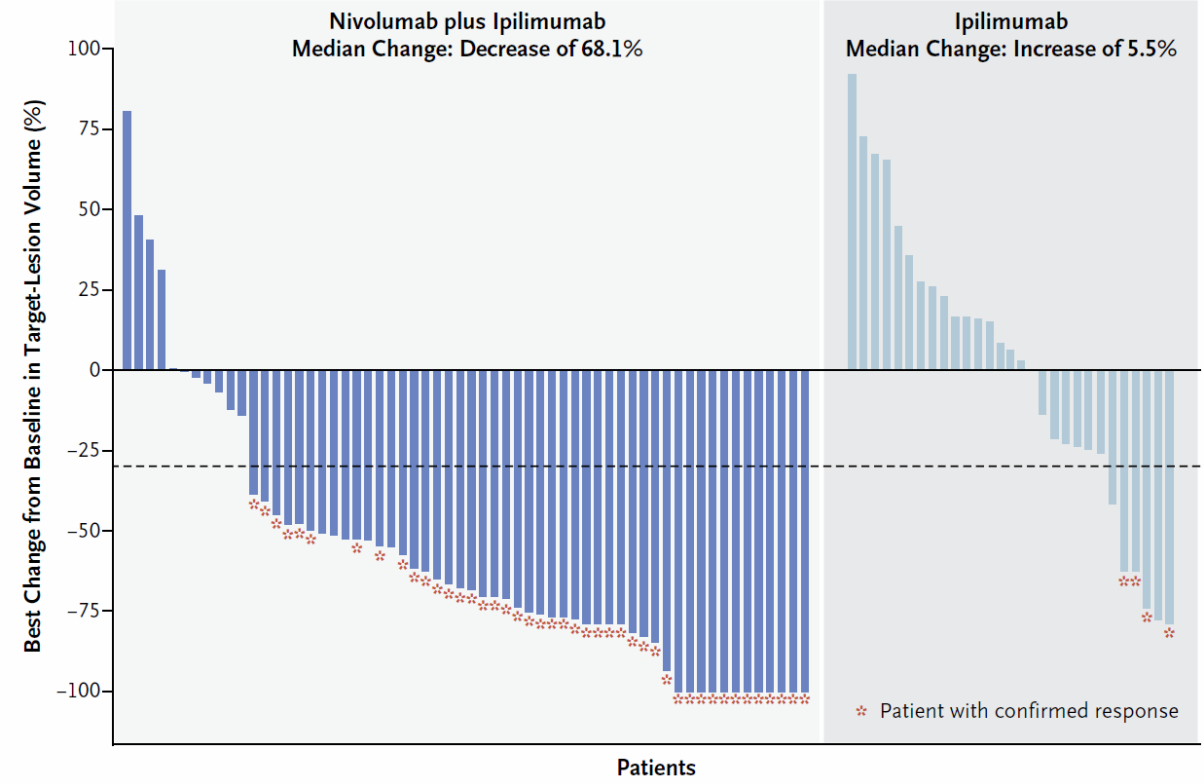


Key: IPI, ipilimumab; NIVO + IPI, nivolumab plus ipilimumab.
Source: Hodi et al. 2015.[95]

The waterfall plot presented in Figure 16 again clearly demonstrates the clinical benefit of the Regimen with more patients in this group experiencing a reduction in tumour size and

achieving at least a partial response to therapy, compared with patients in the ipilimumab group. In patients with BRAF mutation-negative melanoma, the median change in tumour burden was -68.1% in the Regimen group compared with +5.5% in the ipilimumab group. Similarly, in all randomised patients, the median change in tumour burden was -63.5% in the Regimen group compared with +7.8% in the ipilimumab group.[95]

Figure 16: Waterfall plot of best reduction from baseline in sum of diameters of target lesions in CheckMate 069, primary efficacy analysis set



Notes: Horizontal dashed line represents a PR according to RECIST criteria (≥30% reduction in tumour size).
Source: Postow et al. 2015.[85]

Among all patients (ITT population) who discontinued study treatment due to side effects, the ORR was 68% (95% CI, 52 to 81) in the Regimen group (30 of 44 patients), as compared with 10% (95% CI, 0 to 45) in the ipilimumab group (1 of 10 patients). Importantly, clinical response was maintained despite discontinuation of treatment, as demonstrated in Figure 15.

HRQL analysis

Tools used to assess HRQL for which data are presented in this section are summarised in Appendix 8.

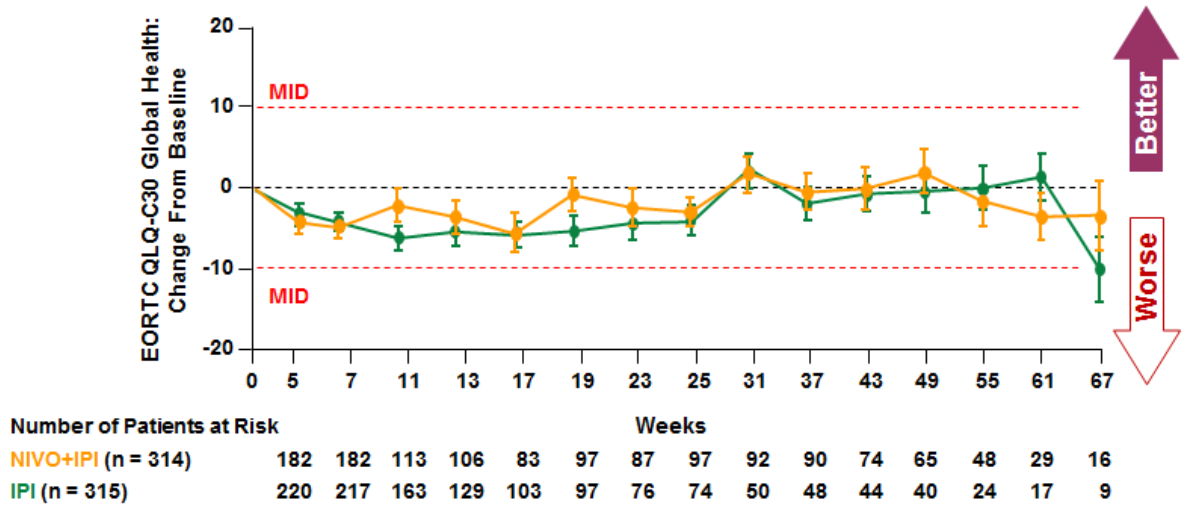
CheckMate 067

Preliminary HRQL analysis has recently become available for CheckMate 067 (November 2015) and a top-line summary of data presented at SMR 2015.[91] Of the 314 and 315 patients randomised to the Regimen and ipilimumab, 274 (87.3%) and 259 (82.2%), respectively had at least one baseline and post baseline HRQL assessment. By week 67, ≤16 patients completed HRQL assessments in each arm (with highest attrition in the ipilimumab arm) so results from this week should be interpreted with caution.

EORTC QLQ-C30 mean global health status scores at baseline were similar in both treatment groups (the Regimen, 70.7; ipilimumab, 73.5).[150] Patients treated with ipilimumab

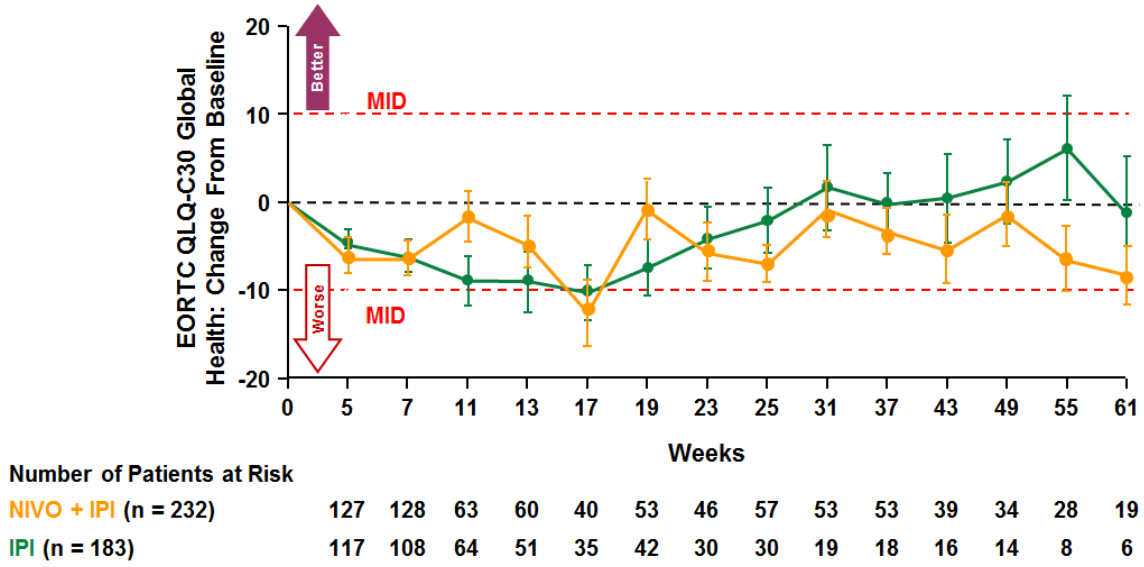
showed slightly greater reductions in global health status during the trial on average, as presented in Figure 17. However, clinically meaningful changes (defined as a minimally important difference of ≥10 points[151]) were not observed at any time points up to week 67. Importantly, in patients who experienced a Grade 3-4 AE, deterioration in EORTC QLQ-C30 global health status was not markedly different between treatment groups (Figure 18).

Figure 17: EORTC QLQ-C30 global health change from baseline in CheckMate 067, HRQL analysis set



Key: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HRQL, health-related quality of life; IPI, ipilimumab; NIVO+IPI, nivolumab plus ipilimumab; MID, minimally important difference.
Source: Schadendorf et al. 2015[91]

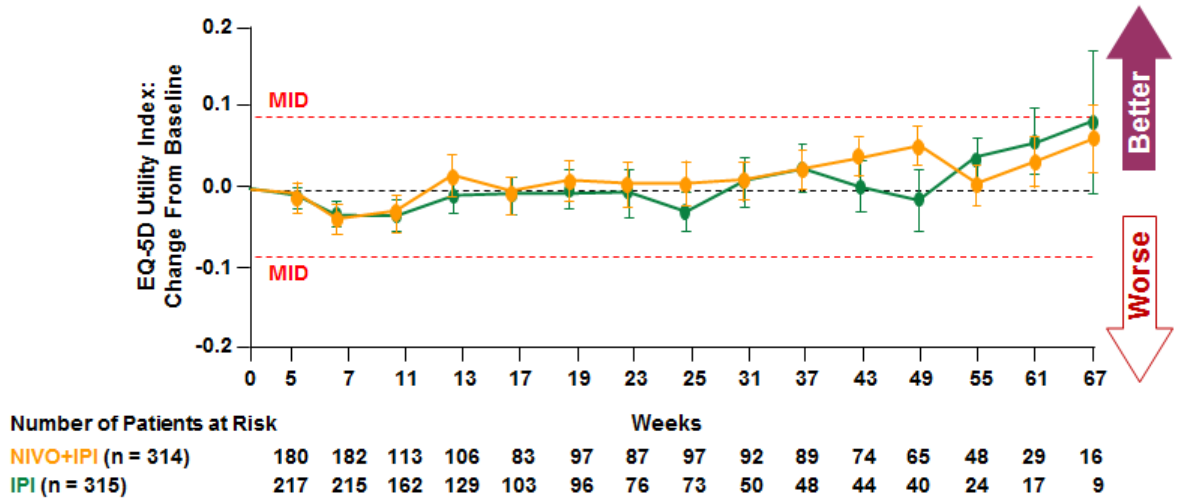
Figure 18: EORTC QLQ-C30 global health change from baseline for patients experiencing Grade 3-4 AE in CheckMate 067, HRQL analysis set



Key: AE, adverse events; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HRQL, health-related quality of life; IPI, ipilimumab; NIVO+IPI, nivolumab plus ipilimumab; MID, minimally important difference.
Source: Schadendorf et al. 2015[91]

Mean EuroQol-five dimension (EQ-5D) utility scores at baseline were again similar in both treatment groups (the Regimen, 0.779; ipilimumab, 0.791).[150] Improvements from baseline in EQ-5D utilities (as demonstrated by higher scores) were generally greater in the Regimen group and were consistently observed from Week 13 (after the switch to nivolumab monotherapy), as presented in Figure 19 but clinically meaningful changes (defined as a minimally important difference of ≥0.08 points[152]) were not observed in either treatment group.

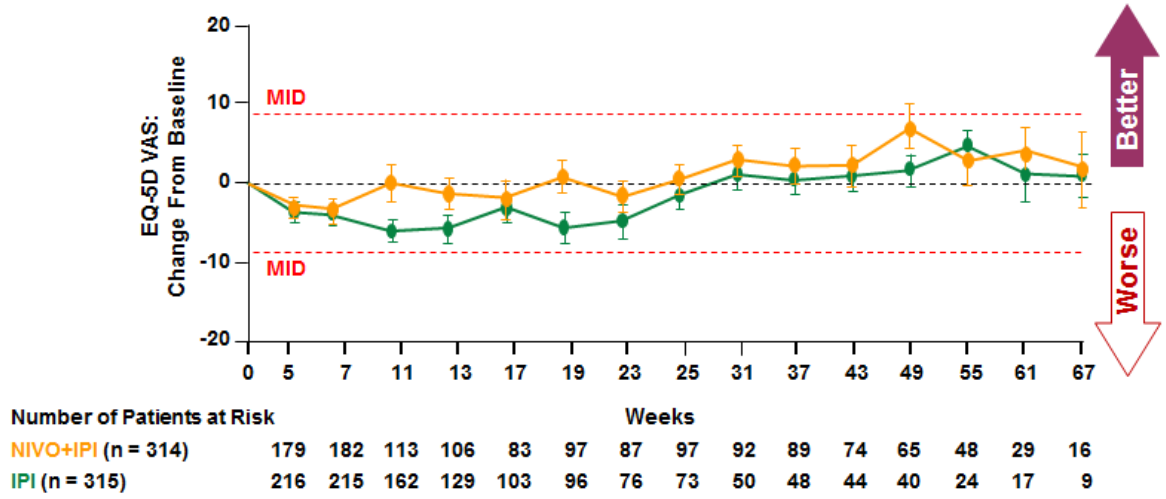
Figure 19: EQ-5D utility change from baseline in CheckMate 067, HRQL analysis set



Key: EQ-5D, EuroQol-five dimension questionnaire; HRQL, health-related quality of life; IPI, ipilimumab; NIVO+IPI, nivolumab plus ipilimumab; MID, minimally important difference.
Source: Schadendorf et al. 2015[91]

Similar to observations in EORTC QLQ-C30 analyses, patients treated with ipilimumab showed slightly greater reductions in EQ-5D VAS (visual analogue scale) (demonstrating worsening HRQL) on average, as presented in Figure 20. Again, no clinically meaningful changes (defined as a minimally important difference of ≥0.7 points[152])were observed in either treatment group.[150]

Figure 20: EQ-5D VAS change from baseline in CheckMate 067, HRQL analysis set



Key: EQ-5D, EuroQol-five dimension questionnaire; HRQL, health-related quality of life; IPI, ipilimumab; NIVO+IPI, nivolumab plus ipilimumab; MID, minimally important difference; VAS, visual analogue scale.
Source: Schadendorf et al. 2015[91]

CheckMate 069

Adjusted HRQL completion rates in CheckMate 069 (patients completing questionnaires divided by patients at each respective time point) were 64.2% to 78.7% at baseline and remained stable throughout the study, with the exception of a notable reduction at Week 13 in the Regimen group (48.4%).[94] In consideration of the low patient numbers in HRQL follow-up of CheckMate 069, conclusions from these data should be made with caution.

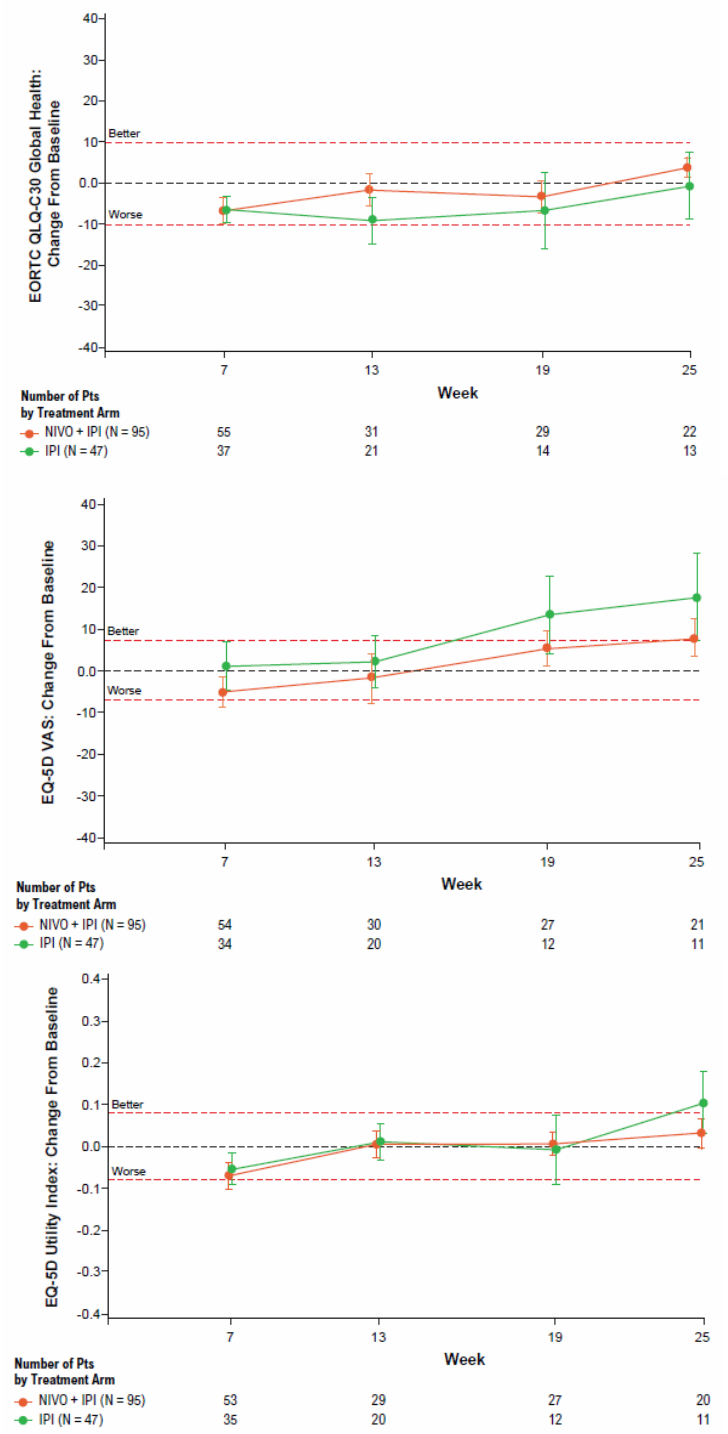
In general, HRQL was shown to deteriorate at the Week 7 assessment but had returned to baseline levels by Week 13 in both treatment groups, as presented in Figure 21. In patients treated with the Regimen, HRQL was maintained or improved from these levels after the switch to nivolumab monotherapy (Figure 21).

Longitudinal mixed-effects modelling (controlling for baseline HRQL) demonstrated statistically significant improvements in dyspnoea and emotional functioning subscales of the EORTC QLQ-C30 with the Regimen. With ipilimumab alone, there were statistically significant improvements in emotional functioning and statistically significant deteriorations in fatigue, global health and physical functioning. No clinically meaningful changes were observed in either treatment group and no significant findings were observed between treatment arms.

No significant differences were observed between treatment groups in EQ-5D utility index and VAS analysis though clinically meaningful improvements from baseline were only observed in the ipilimumab group (Figure 21).

Regression analyses (using a cox proportional hazard model) used to determine the chance of improvement or deterioration in HRQL from baseline confirmed no significant differences between treatment arms for either EORTC QLQ-C30 or EQ-5D.

Figure 21: HRQL change from baseline in CheckMate 069, HRQL analysis set



Key: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol-five dimension questionnaire; IPI, ipilimumab; NIVO, nivolumab; VAS, visual analogue scale.
Source: Abernethy et al. 2015.[94]

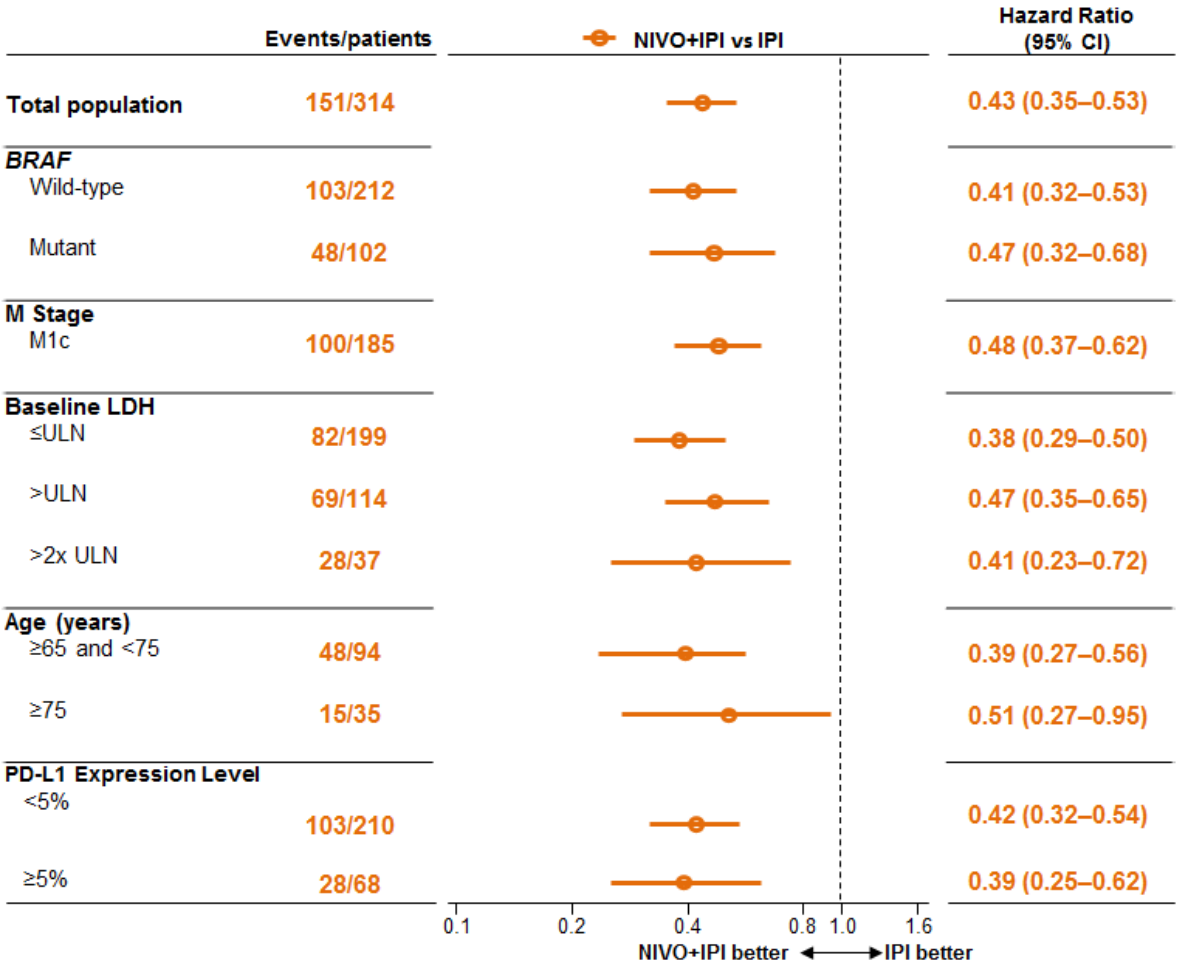
4.8 Subgroup analysis

CheckMate 067

Analyses in pre-specified subgroups showed consistently longer PFS with the Regimen than with ipilimumab treatment alone, including in subgroups defined according to BRAF status, metastatic stage, LDH levels and PD-L1 status, as presented in Figure 22. Of particular note is the significant PFS benefit observed in patients with LDH levels more than two times the upper limit of normal which is particularly striking in consideration of the poor prognosis associated with such high LDH.

Similarly, ORR benefit was observed with the Regimen across pre-defined subsets of patients, as presented in Appendix 7.

Figure 22: Forest plot of treatment effect on PFS in pre-defined subgroups of CheckMate 067, ITT analysis set



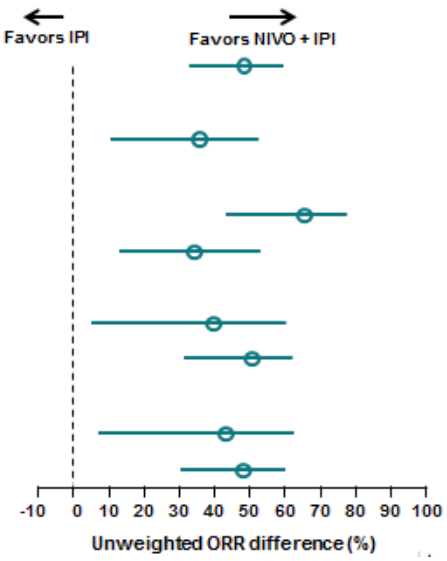
Key: CI, confidence interval; ITT, intention-to-treat; LDH, lactate dehydrogenase; M, metastatic; NIVO+IPI, nivolumab plus ipilimumab; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.
Source: Larkin et al. 2015.[90]

CheckMate 069

In subgroup analyses of the ITT population, the response benefit observed with the Regimen compared with ipilimumab treatment alone (see Section 4.7) was observed across all pre-specified patient subgroups, including patients with stage M1c disease and patients with elevated LDH levels and in post-hoc analysis of patients with PD-L1 negative tumour expression, as presented in Figure 23.[95] This was also the case in subgroup analyses of patients with BRAF mutation-negative tumours, as presented in Appendix 7.[85]

Figure 23: Forest plot of treatment effect on ORR in pre-defined subgroups of CheckMate 069, ITT analysis set

	N	ORR, % (n/N)	
		NIVO + IPI	IPI
Overall	142	59 (56/95)	11 (5/47)
M Stage at study entry			
M1c	65	59 (26/44)	24 (5/21)
Age category I			
<65 years	68	65 (31/48)	0 (0/20)
≥65 years	74	53 (25/47)	19 (5/27)
PD-L1 status[a]			
≥5% expression	35	58 (14/24)	18 (2/11)
<5% non-expression	83	55 (31/56)	4 (1/27)
BRAF status			
MT	32	55 (12/22)	10 (1/10)
WT	110	60 (44/73)	11 (4/37)



Key: IPI, ipilimumab; M, metastatic; NIVO+IPI, nivolumab plus ipilimumab; ORR, objective response rate; PD-L1, programmed death-ligand 1.
Source: [85]Hodi et al. 2015[95]

CheckMate 067/069

In post-hoc, pooled analysis of patients with mucosal melanoma, conducted due to low patients counts within the two trials,[153], significant clinical benefit of the Regimen compared with ipilimumab monotherapy was again clearly demonstrated as presented in Appendix 7.

4.9 Meta-analysis

Meta-analysis was not conducted as data is available from a large Phase III trial (CheckMate 067) to inform outcomes and outcomes from the Phase II trial are consistent with those in the Phase III trial:

- CheckMate 067: significant extension in PFS compared with ipilimumab monotherapy, HR for death or disease progression: 0.42 (99.5% CI, 0.31 to 0.57); p<0.001 (ITT population).
- CheckMate 069: significant extension in PFS compared with ipilimumab monotherapy, HR for death or disease progression: 0.39 (95% CI, 0.25 to 0.63); p<0.0001 (ITT population).

4.10 Indirect and mixed treatment comparisons

Summary

- Head to head trial data (CheckMate 067) has been used to inform treatment comparisons between the Regimen and ipilimumab
- Overall survival is yet to be mature and available for this comparison. Therefore, the head to head data is supported assuming equivalence with long term predictions for nivolumab monotherapy (CheckMate 066) and ipilimumab (MDX010-20)
- Indirect treatment comparisons were required for the comparison of the Regimen with BRAF inhibitors
- Parametric survival models were required to describe the observed data and predict long-term survival. Survival models were designed to produce comparative efficacy estimates and extrapolate data on benefits that could be used within the economic model
- A mixed treatment comparison, combining the Regimen with all comparators of interest within one analysis to form indirect treatment comparisons, was not deemed appropriate for a variety of reasons, including
    - Non-proportional hazards between BRAF inhibitors, palliative chemotherapy and immunotherapies (due to differences seen in Kaplan-Meier data resulting from the differing mechanisms of action of the separate treatment types)
    - High levels of crossover in the BRAF inhibitor trials and subsequent ipilimumab use
    - Lack of homogeneity of trial designs in the evidence base
    - Head to head available for a key comparison (versus ipilimumab)
- A Markov-state transition approach was adopted in the economic model, requiring survival predictions for time to progression (TTP), pre-progression survival (PrePS) and post-progression survival (PPS)
- The vast majority of the benefit for the Regimen compared to ipilimumab was derived from reduction in the TTP
- Due to the limited data available PPS was assumed to be equivalent for the Regimen, nivolumab and ipilimumab, making the conservative assumption that immunotherapies like nivolumab and ipilimumab, which target immune-regulatory signalling pathways, will provide a similar long-term survival benefit profile and that combined treatment will not improve this outcome
- Comparison to BRAF inhibitors was performed based upon extrapolation of digitised data from the latest data-cut of the BRIM-3 trial, the largest trial for BRAF inhibitors with the longest follow-up. BRAF inhibitors were assumed to have equal efficacy based upon NICE Technology Appraisal 321 (TA321)
- BRAF status was found not to be independently prognostic for PFS within the CheckMate 067 trial based upon Cox proportional hazards regression analyses including BRAF status either as a covariate or as a potential treatment effect modifier
- Compared to ipilimumab, the point at which the rapidity of action of BRAF inhibitors is outweighed by the long-term benefit of immunotherapy is considerably sooner, approximately 3 months versus more than 2 years, which is consistent with the increased speed of response and magnitude of survival benefit observed with both nivolumab monotherapy and the Regimen

The treatment comparators of interest considered in this submission are ipilimumab and BRAF inhibitors. The Regimen has been compared to ipilimumab in two head to head clinical trials. However, the Regimen and BRAF inhibitors have not been studied within head to head clinical trials, therefore indirect treatment comparisons were required.

Additionally, for the purposes of economic modelling, it is important that the relative efficacy (OS and PFS) between treatments allows for long-term extrapolation of treatment effects. To achieve this, parametric survival models were required to describe the observed data and predict long-term survival. The availability of data (patient level or summary level) differs for the treatment comparators of interest, as does the approach to constructing relative treatment effects (directly and indirectly). Though not all methods and results are strictly 'indirect comparisons', the estimation of relative treatment effects (and extrapolation thereof) are fully described within this section for ease of reference. This section is split into the following sub-sections that describe the strategy and approaches taken, with rationale, methods and results:

- Evidence base for treatments of interest
- Treatment comparison strategy
- Comparison of the Regimen and ipilimumab
    - Evidence base
    - Methods
    - Results
- Comparison of the Regimen to BRAF inhibitors
    - Evidence base
    - Methods
    - Results

Evidence base for treatments of interest

The systematic literature review methods used to identify RCTs for use in indirect comparison analyses are described in Section 4.1. The resulting evidence base is summarised in Table 9.

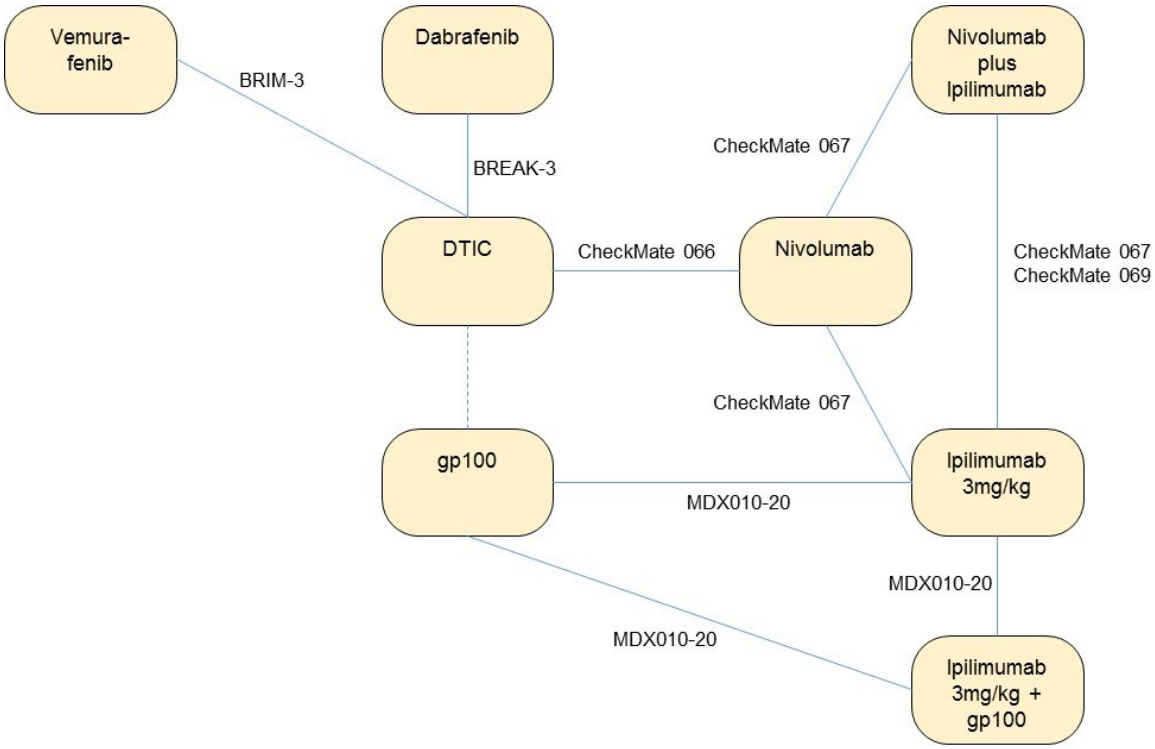
The treatment comparators of interest for the Regimen, by BRAF status and treatment experience, are shown in Table 17.

Table 17: Comparators considered for indirect comparison, relevant to final scope

Population	Comparators[a]
BRAF mutation positive	Ipilimumab 3mg/kg Vemurafenib (960mg) Dabrafenib (150mg)
BRAF mutation negative	Ipilimumab 3mg/kg
Key: kg, kilograms; mg, milligrams **Note**: [a], further details, e.g. dosing frequency, are given in Table 6.	

The relevant trials identified for these treatments, which report PFS and/or OS, and are not 'spider arms' within the network, are shown in the network diagram in Figure 24. Included trials are consistent with those used for indirect comparison with the submission for nivolumab as a monotherapy[154] with the addition of CheckMate 067. Although not formally identified as part of the systematic literature review, CheckMate 066 has been included in these analyses as relevant data to support and enhance overall survival (post-progression survival) evidence. An updated datacut (compared to what was used in the nivolumab monotherapy submission) has been used for CheckMate 066, which includes 2 year data for overall survival.[155] This datacut does however also include some crossover from dacarbazine to nivolumab.

Figure 24: Network diagram



Key: DTIC, dacarbazine; gp-100, gp-100 melanoma peptide vaccine.
Notes: The dotted line between DTIC and gp-100 does not indicate a trial, but rather indicates that if DTIC and gp-100 are considered equivalent, it allows for MDX010-20 to be linked within this network of treatments.

Both OS and PFS data from the CheckMate 069 Phase II trial were not included within this analysis due to lack of maturity (i.e. not enough events) at the time of submission and pollution of the data by substantial crossover to nivolumab monotherapy. As good quality PFS data was available from the Phase III CheckMate 067 trial this was viewed as the best source of information for the estimation of the treatment effect of the Regimen compared to ipilimumab. PFS outcomes from the Phase II trial are consistent with those in the Phase III trial. OS data from CheckMate 067 was not available at the time of submission.

The effect of BRAF status on PFS was investigated for the Regimen using Cox proportional hazards regression analyses in CheckMate 067. As would be expected based upon previously published information[55] and the fact that the mechanism of action of both nivolumab and ipilimumab is independent of BRAF status, BRAF status had neither a substantial nor significant impact on outcomes. Controlling for other prognostic factors (ECOG, M-stage, LDH, brain metastases, age group and gender) BRAF status was not seen to be a treatment effect modifier; i.e. treatment by BRAF status interaction was not statistically significant (p-value=0.49). In a separate model, including BRAF status as a covariate but not an interaction with treatment, and again controlling for the other prognostic

factors, BRAF status was not seen to be an independently prognostic factor; i.e. the BRAF status covariate was not statistically significant (p-value=0.26). BRAF status was therefore not included as an outcome or treatment effect modifying factor in the survival analyses.

The lack of effect of BRAF status on PFS for the Regimen is also demonstrated by Larkin et al. (2015), which presents similar median PFS estimates in both the BRAF mutation positive (11.7 months) and negative (11.2 months) patients.[90] Likewise, ipilimumab demonstrated similar efficacy in both BRAF mutation-positive and -negative patients in CA184-004.[86]

Treatment comparison strategy

Head to head evidence for the Regimen versus ipilimumab is available from the CheckMate 067 trial. Therefore, the required treatment comparisons are formed as follows:

- Head to head comparison (CheckMate 067):
    - Regimen versus ipilimumab
- Indirect treatment comparison:
    - Regimen versus BRAF inhibitors

The key trial design features to consider within this evidence base are shown in Table 18. Quality assessment of these trials is presented in Appendix 6.

Table 18: Key trial design features for selected evidence base

Trial	Treatments	BRAF status	Previously treated?	Patient level data available?	Subsequent therapy / crossover
CheckMate 067	• Nivolumab plus Ipilimumab • Nivolumab • Ipilimumab	Mixed	No	Yes (only for PFS)	No subsequent therapy pre-progression Post progression subsequent therapies included anti-PD1s, ipilimumab and BRAF inhibitors
CheckMate 069	• Nivolumab plus Ipilimumab • Ipilimumab	Mixed	No	Yes (small sample size)	Crossover from ipilimumab to nivolumab on progression
CheckMate 066	• Nivolumab • Dacarbazine	BRAF mutation negative	No	Yes	Crossover (from dacarbazine) & subsequent ipilimumab
MDX010-20	• Ipilimumab 3mg/kg • gp-100 • Ipilimumab 3mg/kg + gp-100	Unknown	Yes	Yes	No subsequent ipilimumab or BRAF inhibitors
BRIM-3	• Vemurafenib • Dacarbazine	BRAF mutation positive	No	No	Crossover (from dacarbazine) & subsequent ipilimumab
BREAK-3	• Dabrafenib • Dacarbazine	BRAF mutation positive	No	No	Crossover (from dacarbazine) & subsequent ipilimumab
Key: PFS, progression free survival					

As previously accepted by the Evidence Review Group within the ongoing appraisal for nivolumab monotherapy[80] a mixed treatment comparison, combining the Regimen with all comparators of interest within one analysis to form indirect treatment comparisons, is not considered appropriate for a variety of reasons, including:

- Non-proportional hazards between BRAF inhibitors, palliative chemotherapy and immunotherapies due to their differing mechanisms of action (see Section 5.2.2, Figure 32 and Figure 33)
    - This means that parametric survival curves cannot be simultaneously estimated for nivolumab and the BRAF inhibitors using one simple constant treatment effect
- High levels of crossover in the BRAF inhibitor trials and subsequent ipilimumab use in CheckMate 066 and the BRAF inhibitor trials are problematic, for example when trying to use dacarbazine (DTIC) as the common comparator.

As previously stated, OS data for the Regimen are not available in CheckMate 067 and are both immature and highly polluted by crossover in CheckMate 069. OS data from CheckMate 066 and MDX010-20 can be used, conservatively assuming similar post-progression survival efficacy for ipilimumab, nivolumab and the Regimen.

However, it should be noted that CheckMate 066 enrolled only treatment naïve BRAF mutation-negative patients. As discussed in previous appraisals it is not expected that either line of therapy or BRAF mutation status would independently impact outcomes.[55, 56, 154]

In addition to differences between the trial designs and populations in terms of BRAF mutation status and line of therapy, there are important differences in the prognostic characteristics of patients within the trials included within the potential network, and it was therefore important that we maximised the use of, and flexibility within, the available patient level data. Treatment comparisons of the Regimen with ipilimumab therefore use only patient level data and will hereafter be described separately to the comparisons with the BRAF inhibitors (vemurafenib and dabrafenib). The optimal strategy for forming comparisons between nivolumab and the comparators is shown in Table 19.

Table 19: Treatment comparison strategy

Comparison	Treatments
Nivolumab plus ipilimumab vs ipilimumab	Use patient level data from CheckMate 067 for PFS. Use CheckMate 066 and MDX010-20 as proxy for OS
Nivolumab plus ipilimumab vs vemurafenib and dabrafenib	Use patient level data from CheckMate 067, CheckMate 066, and MDX010-20, and aggregate/summary data from BRIM-3 / BREAK-3 to form an indirect comparison

Throughout the survival analyses and economic modelling, an assumption is made that line of treatment is not independently prognostic and does not independently impact treatment effectiveness. Based upon available information for ipilimumab and nivolumab, no difference in efficacy has been seen over different lines of treatment (see Section 4.13).[11, 29, 156, 157] This assumption was previously accepted in NICE Technology Appraisal 319 (TA319) in the context of the MDX010-20 study and its applicability to first-line therapy with ipilimumab.[55]

Comparison of nivolumab plus ipilimumab to ipilimumab

Evidence base

The baseline characteristics in CheckMate 067 are shown in Table 13. The prognostic factors selected for use in covariate adjusted parametric models were based upon the Korn meta-analysis, which analysed which factors affect prognosis within advanced melanoma treated with palliative chemotherapy and are consistent with those selected as prognostic for similar analyses carried out in TA319.[29, 55] The selected list of potentially prognostic

covariates (ECOG, LDH, M stage, brain metastases, age group and gender) was validated with UK clinicians during an advisory board conducted for use in the appraisal for nivolumab monotherapy in March 2015.[2]

Methods

Mature OS data is not available for the Regimen, and therefore OS data from CheckMate 066 and MDX010-20 has been used as a proxy assuming equal efficacy between ipilimumab, nivolumab and the Regimen. This assumption is unlikely to hold for OS, but when adopting a Markov state-transition approach, as used in the nivolumab monotherapy submission[154], only post-progression survival (PPS) relies on OS data, and the assumption of equal efficacy is considered conservative for PPS. Additionally, using this approach, and in particular PPS rather than OS, allows increased validity and robustness of survival extrapolations for long-term estimation of treatment effects when data are relatively immature (i.e. they do not reach the median survival point). As a result, the economic model has been designed to adopt a Markov-based state-transition approach using time to progression (TTP), pre-progression survival (PrePS), and PPS for modelling survival.

TTP and PrePS are used to inform the long-term extrapolation of PFS. TTP, PrePS and PPS are used to inform the long-term extrapolation of OS. Participant level data (PLD) from CheckMate 067 has been used to estimate PrePS and TTP, and PLD from MDX010-20 and CheckMate 066 has been used to estimate PPS.

TTP is defined in the same way as PFS. However, patients that are classified as progressors in PFS due to death are censored at death in the TTP outcome. For the CheckMate 067 data (in the absence of OS data), PrePS is defined the same way as PFS. However, patients that progress due to death are counted as events, and all other patients are censored at their PFS time. PPS only includes patients that have progressed and follows time to death, or censoring, from the point of progression.

Parametric survival curves have been fitted to TTP, PrePS and PPS separately in the statistical software R[158]. In line with Decision Support Unit (DSU) guidance (technical support document [TSD] 14)[116], the parametric distributions investigated were:

- Exponential
- Weibull
- Log-Normal
- Log-logistic
- Gamma
- Gompertz

Each model was adjusted for the covariates/prognostic factors shown in Table 20. For the analysis of TTP and PrePS, a trial effect was not required, as only PLD from CheckMate 067 was used. For PPS, a trial effect was included to account for differences between CheckMate 066 and MDX010-20, but a treatment effect was not included as the treatment effect of ipilimumab and nivolumab was conservatively assumed to be equivalent. Note, the glycoprotein-100 (gp100) and dacarbazine treatment arms were not used as they are not relevant comparators. Also, the data for dacarbazine in CheckMate 066 was polluted with treatment cross-over. Equivalence of ipilimumab 3mg/kg+gp100 and ipilimumab 3mg/kg was assumed for MDX010-20. This was required to maximise the data used to estimate the treatment effect of ipilimumab 3mg/kg. As would be expected given the lack of impact of gp100 on outcomes, there was no discernible difference in the OS and PFS results for the ipilimumab+gp100 & ipilimumab groups in the MDX010-20 study, and the previous NICE appraisal for ipilimumab in previously treated patients (NICE TA268) concluded that pooling the datasets was appropriate.[56]

Table 20: Prognostic factors included within the covariate-adjusted parametric survival models

Covariate	Levels
Treatment (only included for TTP and PrePS)	2 levels: nivolumab plus ipilimumab and ipilimumab
Trial (only included for PPS)	2 levels: MDX010-20 and CheckMate 066
Baseline ECOG	2 levels: 0 and ≥1
LDH	2 levels: >ULN and ≤ULN
M stage	2 levels: M1c and 'M0 or M1a or M1b'
History of brain metastases	2 levels: yes and no
Age group	2 levels: <65 and ≥65
Gender	2 levels: male and female
Subsequent ipilimumab (only included for PPS)	2 levels: yes and no
Key: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; PrePS, pre-progression survival; PPS, post-progression survival; TTP, time to progression; ULN, upper limit of normal range. **Notes:** The underlined covariate levels indicate which were used as reference categories in the survival models.	

The best fitting models have been selected (in line with DSU TSD 14 guidance) by considering the visual fit of the parametric curves compared to the KM curves (separately for each trial/treatment), clinical plausibility of extrapolation and comparison of the Akaike information criteria (AIC) and Bayesian information criteria (BIC) values. To make consistent comparisons between fitted curves by treatments related to the KM curves, the parametric model estimates were applied to the covariate values as observed in the specific trial/treatment arm.

Within the base case analysis, all prognostic covariates are included within the model regardless of their statistical significance.

The survival models fitted to each endpoint can only use data from patients with complete covariate information; therefore, patients with missing information for any of the covariates were excluded from the analyses. The amount of missing covariate data was minimal (e.g. more than 98% of patients [622 out of 629 for CheckMate 067] are included in the PrePS and TTP analyses, and more than 99% of patients [481 out of 482 for CheckMate 066/MDX010-20] are included in the PPS analyses, as they have complete covariate information); therefore, it is not expected that inclusion of covariates biases the analysis population or results/findings.

The number of events by outcome are shown in Table 21 for both the full trial population and the group of patients with complete covariate information that are used for fitting survival models:

Table 21: Events by trial and treatment

Study	Treatment group	OS Events n/N(%)	PFS Events n/N(%)	TTP Events n/N(%)	PrePS Events n/N(%)	PPS Events n/N(%)
Full population						
CheckMate 067	Nivolumab plus ipilimumab	Not available	151 / 314 (48.1%)	129 / 314 (41.1%)	22 / 314 (7.0%)	Not available
	Ipilimumab	Not available	234 / 315 (74.3%)	212 / 315 (67.3%)	22 / 315 (7.0%)	Not available
MDX010-20	Ipilimumab pooled	406 / 540 (75.2%)	493 / 540 (91.3%)	Not used	Not used	296 / 383 (77.3%)
CheckMate 066	Nivolumab	80 / 210 (38.1%)	114 / 210 (54.3%)	Not used	Not used	58 / 99 (58.6%)
Population of patients with complete covariate information						
CheckMate 067	Nivolumab plus ipilimumab	Not available	151 / 313 (48.2%)	129 / 313 (41.2%)	22 / 313 (7.0%)	Not available
	Ipilimumab	Not available	233 / 309 (75.4%)	211 / 309 (68.3%)	22 / 309 (7.1%)	Not available
MDX010-20	Ipilimumab pooled	406 / 540 (75.2%)	493 / 540 (91.3%)	Not used	Not used	296 / 383 (77.3%)
CheckMate 066	Nivolumab	74 / 199 (37.2%)	109 / 199 (54.8%)	Not used	Not used	57 / 98 (58.2%)

Key: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival; TTP, time to progression.

Results – TTP

Unadjusted KM curves for CheckMate 067 for TTP are shown in Figure 25.

There are steep drops in the KM curves for both treatments near to the start of the curves. This is because the timing of progression assessment relies on protocol-specified tumour assessment times. For CheckMate 067, the first scheduled time at which tumour assessment occurred was 12 weeks (84 days), meaning that there was a large number of patients seen to progress at or shortly after the 3 month time point; in reality, some of these patients will have progressed at a time earlier than 3 months, but this information cannot be captured. This unrealistic clustering of progression times in both studies makes it difficult to fit meaningful parametric survival curves to these data near to the start of the curves. As a result, we cut the data at Day 84 to allow a more clinically and statistically plausible shape and continuous flow to the occurrence of progression in the data from Day 84 onwards.

The KM curves for TTP split at Day 84 are shown in Figure 26 (KM censored at Day 84) and Figure 27 (KM from Day 84 onwards and rebased at Day 84). The TTP events prior to and after Day 84 are shown in Table 22.

Figure 25: Kaplan–Meier curves for time to progression (CheckMate 067)

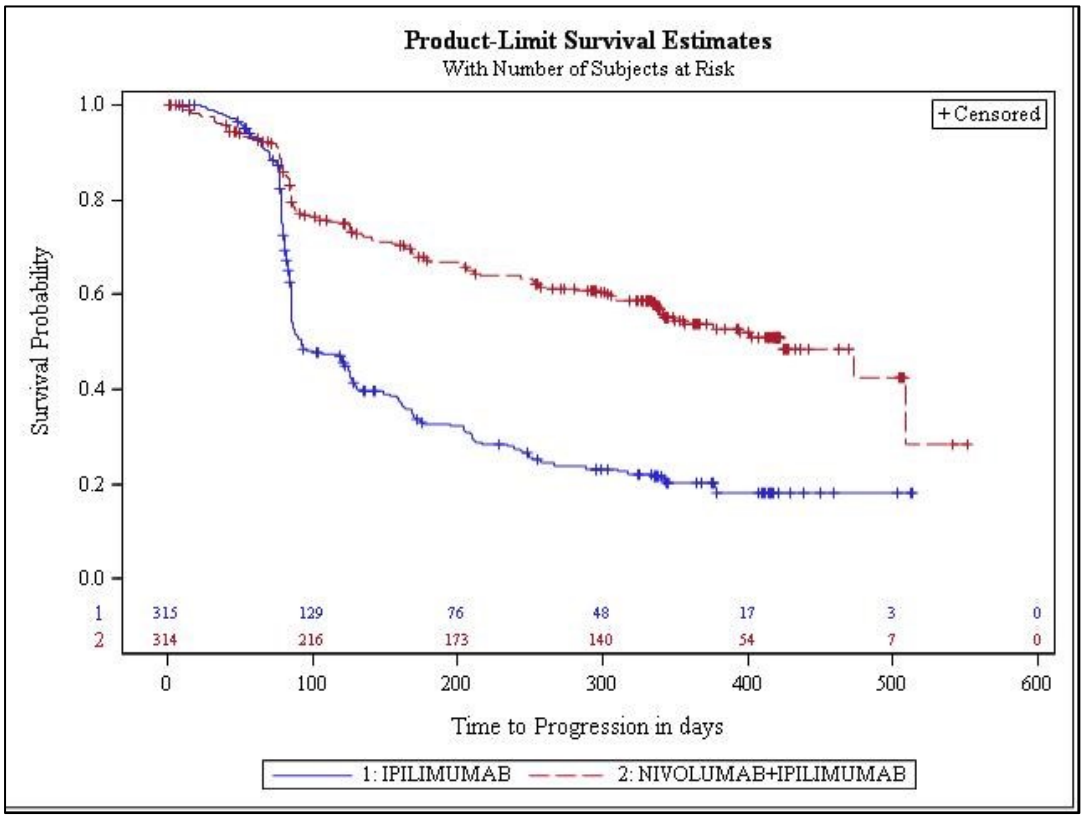


Figure 26: Kaplan–Meier curves for time to progression (patients censored at Day 84) (CheckMate 067)

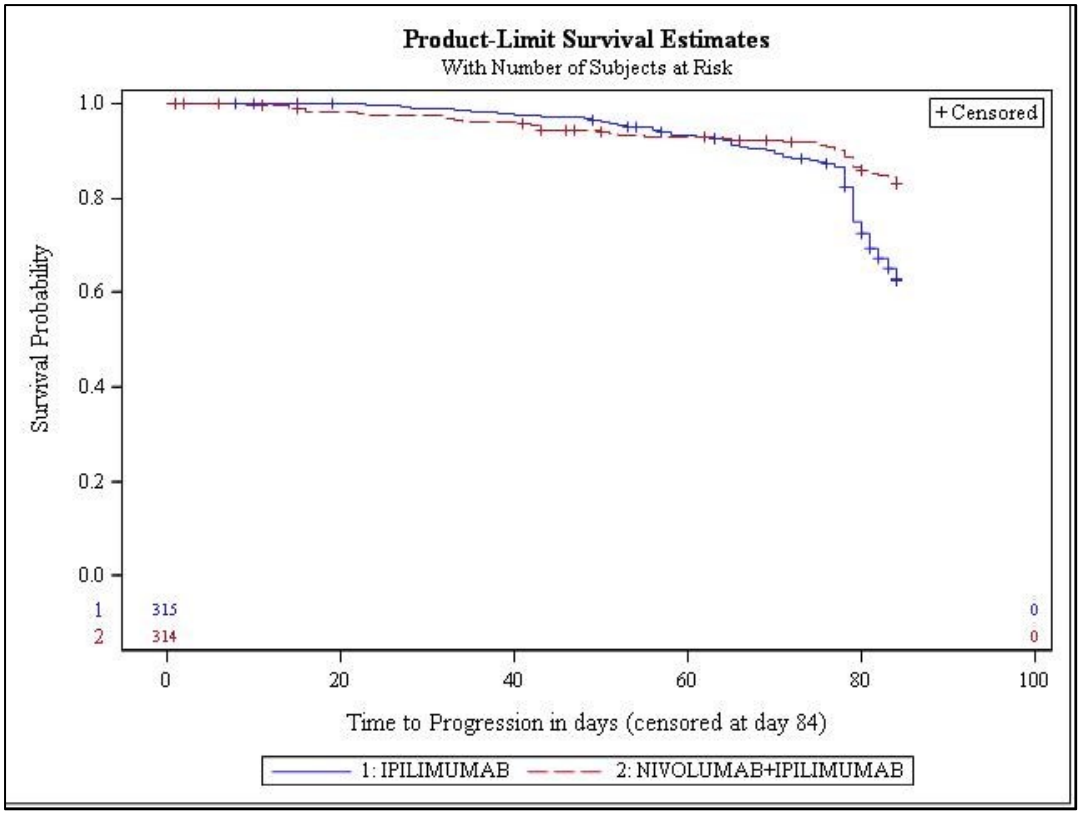
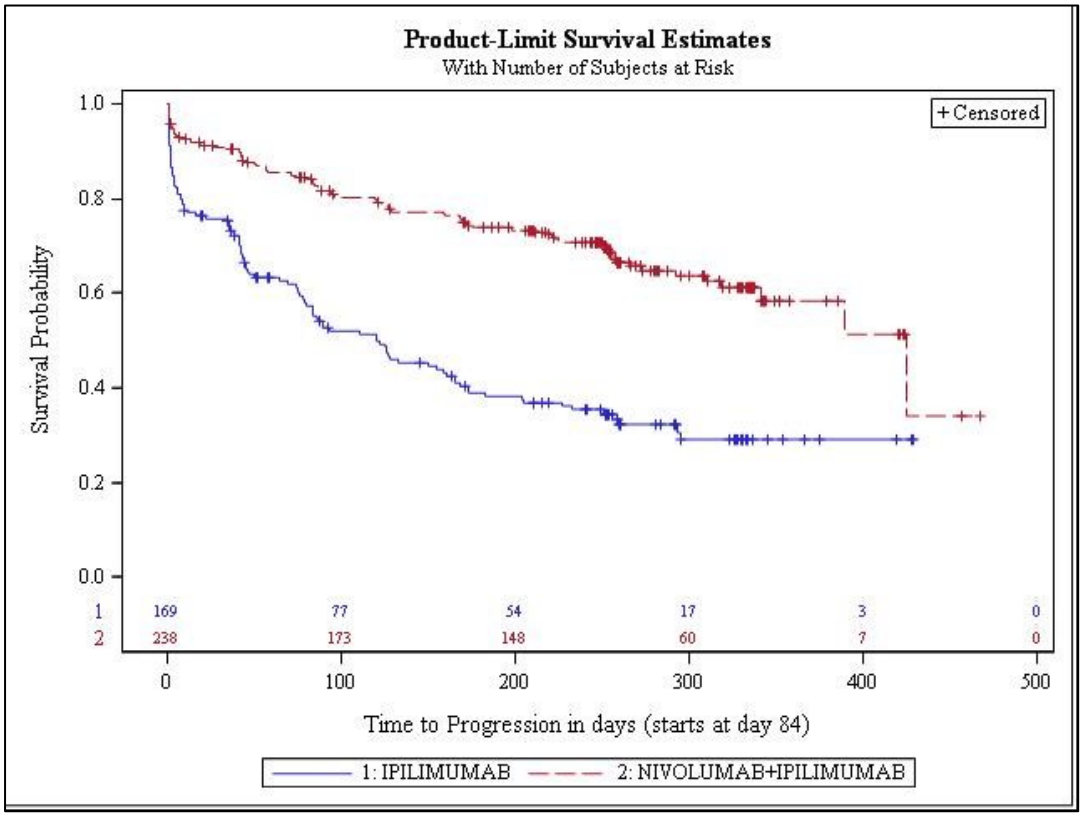


Figure 27: Kaplan–Meier curves for time to progression (measured from Day 84) (CheckMate 067)



Notes: Time zero on the plot equates to day 84 of the trial.

Table 22: Events by trial and treatment for TTP before and after Day 84

Study	Treatment group	TTP ≤84 days Events n/N(%)	TTP >84 days Events n/N(%)
Full population			
CheckMate 067	Nivolumab plus ipilimumab	50 / 314 (15.9%)	79 / 238 (33.2%)
	Ipilimumab	105 / 315 (33.3%)	107 / 169 (63.3%)
Population of patients with complete covariate information			
CheckMate 067	Nivolumab plus ipilimumab	50 / 313 (16.0%)	79 / 238 (33.2%)
	Ipilimumab	105 / 309 (34.0%)	106 / 167 (63.5%)
Key: TTP, time to progression.			

TTP pre-84 days was estimated within the economic model based on the observed KM data up to 84 days (as shown in Figure 26). To estimate relative efficacy and to control for differences of patient prognostic factors between trials and treatment arms, the KM data for TTP pre-84 days were adjusted by applying HRs estimated from a Cox proportional hazards model for the same covariates used for fitting survival curves (Table 23). This method assumes proportionality of the effects of the prognostic factors and use these for adjusting the observed TTP pre-84 days KM data to control for differences of these factors between trials and arms. Proportionality of treatment effects (which clearly does not hold for TTP pre-84 days based on the KM data) is not assumed given that the observed by-treatment KM data (rather than fitted parametric curves) are used in the economic model.

Table 23. Cox proportional hazards model; TTP pre-84 days

Model parameter	Parameter estimate	Standard error	P-value	Hazard ratio
Treatment (ipilimumab vs nivolumab plus ipilimumab)	0.89648	0.17306	<0.0001	2.451
Sex (male vs female)	-0.10989	0.16633	0.5088	0.896
Age group (under 65 vs 65 and over)	-0.03545	0.16317	0.828	0.965
ECOG (ECOG=0 vs ECOG ≥1)	-0.20108	0.1772	0.2565	0.818
Elevated LDH (>ULN vs ≤ULN)	0.83486	0.16578	<0.0001	2.304
History of brain metastases (yes vs no)	-0.62663	0.51079	0.2199	0.534
M stage (M1c vs M0 or M1a or M1b)	0.40334	0.17891	0.0242	1.497

Key: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; ULN, upper limit of normal range; TTP, time to progression.

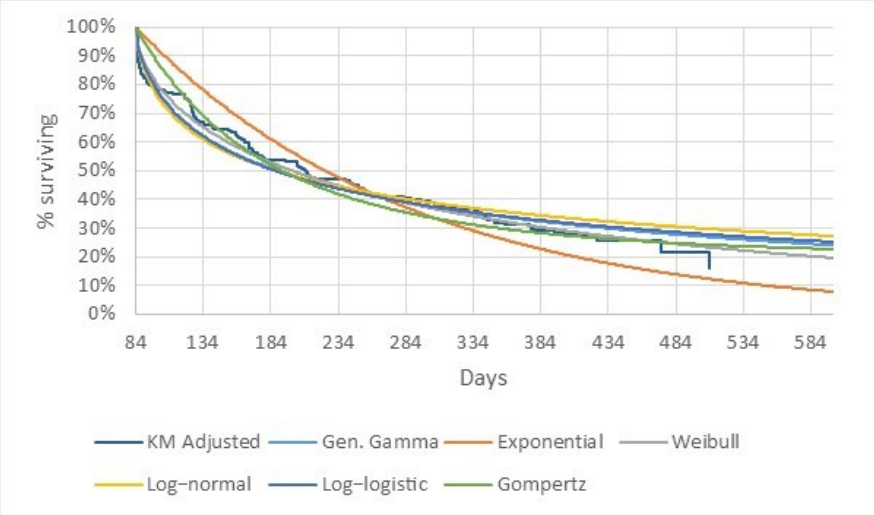
The six covariate-adjusted parametric curves were fitted to the TTP data post 84 days, and the fitted curves are shown against the KM curves by trial and treatment in Figure 28. Note, the amount of missing covariate data was minimal (e.g. more than 99% of patients [405 out of 407 pooled across groups] are included in the TTP post 84 days analyses as they have complete covariate information); therefore, it is not expected that inclusion of covariates biases the analysis population or results/findings. The curves presented in Figure 28 are predicted curves from the estimated parametric equations; i.e. the 2 shown curves (by treatment) are estimated from each parametric equation using summary covariate information observed in the data for the given treatment group. The same curves extrapolated beyond the end of the data (to 1600 days) are also presented in Figure 28.

The model fits were assessed using AIC/BIC, as shown in Table 24, where lower values represent better fitting models. The fits of the parametric curves according to visual fit to 'adjusted KM' data (using predicted survival estimates from a covariate adjusted Cox proportional hazards model) and AIC/BIC indicate that the log normal, generalised gamma, log-logistic and Weibull models are all reasonable fits to the data.

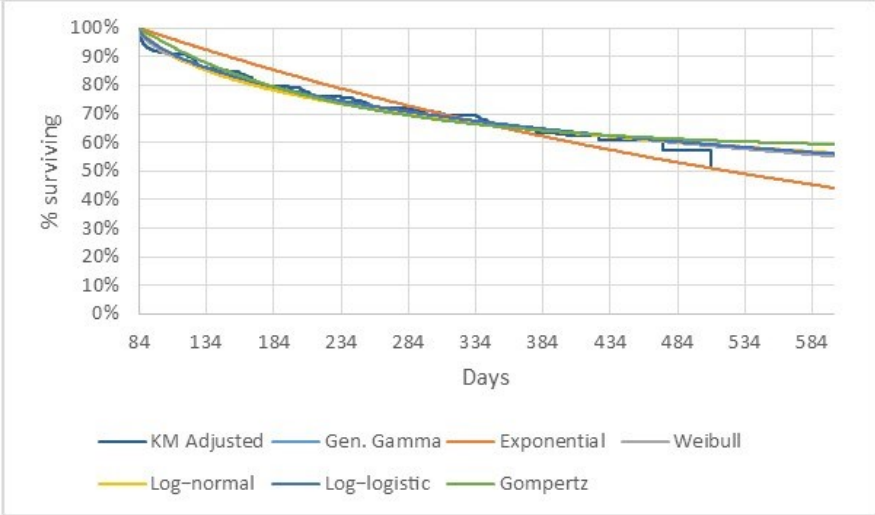
The log-normal curve provided the best statistical fit, and long-term extrapolations for log-normal were judged to be clinically plausible and in line with long-term data available for ipilimumab; therefore, log-normal was selected as the best-fitting/most appropriate model selected for use in the economic model base case. The parameter estimates for this selected model are shown in Table 25. Parameters for alternative model fits are supplied in Appendix 9. Fitted curves are constructed using the "sdlog" value together with the linear combination of the intercept and covariate estimates. For the log-normal distribution, the exponential of the covariate estimates can be interpreted as ratios of mean survival (as with other accelerated failure time distributions). Using this, we observe a strong positive effect in favour of the Regimen versus ipilimumab; ratio of mean survival for TTP post 84 days (Regimen versus ipilimumab) = exp (2.11) = 8.25 (95% confidence interval 4.47 to 15.22, p-value= <0.0001). Although many of the covariates individually had modest effects on the outcome and were not statistically significant, we felt it important to retain these in the model to fully adjust for prognostic factors and to allow more flexibility within the economic model for different patient populations.

Figure 28. Parametric model fits for time to progression post 84 days

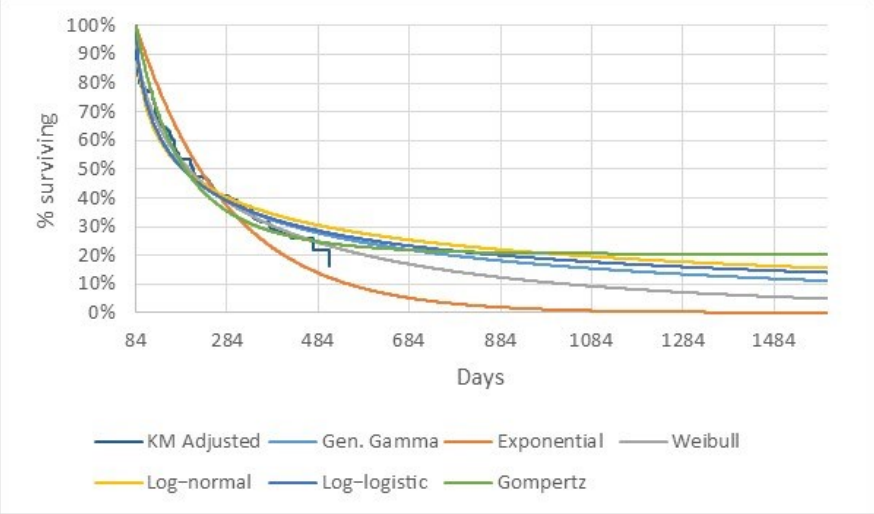
CheckMate 067: Ipilimumab



CheckMate 067: Nivolumab plus ipilimumab



CheckMate 067: Ipilimumab (extrapolated to 1600 days)



CheckMate 067: Nivolumab plus ipilimumab (extrapolated to 1600 days)

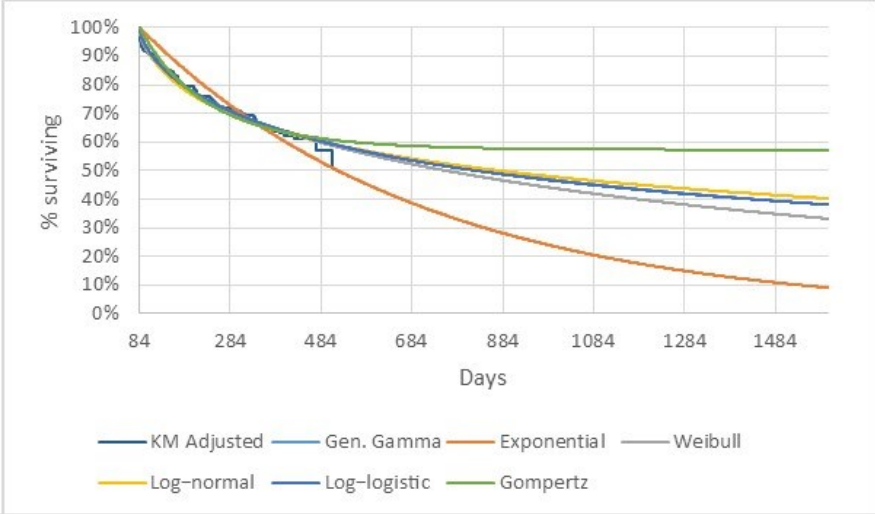


Table 24: Model fit estimates for TTP post 84 days

Model	AIC	BIC
Log-normal	2432.75	2468.79
Generalised Gamma	2433.45	2473.49
Weibull	2433.87	2469.91
Log-logistic	2433.94	2469.98
Gompertz	2488.42	2524.46
Exponential	2521.43	2553.46
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; TTP, time to progression.		

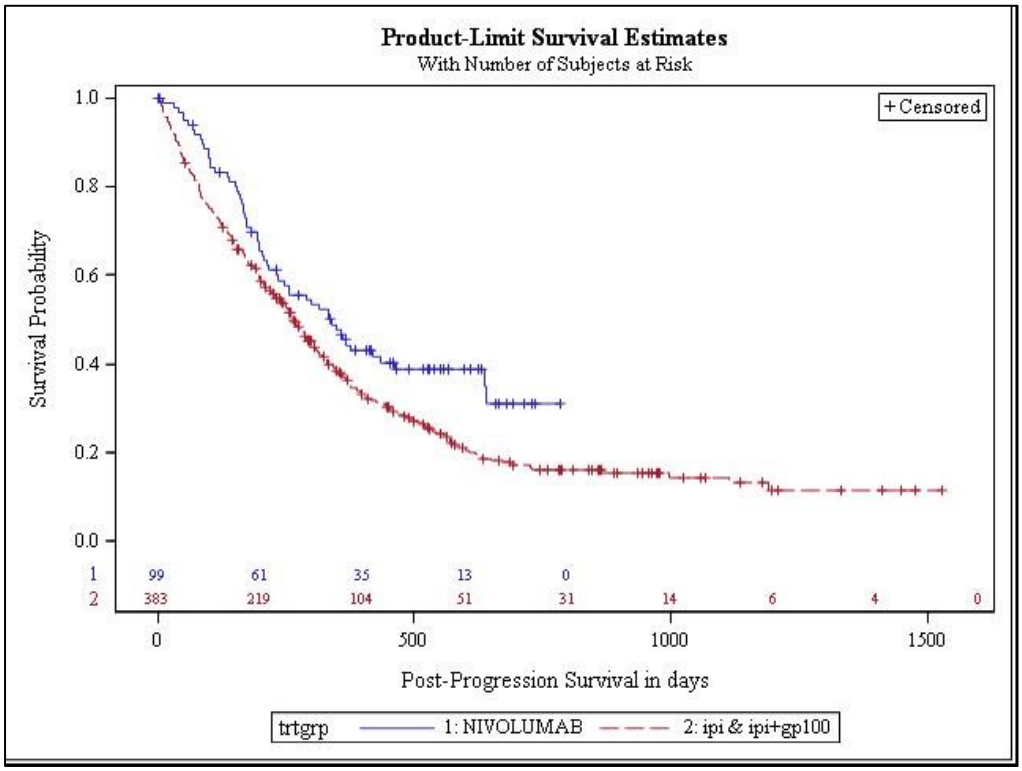
Table 25: Log-normal model parameter estimates for TTP post 84 days

Model Parameter	Estimate	Lower 95% CL	Upper 95% CL
Sdlog	0.973	0.862	1.084
Meanlog (intercept)	5.291	4.338	6.245
Treatment: nivolumab plus ipilimumab vs ipilimumab	2.110	1.498	2.723
ECOG: 0 vs ≥1	-0.034	-0.752	0.683
M stage: M1c vs 'M0 or M1a or M1b'	-0.597	-1.217	0.023
Aged under 65: Yes vs No	-0.453	-1.063	0.157
Sex: male vs female	0.012	-0.620	0.644
History of brain metastases: Yes vs No	1.666	-0.105	3.437
High LDH: Yes vs No	-0.634	-1.311	0.042
Key: CL, confidence limit; ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; TTP, time to progression; ULN, upper limit of normal range			

Results – PPS

Unadjusted KM curves for CheckMate 066 and MDX010-20 for PPS are shown in Figure 29.

Figure 29: Kaplan–Meier curves for PPS (CheckMate 066 and MDX010-20)



Notes: Nivolumab data are from CheckMate 066, and 'ipi & ipi+gp100' are from MDX010-20.

Similarly to TTP, for PPS there is only a small amount of data lost due to lack of covariate information (less than 1% of patients); therefore, we proceeded with covariate-adjusted parametric survival models as the base case analyses. In CheckMate 066, patients were permitted to receive ipilimumab upon progression, hence the inclusion of subsequent ipilimumab (yes/no) as a covariate for PPS.

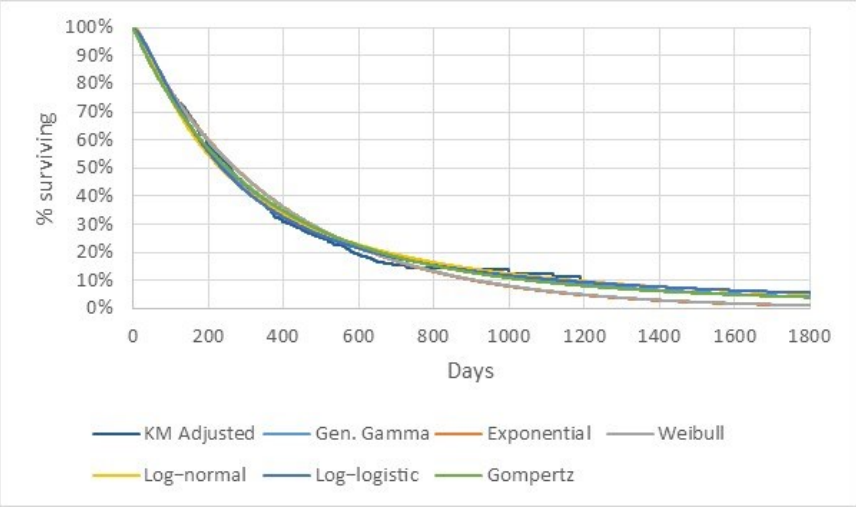
As described, the nivolumab and ipilimumab data from CheckMate 066 and MDX010-20, respectively, are used as proxy to the estimate PPS conservatively assuming equal efficacy between nivolumab, ipilimumab and the Regimen. Using this assumption, the effect of treatment is not included in the PPS covariate adjusted models. However, the effect of study is included to adjust for unmeasured differences between the studies. The six covariate-adjusted parametric curves were fitted to the PPS data, and the fitted curves are shown with the 'adjusted KM' curves (using predicted survival estimates from a covariate adjusted Cox proportional hazards model) by trial and treatment in Figure 30. The model fits were assessed using AIC/BIC in Table 26, where lower values represent better fitting models.

Table 26: Model fit estimates for PPS

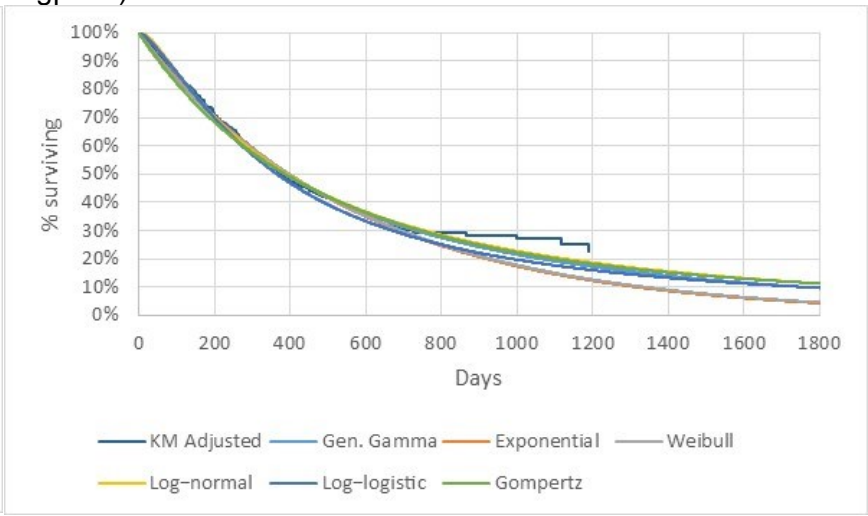
Model	AIC	BIC
Log-logistic	4906.00	4947.76
Log-normal	4908.50	4950.26
Generalised Gamma	4909.10	4955.04
Gompertz	4923.98	4965.74
Exponential	4928.89	4966.47
Weibull	4930.78	4972.54
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; PPS, post-progression survival.		

Figure 30: Parametric model fits for post-progression survival

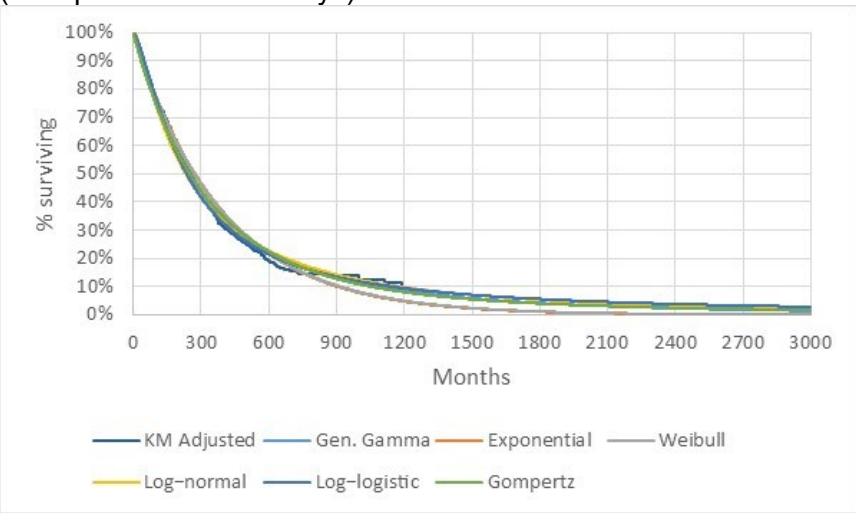
MDX010-20: Ipilimumab (pooled monotherapy and combination with gp100)



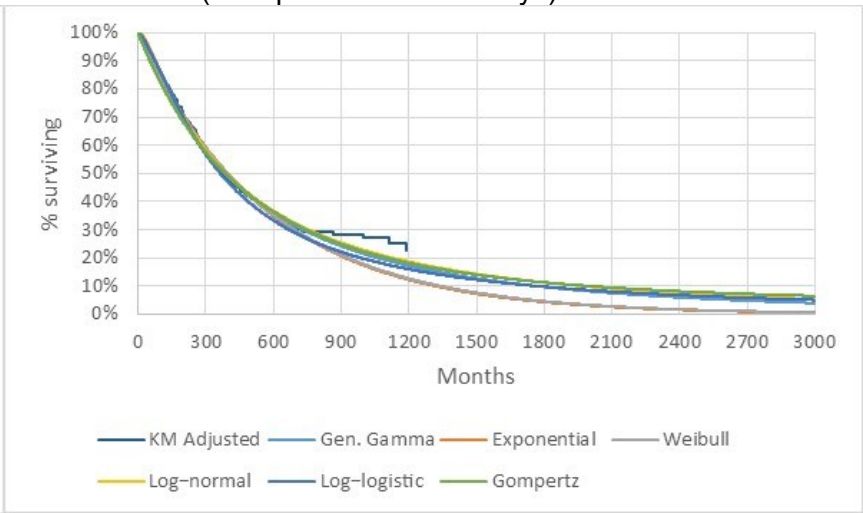
CheckMate 066: Nivolumab



MDX010-20: Ipilimumab (pooled monotherapy and combination with gp100) (extrapolated to 1500 days)



CheckMate 066: Nivolumab (extrapolated to 1500 days)



According to visual fit and AIC/BIC, the generalised gamma, log-logistic and log-normal models are all reasonable, as were the long-term extrapolations for these models. Log-logistic was selected as the best-fitting/most appropriate model selected for use in the economic model base case given the slight superiority in AIC/BIC and validation of the expected survival for ipilimumab (see Section 5.9). The parameter estimates for this selected model are shown in Table 27. Parameters for alternative model fits are supplied in Appendix 9.

Table 27: Log-logistic model parameter estimates for PPS

Model parameter	Estimate	Lower 95% CL	Upper 95% CL	p-value
Scale[a]	0.7152	0.6553	0.7805	
Intercept	5.7804	5.2737	6.2871	<.0001
Study: MDX010-20 vs CheckMate 066	-0.1867	-0.6193	0.2458	0.3975
ECOG: 0 vs ≥1	0.3339	0.0839	0.5838	0.0089
M stage: M1c vs 'M0 or M1a or M1b'	-0.2313	-0.5020	0.0394	0.0940
Aged under 65: Yes vs No	0.1858	-0.0741	0.4456	0.1612
Sex: male vs female	-0.0272	-0.2618	0.2074	0.8203
History of brain metastases: Yes vs No	-0.0581	-0.4610	0.3447	0.7773
High LDH: Yes vs No	-0.9328	-1.1984	-0.6672	<.0001
Subsequent ipilimumab: Yes vs No	0.5646	0.0310	1.0982	0.0381

Key: CL, confidence limit; ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; PPS, post-progression survival; ULN, upper limit of normal range.
Notes: [a] care should be taken as different statistical packages have different model parameterisations and use different terminology for parameters; the estimates reported here are taken from the SAS software parameterisation.

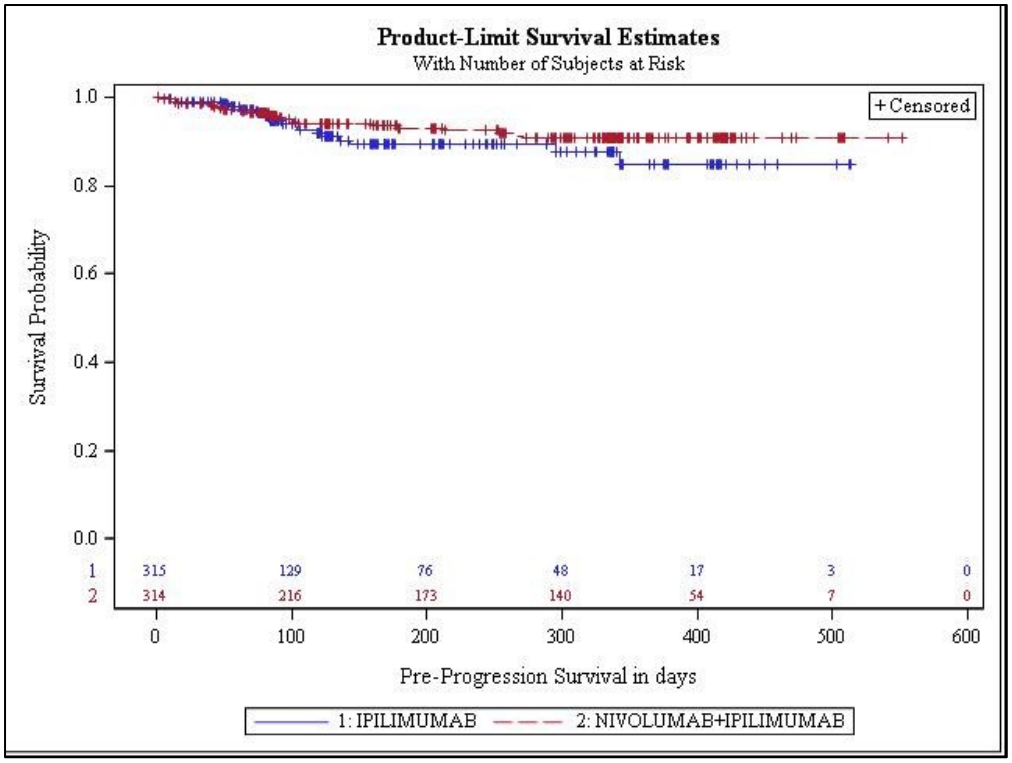
Although some of the covariates individually had modest effects on the outcome and were not statistically significant, we felt it was important to retain these in the model to fully adjust for prognostic factors and to allow more flexibility within the economic model for different patient populations. After adjustment for prognostic factors, the effect of trial (which is fully confounded with any treatment effect) was not significant, adding support to the assumption of equal PPS between nivolumab and ipilimumab.

Results – PrePS

The KM curves for CheckMate 067 for PrePS are shown in Figure 31. Only a small amount of data (events) is available for PrePS for both treatment groups. Curve fits were attempted for PrePS, but none of the standard parametric curves provided an acceptable visual fit to both

treatment arms included in the model (Appendix 9). Instead of a curve fit, direct KM data were used within the economic model with longer-term extrapolation informed by melanoma registry data, long-term OS based on pooled ipilimumab trials, and general population mortality (see Section 5.3).

Figure 31: Kaplan–Meier curves for pre-progression survival (CheckMate 067)



Similarly, for the adjustment of KM data for TTP pre-84 days, the KM data for PrePS were adjusted by applying HRs estimated from a Cox proportional hazards model for the same covariates used for fitting survival curves (Table 28).

Table 28. Cox proportional hazards model; PrePS

Model parameter	Parameter estimate	Standard error	P-value	Hazard ratio
Treatment (ipilimumab vs nivolumab plus ipilimumab)	0.36131	0.31353	0.2492	1.435
Sex (male vs female)	-0.29357	0.31254	0.3476	0.746
Age group (under 65 vs 65 and over)	-0.50544	0.30668	0.0993	0.603
ECOG (ECOG=0 vs ECOG ≥1)	-0.73449	0.31234	0.0187	0.480
Elevated LDH (>ULN vs ≤ULN)	1.41064	0.33771	<.0001	4.099
History of brain metastases (yes vs no)	-0.00987	0.61527	0.9872	0.990
M stage (M1c vs M0 or M1a or M1b)	0.88523	0.39194	0.0239	2.424
Key: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; PrePS, pre-progression survival; ULN, upper limit of normal range.				

Comparison of nivolumab plus ipilimumab to BRAF inhibitors

Evidence base

Only summary data (for BRAF inhibitors) from publications are available for BRIM-3 and BREAK-3. The primary baseline characteristics (i.e. those with known prognostic effects on outcomes) in CheckMate 067, BRIM-3 and BREAK-3 are shown in Table 29. There are some differences between the trials with respect to baseline characteristics of prognostic factors.

In NICE Technology Appraisal 321 (TA321), the committee determined that vemurafenib and dabrafenib have approximately equal efficacy, and a meta-analysis was carried out by the evidence review group (ERG) to support this determination. As such, formal comparison and parametric survival curve fitting is only made for nivolumab versus vemurafenib, with scenarios tested assuming either a HR of 1 for OS and PFS for vemurafenib versus dabrafenib or using the published HRs from TA321 (see Section 5.8.3). BRIM-3 was chosen as the trial on which to base survival curve fitting because the trial was substantially larger than BREAK-3 (n=337 received BRAF inhibitors versus n=187), and the patient characteristics were thought to be more reflective of patients receiving BRAF inhibitors in UK clinical practice, i.e. higher LDH levels.

Additionally, a further trial (Combi-V) including vemurafenib monotherapy (compared to a combination including vemurafenib) was identified. However, the decision was taken to base the comparison with BRAF inhibitors on only BRIM-3 rather than having to make multiple comparisons (which would have been necessary due to the strategy taken for forming these indirect comparisons). BRIM-3 was selected as it was the source with the largest sample size, the longest length of follow-up, and it was the basis for the original NICE recommendation for vemurafenib.

Table 29: Baseline characteristics of CheckMate 067, BRIM-3, and BREAK-3

	CheckMate 067		BRIM-3		BREAK-3	
Characteristic	Ipilimumab (n=315)	Nivolumab plus ipilimumab (n=314)	DTIC (n=338)	Vemurafenib (n=337)	DTIC (n=63)	Dabrafenib (n=187)
ECOG = 0	71.1%	73.3% (unknown= 0.3%)	68%	68%	70%	66%
LDH (>ULN)	36.5% (1.9% not reported)	36.3% (0.3% not reported)	58%	58%	30% (2% unknown)	36% (<1% unknown)
M stage = M1c	58.1%	57.6%	65%	66%	63%	66%
History of brain metastases	4.8%	3.5%	NR	NR	NR	NR
Age (under 65)	57.8% Median=62 years	58.9% Median=61 years	100% Median=52 years	100% Median=56 years	NR% Median=50 years	78.6% Median=53 years
Gender (males)	64.1%	65.6%	54%	59%	59%	60%

	CheckMate 067		BRIM-3		BREAK-3	
Characteristic	Ipilimumab (n=315)	Nivolumab plus ipilimumab (n=314)	DTIC (n=338)	Vemurafenib (n=337)	DTIC (n=63)	Dabrafenib (n=187)
Key: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; NR, not reported; ULN, upper limit of normal range.						

There are two important considerations for the BRIM-3 trial:

- A large proportion of patients crossed over from DTIC to vemurafenib, making the use of DTIC as a common comparator in a network between CheckMate 067, CheckMate 066, and BRIM-3 invalid given the true effects of DTIC would be hard to estimate from BRIM-3 (and for CheckMate 066 which also included treatment crossover).
- The proportional hazards assumption of relative treatment effects does not appear to hold within BRIM-3 (Figure 32 shows that the KM curves cross for BRAF inhibitors vs chemotherapy), making it difficult to use a solitary summary measure (i.e. HR) from these trials within an indirect comparison. Similar non-proportional hazards are observed in the latest data-cut for BREAK-3.[131]

For these reasons, it was not appropriate to simply apply HRs estimated from BRIM-3 to the parametric curves estimated in CheckMate 067. Instead, to form indirect comparisons between the Regimen and both vemurafenib and dabrafenib, we adopted the following strategy:

- Using the published KM curves for OS and PFS for vemurafenib, KM data were estimated using digitisation software
- Using the estimated KM data, pseudo patient level data were created for vemurafenib using the Guyot 2012 method[159]
- Parametric survival curves for OS and PFS were fitted separately to the single arm pseudo patient level data – these curves were then used directly in the economic model
- To compare OS and PFS between vemurafenib and the Regimen, the Regimen estimates of OS and PFS (as constructed within the economic model from TTP, PrePS and PPS) were re-estimated, adjusted for the observed patient characteristics in the BRIM-3 trial. This approach estimates the efficacy of the Regimen in the BRAF mutation-positive patient population, keeping the efficacy observed for vemurafenib within BRIM-3 unaltered.

Source KM data for vemurafenib

As within the submission for nivolumab monotherapy,[154] the OS data for vemurafenib from the BRIM-3 trial were taken from Figure 4 in Hauschild 2013 and are presented in Figure 32.[82] The PFS data for vemurafenib from the BRIM-3 trial were taken from Figure 3 in McArthur 2014 and are presented in Figure 33.[133] These two publications were selected as the most up to date information on OS and PFS for vemurafenib at the time of submission.

Figure 32: Overall survival Kaplan–Meier plot for BRIM-3 (vemurafenib versus DTIC censored at crossover)

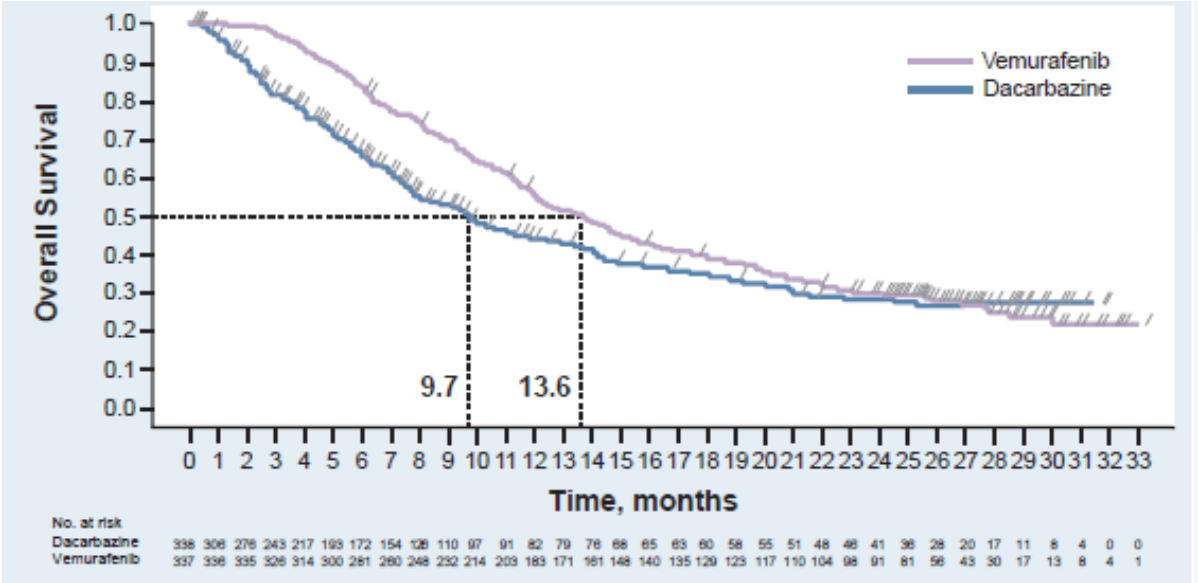
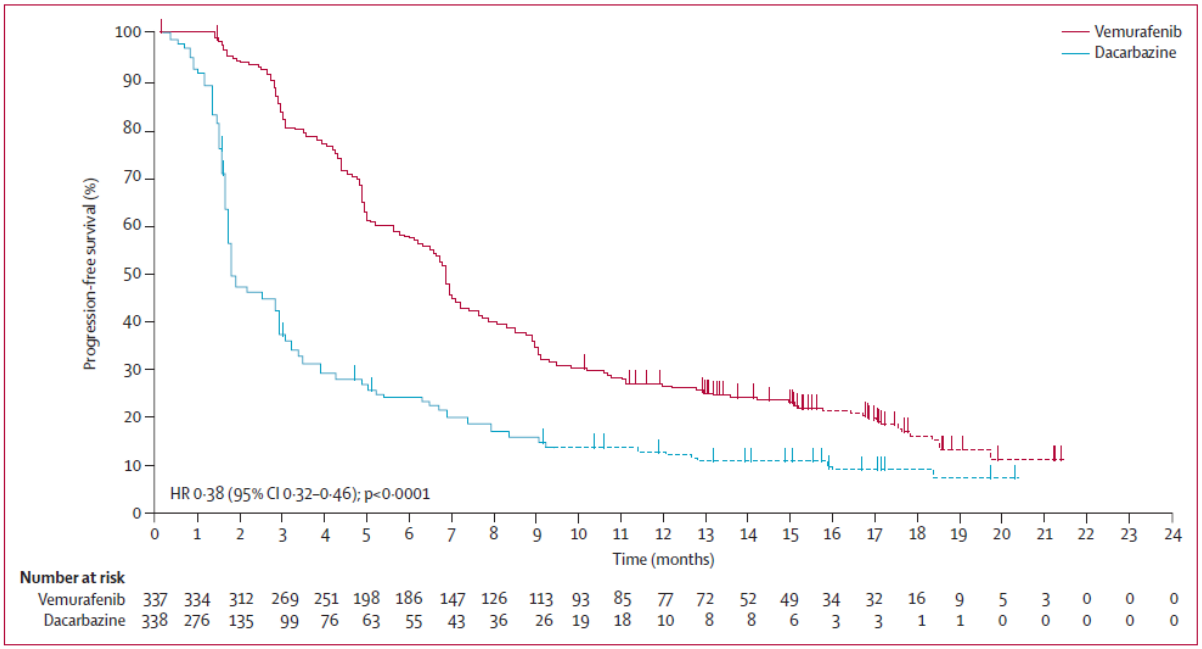


Figure 33: Progression-free survival Kaplan–Meier plot for BRIM-3 (vemurafenib versus DTIC)

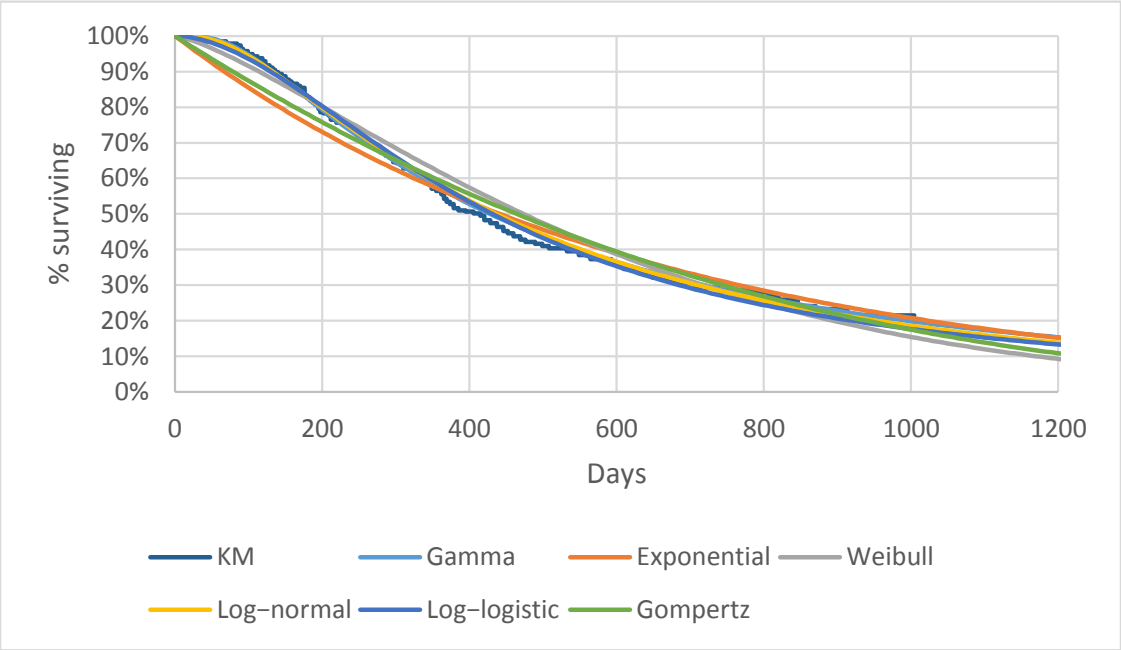


Results

Figure 34 presents the six parametric curves fitted to the pseudo BRIM-3 patient level data for OS. The model fits were assessed both according to visual fit and using AIC/BIC in Table 30, where lower values represent better fitting models.

Using AIC, BIC and visual fit to assess the best fitting model (compared to the KM curve), the log-normal model performed best and was selected for use in the economic model.

Figure 34: Parametric survival curves fitted to BRIM-3 vemurafenib OS data



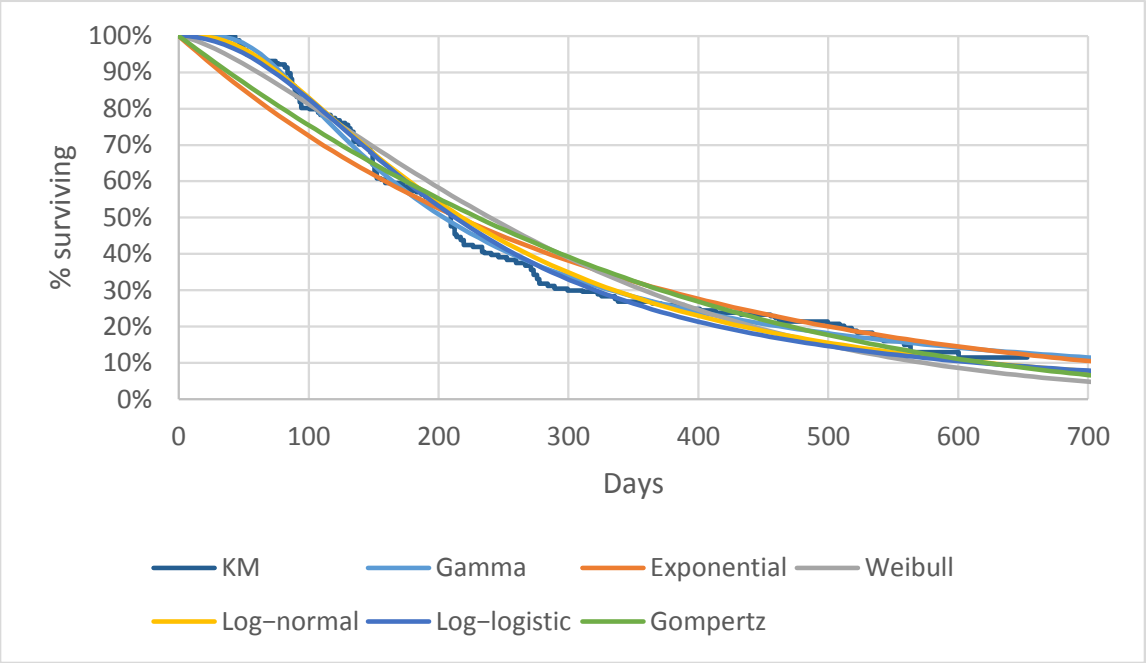
Key: OS, overall survival.

Table 30: Model fit estimates for OS (vemurafenib from BRIM-3)

Model	AIC	BIC
Exponential	3700.23	3704.05
Generalised Gamma	3647.94	3659.41
Gompertz	3698.01	3705.65
Log-logistic	3651.70	3659.34
Log-normal	3647.40	3655.04
Weibull	3677.80	3685.44

Figure 35 presents the six parametric curves fitted to the pseudo BRIM-3 patient level data for PFS. The model fits were assessed according to visual fit and AIC/BIC in Table 31, where lower values represent better fitting models. According to the AIC and BIC and visual fit to the KM data, the generalised-gamma model performed best and was selected for use in the economic model.

Figure 35: Parametric survival curves fitted to BRIM-3 vemurafenib PFS data



Key: PFS, progression-free survival.

Table 31: Model fit estimates for PFS (vemurafenib from BRIM-3)

Model	AIC	BIC
Exponential	3506.86	3510.68
Generalised Gamma	3410.62	3422.08
Gompertz	3503.35	3510.99

Model	AIC	BIC
Log-logistic	3428.62	3436.26
Log-normal	3421.30	3428.94
Weibull	3473.10	3480.74
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; PFS, progression-free survival.		

Results – BRAF inhibitors – selected model estimates

Table 32: Parameters for models selected for BRAF inhibitors

Study, Treatment	Endpoint	Chosen Curve	Model estimates
BRIM-3, vemurafenib	OS	Log-normal	Meanlog=6.078 Sdlog=-0.072
	PFS	Generalised gamma	Mu=5.104 Sigma=-0.220 Q=-0.754
NICE TA321, dabrafenib	OS	ERG meta-analysis	HR=1
	PFS	ERG meta-analysis	HR=0.97
Key: ERG, Evidence Review Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TA; technology appraisal.			

A comparison of the survival outcomes for BRAF inhibitors versus nivolumab is presented within Section 5.3.3 and 5.3.5. Similar to previous findings versus ipilimumab initially BRAF inhibitors are expected to result in increased OS and PFS due to the speed of their mechanism of action. However, in the long-term, it is expected that the Regimen will result in increased survival. The point at which the rapidity of action of BRAF inhibitors is outweighed by the long-term benefit of immunotherapy is considerably sooner for the Regimen versus ipilimumab, approximately 3 months versus more than 2 years, which is consistent with the increased speed of response and magnitude of survival benefit observed with the Regimen.

4.11 Non-randomised and non-controlled evidence

Summary

- CheckMate 004 provides supplementary Phase I evidence to support the benefit of concurrent nivolumab and ipilimumab therapy as demonstrated in Phase II/III RCTs
    - Good-quality, Phase Ib dose-ranging trial that provides longer-term survival data in advanced melanoma patients treated for a maximum duration of 2 years (as anticipated in clinical practice)
    - Inclusive eligibility criteria based on BRAF mutation status and treatment history
- Concurrent nivolumab and ipilimumab therapy demonstrates unprecedented survival benefit in advanced melanoma, irrespective of BRAF mutation status and treatment history:
    - 3-year survival rate of 68% with concurrent nivolumab and ipilimumab therapy in patients with advanced melanoma
    - Extraordinary in consideration of the 22% 3-year survival rate previously associated with immunotherapy (ipilimumab) even within the limitations of a Phase I trial
    - 1-year survival rate of 75% with the Regimen (i.e. concurrent nivolumab and ipilimumab therapy dosed in line with anticipated market authorisation)
- Concurrent nivolumab and ipilimumab therapy resulted in rapid and durable clinical response benefit in advanced melanoma, irrespective of BRAF mutation status and treatment history:
    - ORR of 42% with concurrent nivolumab and ipilimumab therapy and 44% when dosed in line with anticipated market authorisation
    - Median duration of response to date of 22.3 months with concurrent nivolumab and ipilimumab therapy and 13.8 months with the Regimen (i.e. when dosed in line with anticipated market authorisation)
    - Over 50% of patients still responding to nivolumab and ipilimumab therapy at the time of analysis; often despite discontinuation of study drug
    - Median change in tumour burden of ≥ -50%, irrespective of baseline prognosis (LDH, metastatic stage, treatment history)

List of relevant non-randomised and non-controlled evidence

Only one non-RCT is considered relevant to the decision problem as it supplements the RCT data presented to support the use of the Regimen.

CheckMate 004 assessed the safety and efficacy of nivolumab and ipilimumab given concurrently or sequentially in patients with advanced melanoma, irrespective of BRAF status or treatment history.[160] One cohort of patients received combination dosing in line with the expected licence (nivolumab 1mg/kg plus ipilimumab 3mg/kg every 3 weeks for 4 doses followed by nivolumab 3mg/kg every 2 weeks).

A summary of the CheckMate 004 trial is presented in Table 33.

Table 33: List of relevant non-randomised and non-controlled evidence

Trial name (NCT number)	Objective	Population	Intervention	Primary study reference	Justification for inclusion
CheckMate 004 (NCT01024231)	To investigate the safety and efficacy of combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively).	Advanced (unresectable or metastatic) melanoma patients.	Concurrent nivolumab and ipilimumab or Ipilimumab followed by nivolumab	Wolchok et al. 2013[160]	Provides survival data in both treatment naïve and treatment exposed patients. Trial design included treatment discontinuation at 96 weeks.
Key: CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death-1.					

Summary of methodology of the relevant non-randomised and non-controlled evidence

CheckMate 004 is a multi-arm, Phase Ib dose-ranging trial, designed to investigate the safety and efficacy of combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively) in advanced melanoma.[161]

Successive cohorts of patients were treated with escalating doses of nivolumab and ipilimumab but doses were kept constant within each cohort. The trial was initially planned to evaluate various concurrent regimen schedules (cohorts 1 to 5) and two sequenced regimen schedules (cohorts 6 and 7) with eligible patients assigned to a dose cohort in the order they entered the study. Due to maximum tolerated dose (MTD) being exceeded in cohort 3, no patients were enrolled in cohorts 4 or 5 and an alternate dose escalation scheme was added (cohort 2a). Based on data from cohorts 1 to 3, the Regimen schedule was selected for Phase II/III trials. An expansion treatment group matching the Regimen was subsequently implemented in CheckMate 004 (cohort 8); patients were enrolled to this cohort from November 2013.

Protocol-specified dose levels are summarised in Table 34.

Table 34: Dose levels in planned patient cohorts of CheckMate 004

Group	Cohort	Nivolumab dose (mg/kg)	Ipilimumab dose (mg/kg)
Concurrent (n=53) Nivolumab and ipilimumab q3w for 4 doses followed by nivolumab q3w for 4 doses followed by nivolumab and ipilimumab q12w for a maximum of 84 weeks (maintenance)	1	0.3	3
	2	1	3
	2a	3	1
	3	3	3
	4	10	3
	5	10	10
Sequential (n=33) Prior standard ipilimumab therapy (resulting in controlled disease) followed by nivolumab q2w for a maximum of 96 weeks	6	1	3
	7	3	3
Combination (n=41) Nivolumab plus ipilimumab q3w for 4 doses followed by nivolumab q2w for a maximum of 96 weeks	8	1 (dose 1-4) 3 (dose 5+)	3

Key: q2w, every 2 weeks; q3w, every 3 weeks; q12w, every 12 weeks.
Source: CheckMate 004 CSR.[161]

Maintenance nivolumab treatment could be continued for a maximum of 84 weeks in concurrent regimen groups; sequential and combination regimen groups could receive nivolumab maintenance treatment for up to 96 weeks. Patients entering maintenance or follow-up periods with ongoing disease control (complete response, partial response, or stable disease for at least 24 weeks) were permitted re-treatment upon confirmed disease progression after discussions and agreement with the medical monitor.

The primary objective of CheckMate 004 was to assess the safety and tolerability of treatment with assessment based on AEs coded with the use of the Medical Dictionary for Regulatory Activities version 15.1 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Secondary objectives were to specifically assess safety and tolerability of the selected combination regimen (cohort 8); to assess preliminary efficacy of the Regimen; to assess immunogenicity to nivolumab and ipilimumab; and to assess

pharmacokinetics. Efficacy measures included tumour response, assessed as per modified World Health Organisation (mWHO) criteria and by immune-related response criteria (irRC); PFS; OS rate and OS. Tumour assessments were conducted at weeks 12, 18, 24, 30, 36 and every 12 weeks thereafter in concurrent regimen groups and every 8 weeks from week 8 in the sequential and combination regimen groups; survival assessments were conducted via telephone contact every 12 weeks. Patients were followed for safety, survival and response measures for up to 5.5, 3 and 2.5 years after the initiation of therapy, respectively.

Statistical analysis of the non-randomised and non-controlled evidence

Sample size could not be precisely determined as it depended on the observed toxicity but up to approximately 126 patients were planned, based on the study design for dose escalation and safety evaluation requirements.[161]

Safety parameters were summarised using descriptive statistics. ORR was also summarised using descriptive statistics with estimation of exact 95% CI. Time to event analyses (time to treatment response, duration of response, PFS and OS) were summarised by KM methodology. The primary dataset used in CheckMate 004 was the all treated patients group, defined as all patients who received at least one dose of study medication. Response outcomes were assessed on the response-evaluable population, defined as all treated patients with at least one on-treatment tumour assessment, clinical progression or death (the response-evaluable population was the same as the all treated population). The conservative principle was used for data imputation.

Data presented is the latest available: participant flow analysis is based on a primary database lock of June 2014 and clinical efficacy analysis is based on a follow-up database lock of July 2015. Median duration of follow-up as of July 30, 2015 was 32.7 months in cohorts 1-3, 19.9 months in cohort 8 and 23.0 months in all concurrent combination cohorts.

Participant flow in the studies

Participant flow

From trial initiation in December 2009, 127 patients were treated at 4 investigational sites in the US.[161] Twenty three of the 150 patients enrolled did not receive treatment as they did not meet eligibility criteria or withdrew consent.

At the time of primary analysis (June 2014), 72.4% of all patients and 53.7% of patients enrolled to cohort 8 had discontinued treatment. As was the case in RCTs, the most common reason for treatment discontinuation in patients enrolled to cohort 8 was study drug toxicity (24.4%).

Participant flow for all cohorts is presented in Table 35.

Table 35: Patient disposition summary in CheckMate 004

	Cohorts 1-3 (n=53)	Cohorts 6&7 (n=33)	Cohort 8 (n=41)	All cohorts (n=127)
Patients discontinuing, n (%)	42 (79.3)	28 (84.8)	22 (53.7)	92 (72.4)
Reason for discontinuation, n (%)				
Death	1 (1.9)	2 (6.1)	3 (7.3)	6 (4.7)
Study drug toxicity	18 (34.0)	3 (9.1)	10 (24.4)	31 (24.4)

Disease progression	15 (28.3)	20 (60.6)	8 (19.5)	43 (33.9)
AE unrelated to study drug	1 (1.9)	0	0	1 (0.8)
Maximum clinical benefit	4 (7.5)	1 (3.0)	0	5 (3.9)
Other	3 (5.7)	2 (6.1)	1 (2.4)	6 (4.7)

Key: AE, adverse event.
Notes: no patients enrolled in cohorts 4 or 5.
Source: CheckMate 004 CSR.[161]

Patient characteristics

As per trial eligibility criteria, all patients enrolled in CheckMate 004 had histologic diagnosis of melanoma with measureable, unresectable Stage III or IV melanoma.[161, 162] In cohort 8 there were slightly more females than males enrolled but across cohorts, the majority of patients were male and Caucasian with an average age over 55 years.

As observed in RCTs, a high percentage of patients had poor prognostic factors at baseline including M1c stage disease and elevated LDH. According to protocol, patients may have been treated with up to 3 prior systemic treatments for melanoma prior to enrolment. In cohort 8, 49% of all patients were treatment naïve with 27% of patients having received one prior treatment and 24% of patients having received 2 or 3 prior treatments.

There was some variation in patient characteristics across cohorts, representing the broad profile of advanced melanoma patients presenting in clinical practice. In cohort 8, no patients tested positive for PD-L1 expression at the 5% cut-off; 6/21 patients (28.6%) were PD-L1 positive using a 1% cut-off.

Baseline demographics and disease characteristics of patients enrolled to concurrent and combination patient cohorts are presented in Table 36.

Table 36: Characteristics of participants in CheckMate 004 across concurrent and combination treatment groups

	Cohorts 1-3 (n=53)	Cohort 8 (n=41)
Age, median years (range)	58 (22-79)	56 (22-80)
Age, mean years (SD)	56.6 (12.9)	55.2 (12.5)
Gender, male n (%)	32 (60)	18 (44)
Race, Caucasian n (%)	53 (100)	37 (90)
ECOG PS, n (%)	0: 44 (83) 1: 8 (15) Unknown: 1 (2)	0: 25 (61) 1: 11 (27) Unknown: 5 (12)
Metastasis stage, n (%)	M1c: 29 (55)	M1c: 21 (51)
Common metastasis site, n (%)	Lymph node: 28 (53) Lung: 27 (51) Liver: 16 (30)	Lymph node: 19 (46.3) Lung: 19 (46) Liver: 16 (39)
Elevated LDH, n (%)	20 (38)	16 (39)
PD-L1-positive[a], n/N (%)	14/37 (38)	0/21 (0)
BRAF mutation-negative (wild-type), n (%)	39 (74)	27 (66)
Number of prior therapies, n (%)	0: 32 (60) 1: 15 (28) ≥2: 6 (11)	0: 20 (49) 1: 11 (27) ≥2: 10 (24)
Nature of prior therapy, n (%)	Immunotherapy: 10 (19) BRAF inhibitor: 2 (4)	Immunotherapy: 12 (29) BRAF inhibitor: 3 (7)

Key: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death ligand-1; PS; performance status; SD, standard deviation.
Notes: [a], PD-L1 not quantifiable in 16 patients in cohorts 1-3 and 20 patients in cohort 8.
Source: CheckMate 004 CSR[161]; Sznol et al. 2014.[162]

Quality assessment of the relevant non-randomised and non-controlled evidence

Quality assessment of CheckMate 004 has been conducted by assessing risk of common types of bias (selection, performance, attrition and detection) as well as the applicability of study results to the decision problem. A summary of this quality assessment is presented in Table 37; the complete quality assessment is provided in Appendix 6.

Table 37: Quality assessment results for CheckMate 004

Were attempts made to minimise selection bias?	Yes.
Do the selected patients represent the eligible population for the intervention?	Yes.
Did the setting reflect UK practice?	Yes.
Were all participants accounted for at study conclusion?	Yes.
Were outcome measures reliable? And were all clinically relevant outcome measures assessed?	Yes.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No but analysis conducted on all treated patients with the conservative principle used for data imputation.
Are the study results internally valid?	Yes.
Are the study results externally valid?	Yes.

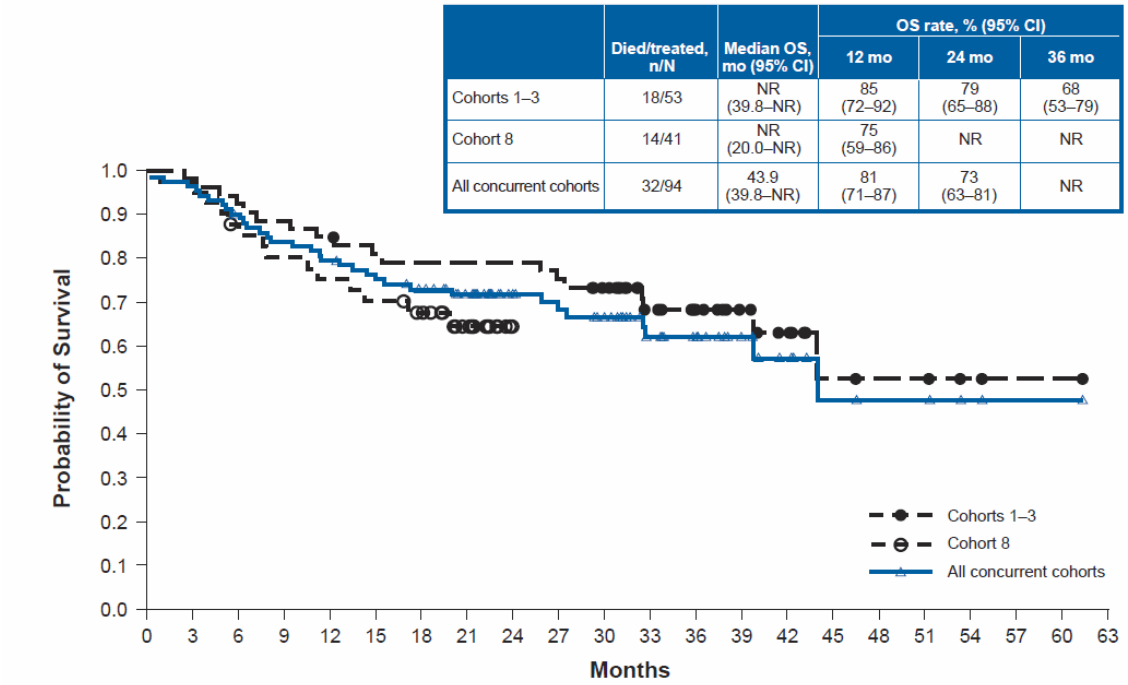
Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

Survival analysis

Analysis of OS showed 1-year, 2-year and 3-year survival rates of 85%, 79% and 68% respectively in cohorts 1 to 3 and a 1-year survival rate of 75% in cohort 8.[163]These survival rates are unprecedented and even within the limitations of a Phase I trial, extraordinary in consideration of the 22% 3-year survival rate previously associated with immunotherapy (ipilimumab monotherapy).[11]

The KM curves for OS are presented in Figure 36.

Figure 36: KM curves for OS in CheckMate 004



	Died/treated, n/N	Median OS, mo (95% CI)	OS rate, % (95% CI)		
			12 mo	24 mo	36 mo
Cohorts 1–3	18/53	NR (39.8–NR)	85 (72–92)	79 (65–88)	68 (53–79)
Cohort 8	14/41	NR (20.0–NR)	75 (59–86)	NR	NR
All concurrent cohorts	32/94	43.9 (39.8–NR)	81 (71–87)	73 (63–81)	NR

Number of Patients at Risk

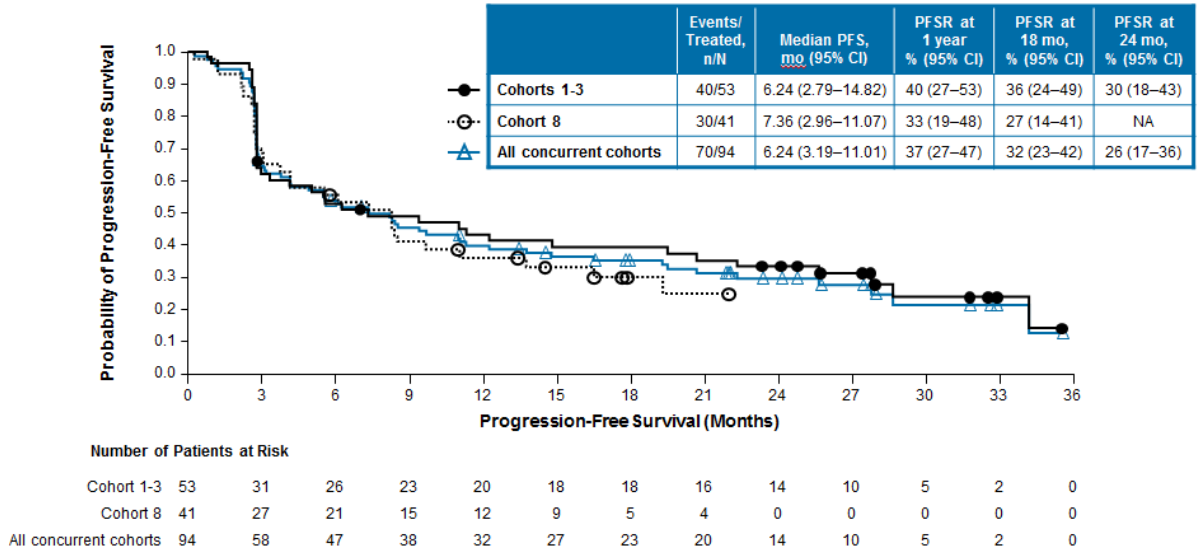
Cohorts 1–3	53	52	49	47	45	42	41	41	41	39	35	26	21	14	10	5	4	4	2	1	1	0
Cohort 8	41	40	35	32	30	28	25	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0
All concurrent cohorts	94	92	84	79	75	70	66	58	41	39	35	26	21	14	10	5	4	4	2	1	1	0

Key: CI, confidence interval; KM, Kaplan-Meier; NR; not reached; OS; overall survival.
Source: Sznol et al. 2015.[163]

Analysis of PFS showed a median PFS of 6.2 months in patients treated with concurrent nivolumab and ipilimumab therapy (cohorts 1 to 3) and a median PFS of 7.4 months in patients treated with the Regimen.

The KM curves for PFS are presented in Figure 37.

Figure 37: KM curves for PFS in CheckMate 004



Key: CI, confidence interval; KM, Kaplan-Meier; NA; not available; PFS; progression-free survival.
Source: Data on file

Response analysis

Response assessment by mWHO demonstrated an ORR of 42% in the dose-escalation concurrent nivolumab and ipilimumab groups (cohorts 1-3) and an ORR of 44% in the Regimen group (cohort 8).[163]

Response analysis from CheckMate 004 is summarised in Table 38.

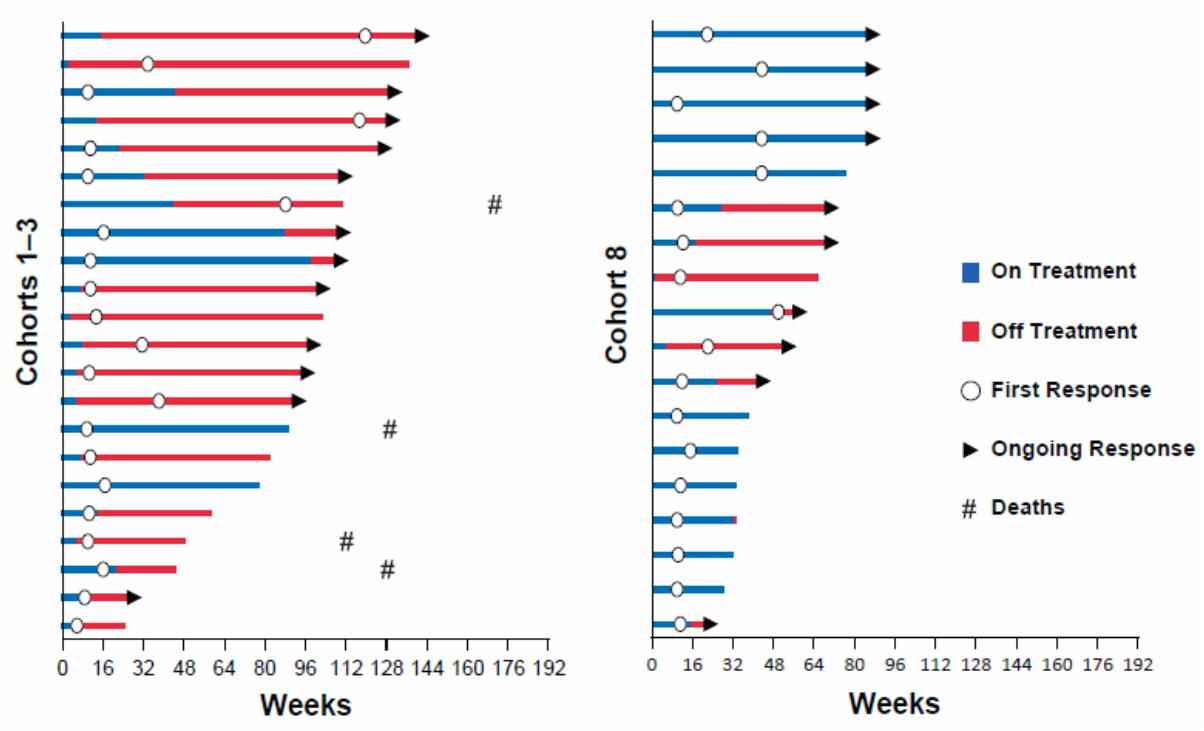
Table 38: Summary of response with concurrent treatment in CheckMate 004

	Cohorts 1-3 (n=53)	**Cohort 8 (n=41)**
Objective response rate[a]		
Responders, n (%)	22 (42)	18 (44)
Best overall response		

CR[b], n (%)	11 (21)	7 (17)
Duration of response		
Median months (95% CI)	22.3 (12.1, not reached)	13.8 (5.6, not reached)
Key: CI, confidence interval; CR, complete response; PR, partial response. **Notes**: [a], confirmed response (CR + PR) as per mWHO criteria; b, confirmed response as per mWHO criteria plus unconfirmed response as per mWHO criteria plus immune CR and immune PR as per irRC criteria. **Source**: Sznol et al. 2015.[163]		

Median duration of response was 22.3 months in cohorts 1-3 and 13.8 months in cohort 8 but many patients had an ongoing response at the time of analysis (12/22 [55%] of responders in cohorts 1-3 and 10/18 [56%] of responders in cohort 8). Importantly, responses were durable despite discontinuation of study treatment, as presented in Figure 38.

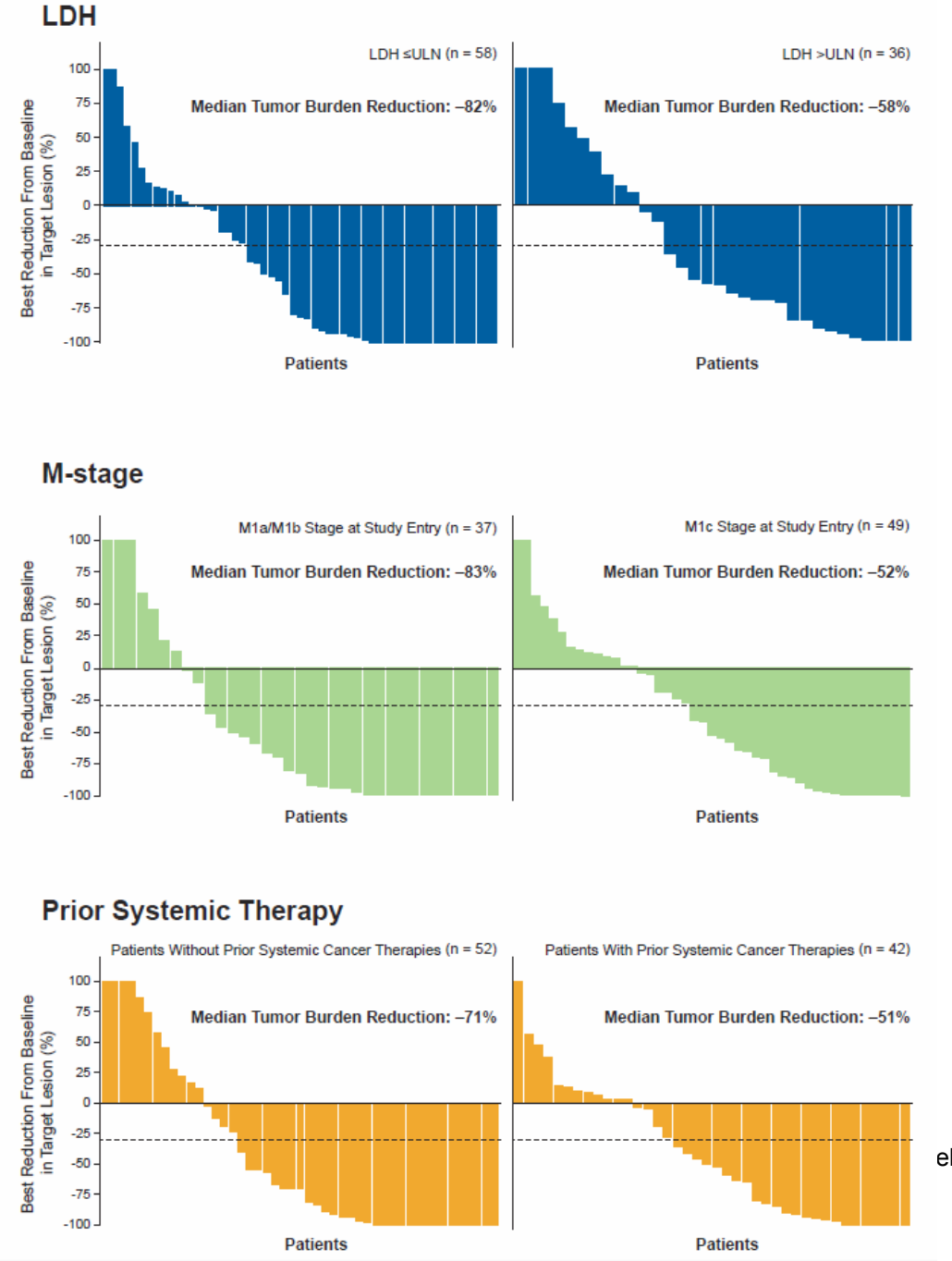
Figure 38: Swimmer plot of response duration in CheckMate 004, ongoing responders analysis set



Source: Sznol et al. 2015.[163]

High response rates and durable tumour responses were observed irrespective of baseline prognosis with a median reduction in tumour burden of at least 50% regardless of baseline LDH, metastatic stage and treatment history, as presented in Figure 39.

Figure 39: Waterfall plot of best reduction from baseline in sum of diameters of target lesions in CheckMate 004, response-evaluable analysis set


LDH
LDH ≤ULN (n = 58)
Median Tumor Burden Reduction: –82%
LDH >ULN (n = 36)
Median Tumor Burden Reduction: –58%
Best Reduction From Baseline in Target Lesion (%)
100
75
50
25
0
-25
-50
-75
-100
Patients
Patients
M-stage
M1a/M1b Stage at Study Entry (n = 37)
Median Tumor Burden Reduction: –83%
M1c Stage at Study Entry (n = 49)
Median Tumor Burden Reduction: –52%
Best Reduction From Baseline in Target Lesion (%)
Patients
Patients
Prior Systemic Therapy
Patients Without Prior Systemic Cancer Therapies (n = 52)
Median Tumor Burden Reduction: –71%
Patients With Prior Systemic Cancer Therapies (n = 42)
Median Tumor Burden Reduction: –51%
Best Reduction From Baseline in Target Lesion (%)
Patients
Patients

Source: Sznol et al. 2015.[163]

Retrospective analysis intended to establish a relationship between tumour shrinkage and OS has been conducted using data from CheckMate 004; this is of particular interest to the decision problem in consideration of the absence of mature survival data. This exploratory analysis suggests that there is an association between the extent of tumour shrinkage and OS with the risk of death increasing with lower percentage tumour shrinkage at Week 8. [164]

4.12 Adverse reactions

Summary

- The Regimen demonstrates a predictable safety profile consistent with the mechanisms of actions of nivolumab and ipilimumab
- The Regimen was well tolerated under controlled settings with few serious complications:
    - No deaths attributed to treatment with the Regimen in pivotal Phase III trial Checkmate 067
    - In Phase II Checkmate 069 study three deaths were considered to be related to the Regimen
- Study drug toxicity often managed through discontinuation of study drug, but importantly this did not appear to impact clinical benefit (see Section 4.7):
    - Median duration of treatment with the Regimen did not exceed 28.0 weeks across trials (range 2.2 months to 28.0 weeks)
    - Discontinuations due to TRAEs reported in over twice as many patients treated with the Regimen compared with ipilimumab monotherapy:
        - CheckMate 067: 36.4% vs 14.8%
        - CheckMate 069: 46.8% vs 17.4%
- Immune-related adverse events were more common with the Regimen but were generally reversible in line with established safety algorithms:
    - Frequently reported TRAEs in patients treated with the Regimen or ipilimumab monotherapy included diarrhoea, fatigue, pruritus and rash
    - Select AEs in the endocrine, hepatic and skin organ categories were particularly increased with the Regimen:
        - CheckMate 067: endocrine events, 33.5% vs 12.2%; hepatic events, 33.5% vs 10.9%
        - CheckMate 069: endocrine events, 34.0% vs. 17.4%; hepatic events, 27.7% vs 4.3%; skin events, 71.3% vs 56.5%
    - Resolution rates for Select AEs in patients treated with the Regimen were ≥70% for all organ categories with the exception of the endocrine category
    - Aside from the endocrine Select AE category, median time to resolution of Select AEs associated with the Regimen rarely exceeded 10 weeks:
        - CheckMate 067: time to resolution ranged from 0.3 to 9.9 weeks
        - CheckMate 069: time to resolution ranged from 0.4 to 18.6 weeks
    - Grade 3-4 Select AEs were only reported by >10% of patients treated with the Regimen in the hepatic and gastrointestinal categories
- Side effect profile consistent regardless of prognosis (age, metastases stage

Apart from those studies presented in Sections 4.2 and 4.11, no other studies investigate the Regimen; safety data are therefore only presented from CheckMate 067, CheckMate 069 and CheckMate 004.

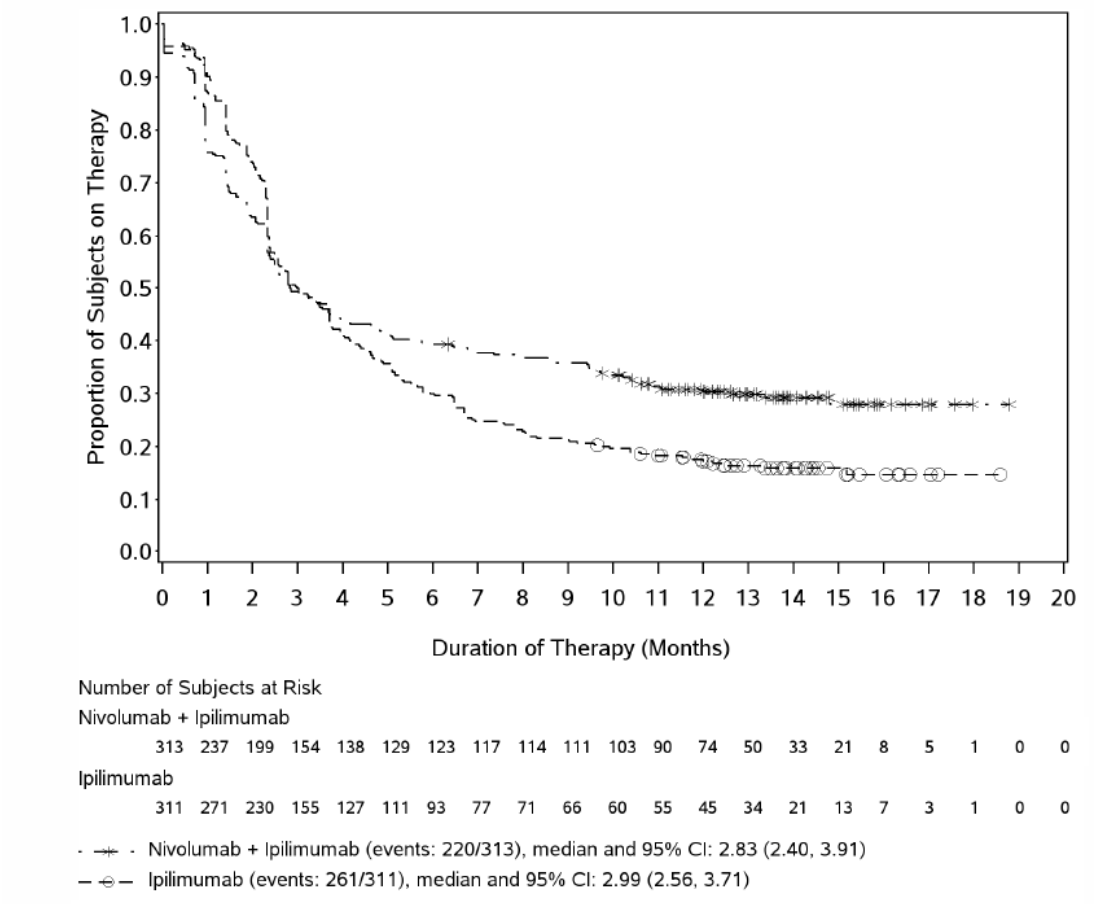
Treatment exposure

CheckMate 067

Of the 314 patients randomised to the Regimen in CheckMate 067, 313 received at least one dose of therapy.[10, 93] The median number of doses received was 4 (of both nivolumab and ipilimumab) with 147/313 (47%) patients receiving more than 4 doses of nivolumab and 57.2% of patients receiving all 4 doses of ipilimumab. Median duration of study therapy was 2.8 months (95% CI, 2.4 to 3.9) making the clinical benefit associated with this treatment regimen even more remarkable; that is, patients treated with the Regimen in CheckMate 067 lived without disease progression for nearly 12 months having received treatment for just under 3 months on average.

Of the 315 patients randomised to ipilimumab monotherapy, 311 received at least one dose. The median number of doses received was 4 and the median duration of study therapy was 3.0 months (95% CI, 2.6 to 3.7). In total, 69.8% of patients received all 4 doses of ipilimumab. The KM curve for time on treatment is presented in Figure 40.

Figure 40: Kaplan-Meier curve for time-on-treatment in CheckMate 067, safety analysis set



Key: CI, confidence interval.
Notes: symbols represent censored observations.
Source: CheckMate 067 CSR.[93]

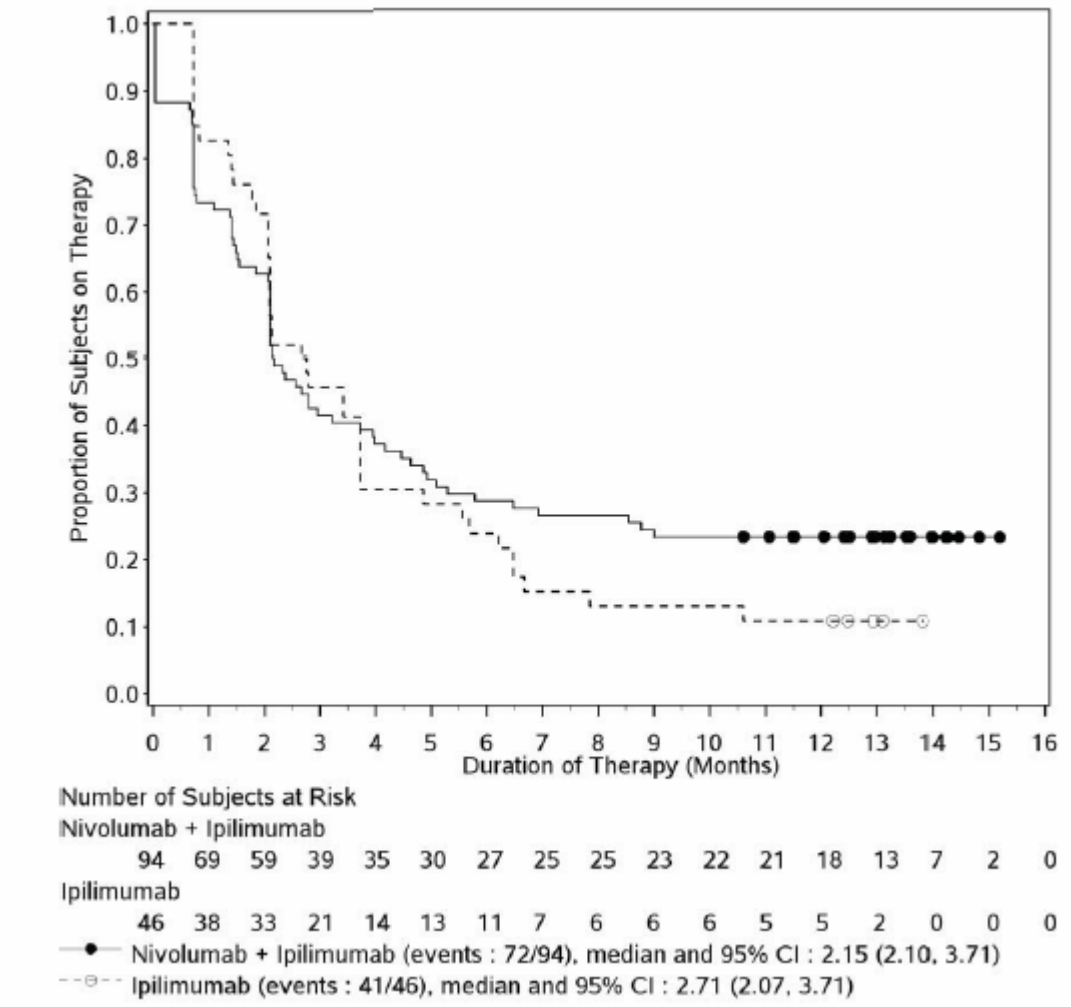
CheckMate 069

Of the 95 patients randomised to the Regimen in CheckMate 069, 94 received at least one dose of therapy; 71 of whom had BRAF mutation-negative melanoma.[85, 96] The median number of doses received was 4 (of both nivolumab and ipilimumab) with 38/94 (40.4%) patients received more than 4 doses of nivolumab and 57.4% of patients received all 4 doses of ipilimumab. Median duration of study therapy was 2.2 months (95% CI, 2.1 to 3.7) (all treated and BRAF mutation-negative patients).

Of the 47 patients randomised to ipilimumab, 46 received at least one dose of therapy; 37 of whom had BRAF mutation-negative melanoma. The median number of doses received was 4 and the median duration of study therapy was 2.7 months (95% CI, 2.1 to 3.7) (all treated and BRAF mutation-negative patients). In total, 69.6% of patients received all 4 doses of ipilimumab.

The KM curve for time on treatment is presented in Figure 41.

Figure 41: Kaplan-Meier curve for time-on-treatment in CheckMate 069, safety analysis set



Key: CI, confidence interval.
Notes: symbols represent censored observations; excludes exposure data collected in crossover patients.
Source: CheckMate 069 CSR.[96]

CheckMate 004

In cohorts 1-3 of CheckMate 004, median duration of therapy was 23.9 weeks and 13.0 weeks for nivolumab and ipilimumab, respectively.[161] Of the 41 patients treated with the Regimen (cohort 8), median duration of therapy was 28.0 weeks and 11.9 weeks for nivolumab and ipilimumab, respectively.

Again, it is important to consider these treatment exposure times alongside the clinical efficacy profile as it makes the survival benefit even more extraordinary; that is, median treatment duration of approximately 6 months resulted in a 3-year survival rate of 68% (cohorts 1 to 3), compared with the 22% 3-year survival rate previously associated with immuno-oncology therapy [ipilimumab monotherapy][11].

Safety profile

In general, the safety profile of the Regimen was consistent with the mechanisms of action of nivolumab and ipilimumab monotherapy. No new safety signals were identified and AEs were manageable with established treatment guidelines suggesting this combination regimen can be well tolerated under controlled settings.

CheckMate 067

All causality AE rates were similar in both treatment groups with the majority of patients experiencing at least one AE of any grade.[10, 93] Treatment related adverse events (TRAE) rates, serious adverse event (SAE) rates, treatment related serious adverse event (TRSAE) rates were higher with the Regimen. Discontinuation rates due to AEs (all causality and treatment related) were also higher in the Regimen group; importantly, this did not appear to impact clinical benefit (see Section 4.7).

One death in the ipilimumab monotherapy group was reported by the investigators as being due to study drug toxicity (cardiac arrest); no deaths were considered to be related to treatment in the Regimen group.

Summary safety data are presented in Table 39.

Table 39: Summary of safety data from CheckMate 067, safety analysis set

	Nivolumab plus ipilimumab (n=313)		**Ipilimumab (n=311)**	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All AEs, n (%)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
TRAEs, n (%)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
All SAEs, n (%)	217 (69.3)	159 (50.8)	162 (52.1)	119 (38.3)
TRSAEs, n (%)	150 (47.9)	112 (35.8)	69 (22.2)	51 (16.4)

	Nivolumab plus ipilimumab (n=313)		Ipilimumab (n=311)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
DC due to AEs, n (%)	135 (43.1)	105 (33.5)	70 (22.5)	62 (19.9)
DC due to TRAEs, n (%)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)
Deaths relating to study drug, n	0		1	

Key: AE, adverse event; DC, discontinuation; SAE, serious adverse event; TRAE, treatment related adverse event; TRSAE, treatment related serious adverse event.
Source: Larkin et al. 2015[10]; CheckMate 067 CSR.[93]

The most common TRAEs in the Regimen group and the ipilimumab group were diarrhoea (44.1% and 33.1%), fatigue (35.1% and 28.0%) and pruritus (33.2% and 35.4%). Diarrhoea and colitis were the most common TRAEs that led to discontinuation of the study drug.

With the Regimen, the following TRSAEs were reported with a frequency ≥2%: diarrhoea (9.3%), colitis (9.3%), pyrexia (3.8%), increased transaminases (2.6%), nausea (2.2%) and hypophysitis (2.2%). In the ipilimumab monotherapy group, colitis (9.0%), diarrhoea (7.1%) and hypophysitis (2.6%) were reported in ≥2% of patients.

In both treatment groups, a similar incidence was observed for SAEs (all causality and treatment related) reported within 100 days of last dose compared to those reported within 30 days of last dose.

Select AEs, defined as AEs with a potential immunological cause, were analysed according to organ category (skin, gastrointestinal, endocrine, pulmonary, hepatic, and renal) as in previous studies. The most frequent Select AEs occurred in the skin, gastrointestinal, endocrine and hepatic organ categories and were observed more frequently in the Regimen group.

Median time to onset of Select AEs did not exceed 12.1 weeks across organ categories (irrespective of Grade). Resolution rates for Select AEs were greater than 70% in the Regimen group for all organ categories with the exception of the endocrine category where events were not considered resolved in approximately 50% of patients at the time of analysis (February 2015). Aside from the endocrine Select AE category, median time to resolution of Select AEs was <10 weeks in the Regimen group.

Immune modulatory agents to manage AEs were used in 83.4% of patients in the Regimen group and 55.9% of patients in the ipilimumab group; secondary immunosuppressive agents were used in 6.1% and 5.1% of patients, respectively. Aside from the endocrine Select AE category, median time to resolution of Select AEs in patients who received immune modulating medication (IMM) did not exceed 9 weeks in the Regimen group. Select AEs in patients who received IMM were resolved in between 75 and 100% of patients in the Regimen group with the exception of Select AEs in the endocrine category; similar trends were observed in Grade 3-4 Select AEs analyses (data not shown).

Select AE data are summarised in Table 40.

Table 40: Select AE data from CheckMate 067, safety analysis set

	Nivolumab plus ipilimumab (n=313)		Ipilimumab (n=311)	
	All causality	**Drug related**	**All causality**	**Drug related**
Endocrine category				
All AEs, n (%)	105 (33.5)	94 (30.0)	38 (12.2)	34 (10.9)
Grade 3-4 AEs, n (%)	19 (6.1)	15 (4.8)	7 (2.3)	7 (2.3)
Resolution of event, n (%)[a]	53 (50.5)	51 (54.3)	15 (40.5)	13 (38.2)
Time to resolution, median weeks[a]	Not reached	Not reached	Not reached	Not reached
Resolution of event after treatment with IMM, n/N (%)[a]	14/37 (37.8)	14/34 (41.2)	4/15 (26.7)	4/14 (28.6)
Time to resolution with IMM, median weeks[a]	Not reached	Not reached	Not reached	Not reached
Gastrointestinal category				
All AEs, n (%)	171 (54.6)	145 (46.3)	150 (48.2)	114 (36.7)
Grade 3-4 AEs, n (%)	50 (16.0)	46 (14.7)	40 (12.9)	36 (11.6)
Resolution of event, n (%)[a]	162 (95.3)	138 (95.8)	134 (90.5)	102 (90.3)
Time to resolution, median weeks[a]	2.4	2.7	2.4	2.9
Resolution of event after treatment with IMM, n/N (%)[a]	61/65 (93.8)	62/66 (93.9)	43/49 (87.8)	44/50 (88.0)
Time to resolution with IMM, median weeks[a]	4.7	4.5	5.3	4.9
Hepatic category				
All AEs, n (%)	105 (33.5)	95 (30.4)	34 (10.9)	22 (7.1)
Grade 3-4 AEs, n (%)	62 (19.8)	60 (19.2)	14 (4.5)	5 (1.6)
Resolution of event, n (%)[a]	92 (87.6)	88 (92.6)	26 (76.5)	21 (95.5)

	Nivolumab plus ipilimumab (n=313)		Ipilimumab (n=311)	
	All causality	**Drug related**	**All causality**	**Drug related**
Time to resolution, median weeks[a]	5.3	5.0	4.3	4.2
Resolution of event after treatment with IMM, n/N (%)[a]	42/44 (95.5)	43/45 (95.6)	5/6 (83.3)	3/3 (100)
Time to resolution with IMM, median weeks[a]	5.7	5.9	8.1	4.1
Pulmonary category				
All AEs, n (%)	23 (7.3)	22 (7.0)	10 (3.2)	6 (1.9)
Grade 3-4 AEs, n (%)	4 (1.3)	3 (1.0)	2 (0.6)	1 (0.3)
Resolution of event, n (%)[a]	20 (87.0)	20 (90.9)	9 (90.0)	5 (83.3)
Time to resolution, median weeks[a]	7.0	6.7	4.6	6.3
Resolution of event after treatment with IMM, n/N (%)[a]	16/17 (94.1)	16/17 (94.1)	4/5 (80.0)	2/3 (66.7)
Time to resolution with IMM, median weeks[a]	6.1	6.1	6.0	6.1
Renal category				
All AEs, n (%)	32 (10.2)	17 (5.4)	14 (4.5)	8 (2.6)
Grade 3-4 AEs, n (%)	11 (3.5)	6 (1.9)	4 (1.3)	1 (0.3)
Resolution of event, n (%)[a]	26 (81.3)	15 (88.2)	14 (100)	8 (100)
Time to resolution, median weeks[a]	2.1	1.9	2.5	2.5
Resolution of event after treatment with IMM, n/N (%)[a]	3/3 (100)	3/3 (100)	4/4 (100)	3/3 (100)
Time to resolution with IMM, median weeks[a]	1.7	1.7	4.7	4.6
Skin category				

	Nivolumab plus ipilimumab (n=313)		Ipilimumab (n=311)	
	All causality	**Drug related**	**All causality**	**Drug related**
All AEs, n (%)	201 (64.2)	185 (59.1)	194 (62.4)	168 (54.0)
Grade 3-4 AEs, n (%)	19 (6.1)	18 (5.8)	12 (3.9)	9 (2.9)
Resolution of event, n (%)[a]	143 (71.5)	135 (73.0)	139 (71.6)	123 (73.2)
Time to resolution, median weeks[a]	9.9	9.4	12.1	11.0
Resolution of event after treatment with IMM, n/N (%)[a]	58/77 (75.3)	55/73 (75.3)	42/59 (71.2)	41/55 (74.5)
Time to resolution with IMM, median weeks[a]	9.0	8.6	12.9	12.4
Hypersensitivity/infusion reactions category				
All AEs, n (%)	14 (4.5)	13 (4.2)	9 (2.9)	8 (2.6)
Grade 3-4 AEs, n (%)	0	0	1 (0.3)	1 (0.3)
Resolution of event, n (%)[a]	12 (85.7)	11 (84.6)	9 (100)	8 (100)
Time to resolution, median weeks[a]	0.3	0.3	0.1	0.1
Resolution of event after treatment with IMM, n/N (%)[a]	1/1 (100)	1/1 (100)	2/2 (100)	1/1 (100)
Time to resolution with IMM, median weeks[a]	0.1	0.1	0.2	0.3

Key: AE, adverse event; IMM, immune modulating medication.
Notes: [a], any grade events.
Source: Larkin et al. 2015[10]; CheckMate 067 CSR.[93]

CheckMate 069

TRAE rates were similar in both treatment groups with approximately 90% of patients experiencing at least one TRAE of any grade.[85] Discontinuation rates due to TRAEs were higher in the Regimen group; importantly, this did not appear to impact clinical benefit (see Section 4.7).

Three deaths in the Regimen group were reported by the investigators as being related to study drug. One patient with a history of cardiac disease died from ventricular arrhythmia 29 days after the last dose of study treatment; the second died suddenly 69 days after the last dose of study treatment while clinically improving from pneumonitis and having an iatrogenic pneumothorax; the third patient died suddenly 86 days after the last dose of study treatment, 3 days after the resolution of Grade 3 pneumonia and Grade 4 hypercalcaemia. There were no deaths in the ipilimumab monotherapy group.

Summary safety data are presented in Table 41.

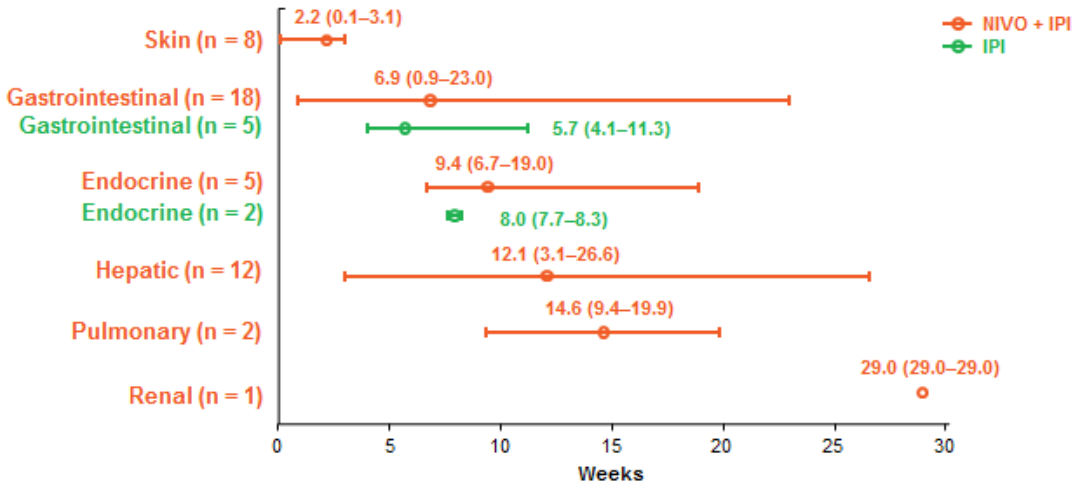
Table 41: Summary of safety data from CheckMate 069, safety analysis set

	Nivolumab plus ipilimumab (n=94)		**Ipilimumab (n=46)**	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
TRAEs, n (%)	86 (91.5)	51 (54.3)	43 (93.5)	11 (23.9)
Age <65 years, n/N (%)	43/48 (89.6)	26/48 (54.2)	19/19 (100)	5/19 (26.3)
Age ≥65 years, n/N (%)	43/46 (93.5)	24/46 (52.2)	24/27 (88.9)	4/27 (14.8)
M1c disease, n/N (%)	39/44 (88.6)	26/44 (59.1)	18/20 (90.0)	4/20 (20.0)
DC due to TRAEs, n (%)	44 (46.8)	36 (38.3)	8 (17.4)	6 (13.0)
Deaths relating to study drug, n (%)	3		0	
Key: AE, adverse event; DC, discontinuation; M1c, metastases stage 1c; TRAE, treatment-related adverse event. **Source:** Hodi et al. 2015[95]; Postow et al. 2015.[85]				

The most common TRAEs in the Regimen group and the ipilimumab group were diarrhoea (44.7% and 37.0%), rash (41.5% and 26.1%), fatigue (39% and 43%) and pruritus (35.1% and 28.3%). The most common Grade 3-4 TRAEs with the Regimen were colitis (17.0%), diarrhoea (10.6%) and elevated alanine aminotransferase (10.6%).

As was observed in CheckMate 067, Select AEs occurred most frequently in the skin, gastrointestinal, endocrine and hepatic organ categories and were observed more frequently in the Regimen group. Most Select AEs occurred during the concurrent period of treatment with the Regimen, as presented in Figure 42.

Figure 42: Time to onset of Grade 3-4 Select AEs in CheckMate 069, safety analysis set



Key: AE, adverse event; IPI, ipilimumab; NIVO + IPI, nivolumab plus ipilimumab
Source: Hodi et al. 2015.[95]

Immunosuppressive medications for the management of AEs, including topical agents for dermatologic AEs were used in 89% of patients in the Regimen group and 59% of patients in the ipilimumab group. Median time to resolution in patients who received IMM was not reached in the endocrine Select AE category but ranged from 0.4 to 18.6 weeks in all other Select AE categories (depending on organ). Grade 3-4 Select AEs in patients who received IMM were resolved in between 80 and 100% of patients in the Regimen group with the exception of Grade 3-4 Select AEs in the endocrine and pulmonary categories. There was a similar resolution rate across organ categories in both treatment groups.

Select AE data are summarised in Table 42.

Table 42: Select AE data from CheckMate 069, safety analysis set

	Nivolumab plus ipilimumab (n=94)		Ipilimumab (n=46)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
Endocrine category				
Events, n (%)	32 (34.0)	5 (5.3)	8 (17.4)	2 (4.3)
Resolution of event after treatment with IMM, n/N (%)	2/14 (14.3)	1/4 (25.0)	1/3(33.3)	1/2 (50.0)
Time to resolution, median weeks	Not reached	Not reached	Not reached	Not reached
Gastrointestinal category				
Events, n (%)	48 (51.1)	20 (21.3)	17 (37.0)	5 (10.9)
Resolution of event after treatment with IMM, n/N (%)	26/28 (92.9)	15/17 (88.2)	7/9 (77.8)	4/5 (80.0)
Time to resolution, median weeks	4.7	4.3	5.0	3.6
Hepatic category				
Events, n (%)	26 (27.7)	14 (14.9)	2 (4.3)	0
Resolution of event after treatment with IMM, n/N (%)	11/13 (84.6)	10/12 (83.3)	-	-
Time to resolution, median weeks	14.1	8.3	-	-
Pulmonary category				
Events, n (%)	11 (11.7)	3 (3.2)	2 (4.3)	1 (2.2)
Resolution of event after treatment with IMM, n/N (%)	6/8 (75.0)	2/3 (66.7)	2/2 (100)	1/1 (100)
Time to resolution, median weeks	6.1	9.0	3.2	3.6

	Nivolumab plus ipilimumab (n=94)		Ipilimumab (n=46)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
Renal category				
Events, n (%)	3 (3.2)	1 (1.1)	1 (2.2)	0
Resolution of event after treatment with IMM, n/N (%))	2/2 (100)	1/1 (100)	-	-
Time to resolution, median weeks	0.4	0.6	-	-
Skin category				
All AEs, n (%)	67 (71.3)	9 (9.6)	26 (56.5)	0
Resolution of event after treatment with IMM, n/N (%)	24/35 (68.6)	8/9 (88.9)	11/13 (84.6)	-
Time to resolution, median weeks	18.6	6.1	8.6	-
Key: AE, adverse event; IMM, immune modulating medication. **Source:** Postow et al. 2015.[85]				

More patients treated with the Regimen experienced Select AEs in more than one organ category, though only 8.5% of patients experienced Select AEs in multiple (more than two) organ categories, as summarised in Table 43.

Table 43: Grade 2-4 Select AEs across organ categories in CheckMate 069, safety analysis set

Number of organ categories	Nivolumab plus ipilimumab (n=94)	Ipilimumab (n=46)
0, n (%)	20 (21.3)	24 (52.2)
1, n (%)	44 (46.8)	19 (41.3)
2, n (%)	22 (23.4)	3 (6.5)
3, n (%)	7 (7.4)	0
>3, n (%)	1 (1.1)	0

Number of organ categories	Nivolumab plus ipilimumab (n=94)	Ipilimumab (n=46)
Key: AE, adverse event. **Source:** Hodi et al. 2015.[95]		

CheckMate 004

As anticipated a priori, there were fewer Grade 3-4 AEs, SAEs (all causality and treatment related), Grade 3-4 SAEs and AEs leading to discontinuation in the lowest dose cohort of CheckMate 004 (cohort 1) compared with the higher dose escalation cohorts. This is because the higher dose escalation cohort (3mg/kg nivolumab plus 3mg/kg ipilimumab) exceeded the maximum tolerated dose (MTD).

The safety profile observed in cohort 8 was similar to that observed in RCTs; most patients experienced a TRAE but the nature of events was consistent with the mechanisms of action of nivolumab and ipilimumab.

4.13 Interpretation of clinical effectiveness and safety evidence

Despite significant and continued advances in melanoma treatments in recent years, durable response and long-term survival remains elusive for a broad range of melanoma patients.

Nivolumab plus ipilimumab therapy represents the next generation in immuno-oncology treatment and its introduction into the clinical pathway of care for advanced melanoma would benefit patients by offering the potential of longer-term survival than current treatments offer.

Principal findings from the clinical evidence

The clinical benefits and potential harms associated with the Regimen have been comprehensively demonstrated in an extensive clinical trial programme as summarised below:

The Regimen has demonstrated high rates of rapid and durable clinical response in a broad range of patients with advanced melanoma

Across clinical trials of concurrent nivolumab and ipilimumab therapy, ORR ranged from 40 to 60%. In comparative trials, ORR in patients treated with the Regimen at first-line was significantly superior to the ORR in patients treated with ipilimumab monotherapy ($p<0.001$). Depth of response was similarly superior with a median change in tumour burden of at least -50% associated with the Regimen (compared with at least +6% in patients treated with ipilimumab monotherapy).

In the majority of responders there was no suggestion of delayed response kinetics (previously associated with ipilimumab monotherapy) at the time of first scan. Furthermore, response continued to be observed despite patients discontinuing treatment due to reasons other than progressive disease such as study drug toxicity. This is an important consideration for clinical practice; as extending treatment-free intervals

delays the introduction of subsequent line of therapy and reduces the therapeutic burden to the patient, as well as lessening the demand on the health service.

The Regimen offers a long-term survival benefit to a broad range of patients with advanced melanoma

Treatment with the Regimen is expected to more than double the rate of long-term survival compared with ipilimumab monotherapy (see Section 5.3), representing a step-change in the management of this condition. Long-term survival estimates based on RCT data are supported by Phase II trial data that shows a 18-month OS rate of 69% associated with the Regimen, and with Phase I data that shows an unprecedented 3-year survival rate of 68% in patients treated with concurrent nivolumab and ipilimumab therapy (pooled analyses reports an 18-month and 3-year survival rate of 35% and 22%, respectively in patients treated with ipilimumab monotherapy).

Analyses of PFS similarly demonstrate the superior clinical benefit of the Regimen compared with ipilimumab monotherapy, reducing the risk of death or disease progression by over 50% ($p<0.001$). Furthermore, continued response to treatment has been observed despite discontinuation of the Regimen. In the ongoing Phase III trial, many patients have lived without disease progression for nearly a year having received treatment (on average) for less than 3 months and this is expected to increase with longer-term follow-up.

The Regimen has an established and predictable safety profile

The Regimen is associated with a predictable safety profile, reflective of its therapeutic class, and one which is familiar to clinicians using immuno-oncology therapy in advanced melanoma. In comparative trials, the Regimen was associated with higher rates of all-causality AEs and TRAEs including Select AEs of a potentially immunological cause compared with ipilimumab monotherapy. Specifically, Select AEs in the endocrine, hepatic and skin organ categories were increased with the Regimen and more patients experienced Select AEs in two or more organ categories. This additive toxicity was anticipated *a priori* due to the mechanistically different nature of nivolumab and ipilimumab.

Crucially, the majority of AEs experienced in patients treated with the Regimen were manageable using established safety algorithms; as a result, the median duration of Select AEs was short, rarely exceeding 10 weeks, and deaths due to study drug toxicity were rare across all clinical trials. The management of side effects associated with use of the Regimen is likely to continually improve as clinician familiarity with this regimen increases.

Whilst study drug toxicity often resulted in discontinuation of study drug, this did not appear to impact the clinical benefit of treatment with the Regimen. It is therefore important to consider the potential harms of therapy alongside the potential clinical benefits; it may be that clinicians and patients alike would consider a short term acute toxicity, that is medically manageable, worthwhile considering the potential long-term survival benefits.[3] In addition, Select AEs could be viewed as a positive sign in that they suggest the body's immune system is responding to treatment.

The Regimen did not result in clinically meaningful changes in patient quality of life

The Regimen did not result in clinically meaningful changes in EORTC QLQ-C30 or EQ-5D assessed HRQL and there were no significant differences in improvement or deterioration in HRQL from baseline compared with ipilimumab monotherapy in comparative trials. In general, a small deterioration in HRQL was observed during the concurrent treatment period (up to week 12) before returning to baseline levels with nivolumab maintenance. In patients who experienced a Grade 3-4 AE, HRQL was not markedly different between treatment groups suggesting the impact of additive toxicity with the Regimen on patient HRQL is limited.

Strengths and limitations of the clinical evidence

Overall, the clinical evidence available provides an appropriate base to inform the assessment of clinical-effectiveness and cost-effectiveness of the Regimen for the treatment of advanced melanoma in clinical practice.

Broad range of patients enrolled that is reflective of patient profiles in UK clinical practice

Taken together, the clinical evidence for the Regimen provides data for the broad range of patient groups diagnosed with advanced melanoma in clinical practice and are considered generalisable to UK practice. Importantly, consistently superior clinical benefit was observed across all pre-determined subgroups including those based on BRAF mutation status, treatment history and prognostic factors such as LDH levels and metastatic stage.

In the pivotal Phase III trial, European patients represented over half of the total study population, including 30 patients randomised to treatment with the Regimen in the UK. Furthermore, on consultation, clinical experts practising in the field of melanoma confirmed that these clinical trial populations are generally representative of patients presenting in UK clinical practice.[3]

Head to head trials provide comparative evidence to standard of care

Both CheckMate 067 and CheckMate 069 provide direct RCT evidence of the Regimen compared with ipilimumab monotherapy in previously untreated patients with advanced melanoma. Ipilimumab monotherapy is the current standard of care in UK clinical practice for both BRAF mutation-negative and BRAF mutation-positive advanced melanoma in the first-line setting (see Section 3.2).

Head-to-head clinical trial data are not available for comparisons outside of ipilimumab, therefore an indirect treatment comparison has been conducted to estimate comparative efficacy of the Regimen versus BRAF inhibitor therapy (the only other first-line treatment in the current clinical pathway of care). As with all indirect estimates, there is uncertainty associated with these analyses, but the approach taken was designed to minimise this uncertainty, despite the paucity of data available.

Trials are well designed with clinically relevant study endpoints

All clinical trials are being conducted in line with good clinical practice (GCP) guidelines with steps taken to minimise bias. In both CheckMate 067 and CheckMate 069, independent data monitoring committees were in place to provide oversight of safety and efficacy considerations, study conduct and risk-benefit ratio; a similar role is being played by an Early Development Advisory Committee in CheckMate 004.

The clinical trial programme for the Regimen was designed to capture the endpoints most relevant to advanced melanoma patients and clinicians alike, as well as to healthcare providers. They therefore not only include clinical efficacy and safety endpoints consistent with other studies of therapeutic agents in advanced melanoma, but also RCT endpoints including validated assessments of HRQL. In addition, the pivotal Phase III trial captures resource use to aid cost-effectiveness modelling (see Section 5.5).

Estimates of long-term benefit are clinically valid despite immaturity of survival data

The clinical trial programme supporting the use of the Regimen in advanced melanoma is ongoing and therefore some data are currently immature. Nonetheless, considering analyses are testing superiority rather than equivalence, under-powering of interim primary outcomes analyses should not influence interpretation of reported analyses.

The availability of survival data for the Regimen is particularly restricted with the pivotal Phase III trial yet to report OS. However, (as observed in the principal findings), Phase II and Phase I OS data indicate unprecedented OS benefit based upon up to 3-years of follow-up. In addition, the long-term clinical benefit of immuno-oncology therapy in advanced melanoma is well recognised since the introduction of ipilimumab monotherapy.

The significant PFS and response benefit demonstrated in these trials is also indicative of the long-term survival benefit that can be expected with the Regimen. A strong correlation between PFS and OS in metastatic melanoma is observed across RCTs, independent of treatment type[165], and there is consensus within the clinical community that extended PFS and improved response translates to extended OS in advanced melanoma.[3] Therefore, whilst there is an immaturity of data for the Regimen that adds uncertainty to estimates of its long-term benefit, the high degree of improved clinical benefit observed in clinical trial data available to date can only support the introduction of the Regimen into the clinical pathway of care for advanced melanoma.

End-of-life treatment considerations

The life expectancy of patients with advanced melanoma is historically poor (6-10 months with conventional chemotherapy [29, 31, 51, 53, 54]) and whilst this is expected to have improved with recent advances in melanoma therapeutics, a significant impact on median survival has yet to be confirmed. Ipilimumab monotherapy is the established standard of care in current UK clinical practice and whilst this treatment offers long-term survival to a proportion of patients, median survival estimates associated with this monotherapy do not exceed 13.5 months.[11]

Median survival estimates are not yet available for the Regimen but in-trial analyses of the most mature OS data available for the licensed dose demonstrates that the Regimen offers an extension to life of at least 3 months compared with ipilimumab monotherapy. This should be considered a conservative estimate of the extension to life given the high rate of crossover in the control arm of the CheckMate 069 study on which they are based (see Section 4.7).

The expected number of new cases and relapsed cases of advanced melanoma in England for 2016 is 1,577. This represents the maximum population who would potentially be eligible for treatment with the Regimen in accordance with its anticipated marketing authorisation and the decision problem.

Table 44: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median life expectancy: up to 13.5 months with established standard of care (9.5 to 13.5 months depending on data source, treatment history and dosing) Source: pooled analyses of key clinical trials and real world evidence[11]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	75% survival times[a]: Nivolumab plus ipilimumab: 341 days Ipilimumab: 220 days Between group difference: 121 days (4 months) Source: CheckMate 069 patient level data
The treatment is licensed or otherwise indicated for small patient populations	Advanced melanoma population for 2016: 1,577 (anticipated new cases and relapsed cases) Source: ONS population estimates for 2013[69] and melanoma incidence estimates for 2012[35] extrapolated using increased incidence rate of 3.5% previously used in melanoma submissions[55, 56, 58, 60] Advanced melanoma proportion based on reported epidemiology data (10%)[70-72] Patients requiring second- or subsequent-line therapy based on previous precedence in melanoma submissions (21%)[56]
Key: ONS, Office for National Statistics. **Notes**: [a], when a quarter of the patients have died.	

4.14 Ongoing studies

Additional evidence from trials presented in this submission to support the use of the Regimen for the treatment of advanced melanoma is likely to become available in the next 12 months, as summarised in Table 45.

[redacted] This document has been supplied to NICE under separate cover on a confidential basis.

Table 45: Data likely to be available in the next 12 months to further support the use of the Regimen for the treatment of advanced melanoma

Study	Additional evidence	Expected date of availability
CheckMate 067	Overall survival Progression-free survival; extended follow-up HRQL	Q4 2016 at the earliest
CheckMate 069	Overall survival	Q2 2016
Key: HRQL, health-related quality of life; Q2, quarter 2; Q4, quarter 4.		

5 Cost effectiveness

Summary

- A de novo economic decision model was developed based upon the model submitted for nivolumab monotherapy and the accepted model used within the recent ipilimumab STA submissions. The model structure captures the unique characteristics of immunotherapy, including nivolumab plus ipilimumab, for the treatment of advanced melanoma and facilitates the use of the best available efficacy, safety, HRQL and resource use data. The model:
    - Established the comparative efficacy of the Regimen and ipilimumab through the use of patient-level data analysis based on the head-to-head trials
    - Established the comparative efficacy of the Regimen and BRAF inhibitors through the use of covariate adjusted survival curves for nivolumab plus ipilimumab and published OS and PFS for BRAF inhibitors because the proportional hazard assumption does not hold
    - Utilised the results from trial-based utility and safety analyses and the most relevant resource use inputs based upon current UK clinical practice
- In line with expected UK practice and the previous nivolumab monotherapy submission, treatment with nivolumab within the Regimen arm is modelled to continue until the first of either loss of clinical benefit, unacceptable toxicity or 2 years of continuous treatment
- The structure and key assumptions of the decision model were validated by health economics experts, and the model estimations of OS and PFS were comparable to clinical data and expectation
- The cost-effectiveness results for ipilimumab compared to BRAF inhibitors are in line with published cost-effectiveness literature
- The analyses were performed and the results were presented for BRAF mutation-negative and BRAF mutation-positive patients separately due to differing patient characteristics and relevant comparators
- The analyses show that the Regimen is cost effective versus all comparators both with and without the inclusion of a PAS for the comparator technologies
- At the threshold of £30,000, the probabilities of nivolumab being most cost effective are 100% and 100% for BRAF mutation-negative and BRAF mutation-positive patients, respectively
- Extensive sensitivity and scenario analyses demonstrated that the base case results are robust to uncertainties of key model parameters and assumptions

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

In line with the NICE methods guide, two separate systematic reviews were conducted to identify cost-effectiveness studies for the treatment of advanced melanoma with nivolumab and ipilimumab. The first systematic review was conducted in November 2014 for the nivolumab monotherapy NICE submission (ID845).[154] An update to this systematic review was conducted using the same methods and process (apart from the span of the search period) as the first review in October 2015 to identify more recent literature. The detailed search strategy is presented in Appendix 10.

To ensure that the literature was comprehensively reviewed, a wide range of databases were searched for the two systematic reviews: MEDLINE, EMBASE, ECONLIT, NHS EED, CDSR, HTA, DARE and CINAHL. In addition to the formal electronic searches, reference lists of included cost-effectiveness studies identified were hand searched and scanned for additional publications of relevance to the research question.

After identifying the studies, the titles and abstracts were reviewed in greater detail and their relevance for informing the overall decision problem was assessed. Table 46 shows the eligibility criteria used for assessing the relevance of the different studies.

Following a detailed review of the title and abstract, the papers that met the inclusion criteria were obtained for a secondary review. This secondary review involved the entire article being assessed according to the eligibility criteria outlined in Table 46.

Table 46: Eligibility criteria for economic evaluation publications and rationale for each criterion

Inclusion criteria		
Category	**Inclusion criteria**	**Rationale**
Study type	Full economic evaluation (including cost-consequence, cost-minimisations, cost-effectiveness, cost-utility and cost-benefit evaluations) that compares nivolumab to any comparator(s)	The aim of the review was to identify relevant economic evaluations.
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population.
Interventions	The intervention of interest is nivolumab or nivolumab in combination with ipilimumab	This is the relevant intervention.
Comparators	No restriction to comparators	To allow all relevant papers to be identified.
Outcomes	Incremental costs and QALYs; any other measure of effectiveness reported together with costs	The aim of the review was to identify relevant economic evaluations, which reported costs.

Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed, and the study's data and results must be extractable	Only studies that provided extractable data and results were usable.
Exclusion criteria		
Category	Exclusion criteria	Rationale
Publication year	Studies before 1970	The earliest melanoma trial was published in 1972.
Language	Non-English language literature	Time and resource required for translation and relevance for UK setting.
Publication type	Letters, editorials and review studies	Primary study articles are required.
Key: QALY, quality-adjusted life year; UK, United Kingdom.		

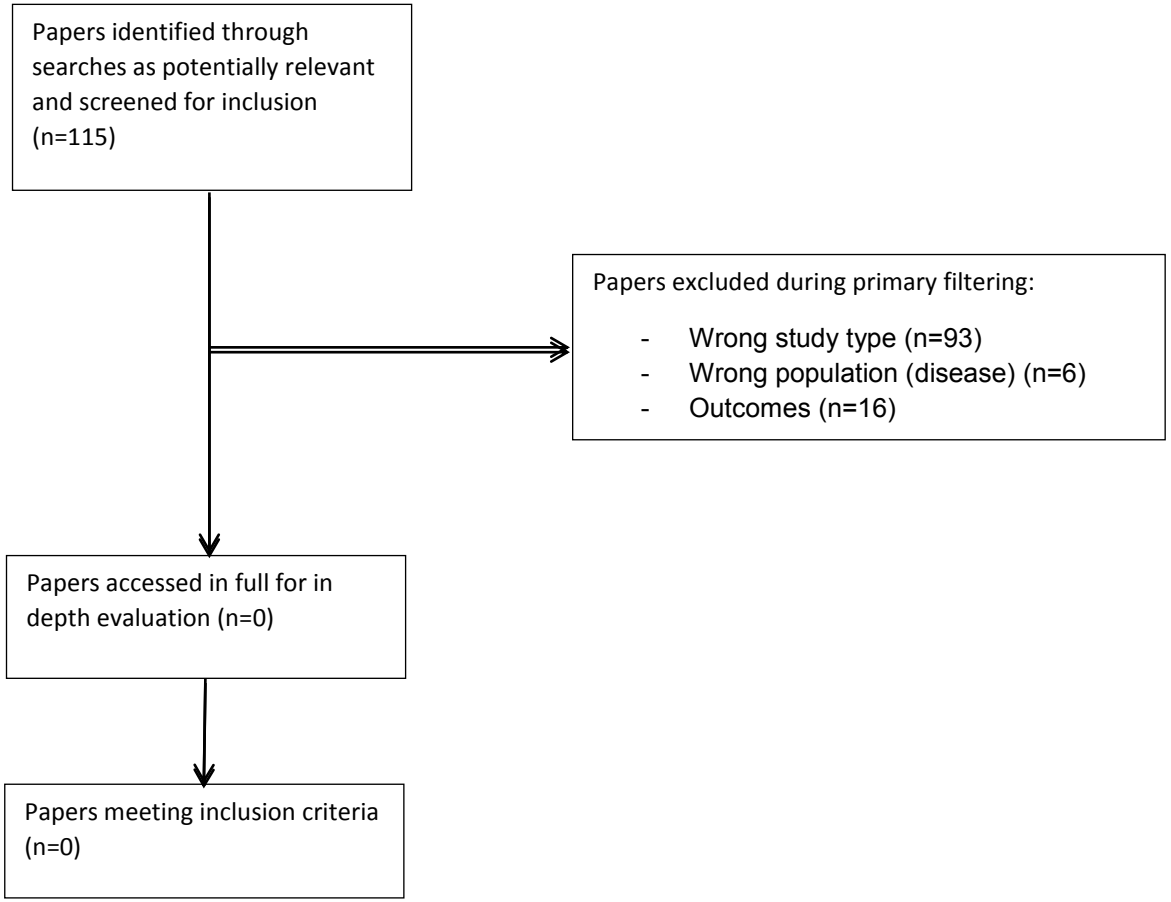
5.1.2 Description of identified studies

For the systematic review update performed in October 2015, 115 studies were identified and all of these studies were excluded during primary filtering (references available upon request), as illustrated in Figure 43. The main reason for exclusion was on the basis of study type (93 out of 115 papers). Other papers were excluded on the basis of patient population and outcomes.

For the first systematic review which was conducted in November 2014, 140 studies were identified and 139 were excluded during primary filtering (references available upon request). One study remained for secondary filtering, but following assessment of the whole paper, this study was also excluded on the basis of study type (i.e. not a full economic evaluation). Consequently no studies were identified that met all the eligibility criteria for the first systematic review.

A de novo cost-effectiveness model was therefore developed as no economic evaluations were identified that compared the Regimen with other comparators.

Figure 43: Identification of economic evaluations relevant to the decision problem



5.2 De novo analysis

5.2.1 Patient population

The proposed indication for the Regimen in the EU is "for the treatment of adult patients with advanced (unresectable or metastatic) melanoma."[166] The indication for the Regimen is not expected to be restricted by BRAF status or line of treatment (e.g. treatment naïve/first-line, pre-treated/subsequent-lines).

As stated in Section 3, the majority of patients in the UK will undergo a molecular analysis of their tumour to determine the mutational status of the BRAF V600 gene, to identify those suitable for treatment with BRAF inhibitors (e.g. dabrafenib and vemurafenib). BRAF mutation-positive patients have two options for first-line treatment: ipilimumab or a BRAF inhibitor, with selection dependent upon patient characteristics. BRAF mutation-negative patients receive ipilimumab for first-line treatment.

Consequently, patients in the cost-effectiveness model are divided into two sub-populations:

- BRAF mutation-positive patients, eligible for first-line treatment with ipilimumab, dabrafenib or vemurafenib.
- BRAF mutation-negative patients, eligible for first-line treatment with ipilimumab.

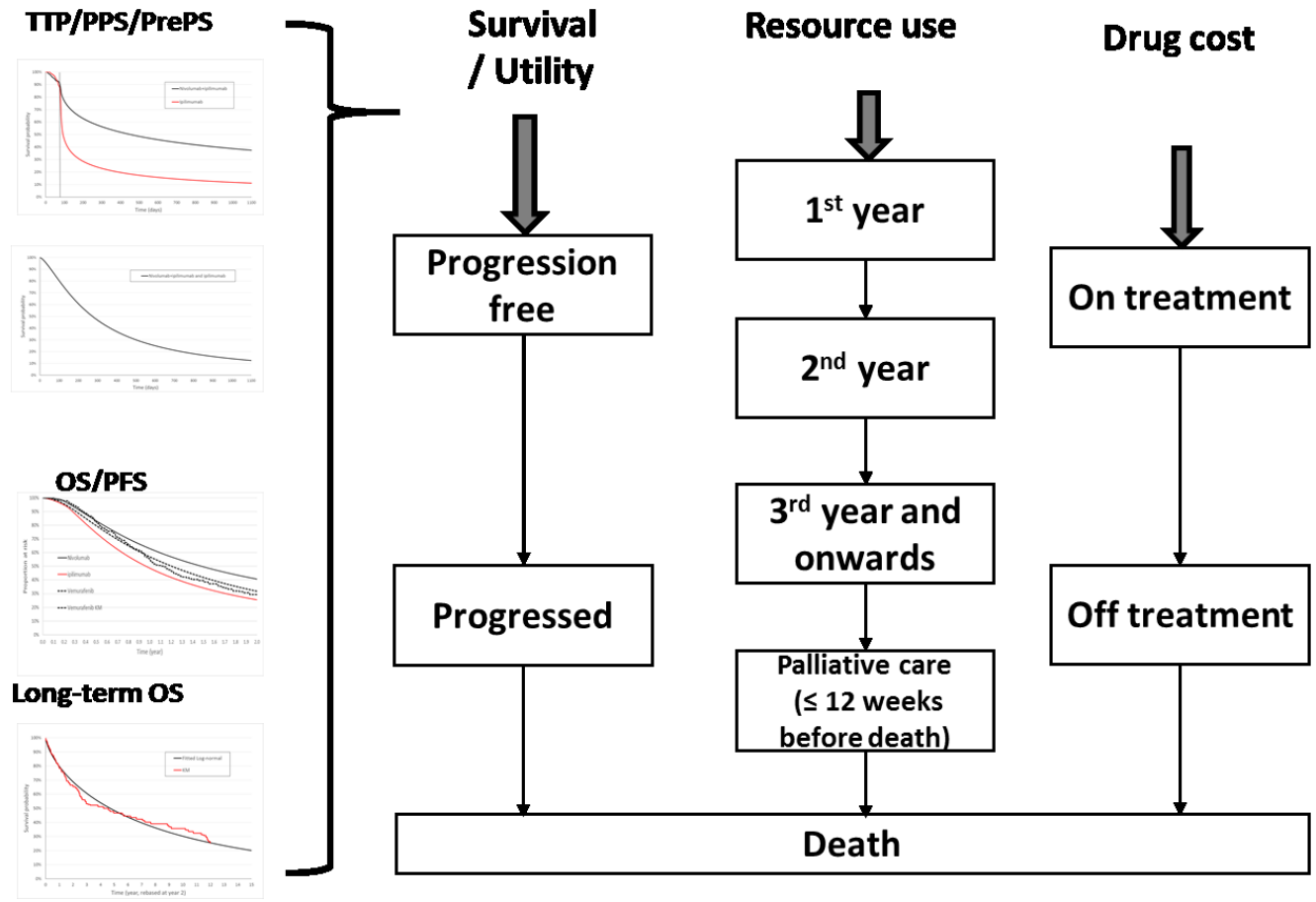
The base case model was developed for all lines of therapy based upon the available evidence for first-line treatment. This is supported by published evidence that demonstrates no independent impact of line of therapy on outcomes.[29, 55] The patient groups are defined in line with the scope and decision problem for this appraisal with the exception that pembrolizumab is not included within the model for the reasons described previously.

5.2.2 Model structure

A de novo semi-Markov survival model was developed based upon the model submitted and accepted for the nivolumab monotherapy NICE submission (ID845) [154], where health-states were defined by three different measures relevant to the evaluation of the clinical effectiveness and cost effectiveness of the Regimen compared to its comparators (see Figure 44 for a simplified model structure):

- Progression status for modelling survival and utility (3 states): progression-free, progressed and dead.
- Time since treatment initiation and time to death for modelling resource use (4 states): first year after treatment initiation; second year after treatment initiation, third and subsequent years after treatment initiation, 12 weeks before death (palliative care) and death.
- Treatment status for modelling drug cost and adverse events (2 states): on treatment and off treatment.

The same overall model structure is applied to all treatments within both the BRAF mutation-positive and BRAF mutation-negative patient subgroups. Figure 44: Economic model structure (simplified)



Key: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival; TOT, time on treatment; TTP, time to progression.

Structure for modelling survival

For the Regimen and ipilimumab, a Markov state-transition method was applied to estimate the proportion of patients in the progression-free, progressed and death states in each Markov cycle (1 week) using time to progression (TTP), post-progression survival (PPS) and pre-progression survival (PrePS). Conceptually, the Markov state-transition method first estimates survival by first calculating the time to progression using TTP and then calculating the time from progression to death using PPS; to account for death events in the trial where progression is censored (i.e. the patient dies before progression is observed), the method also uses PrePS to estimate time to death directly.

The state-transition method is a standard approach for modelling survival and has been used in previous NICE appraisals.[167-169] It was also deemed appropriate for the decision problem by UK health economics and clinical experts during validation meetings.[2]

An advantage of the state-transition method is that when OS data is not available or immature (which is the case for this analysis for the Regimen arm), the method can be flexible to use separate data sources for estimating PPS. In another word, PrePS and TTP can be estimated based on the pivotal trial with large sample size and mature PFS; while PPS can be estimated based on earlier longer follow-up trials or observational studies if OS from the pivotal trial and other trials are not available or immature. This analysis has used this advantage of the state-transition method to estimate PrePS and TTP from the pivotal phase III CheckMate 067 trial which has the largest sample size for the Regimen and ipilimumab arms (N=629) among all relevant trials and the most robust PFS data; and to estimate PPS from previous nivolumab (CheckMate 066) and ipilimumab (MDX010-020) trials because no OS is available from the pivotal CheckMate 067 trial and OS is too immature within CheckMate 069 for it to be used for fitting statistical models.

Therefore, for the Regimen and ipilimumab, parametric curves for TTP and PrePS were fitted based on a covariate-adjusted statistical model using patient level data from CheckMate 067 (the Regimen and ipilimumab).

Regarding PPS, due to the absence of OS from CheckMate 067 and immature OS from CheckMate 069, parametric curves for the Regimen and ipilimumab arms were fitted based on a covariate-adjusted statistical model using patient level data from the nivolumab arm of CheckMate 066 (latest datacut available in July 2015 with up to 28 months OS follow up) and ipilimumab arm of MDX010-020 (up to 4.5 year OS follow up and at the approved monotherapy dose of 3mg/kg). In order to apply the PPS estimated from the nivolumab and ipilimumab OS data, it is conservatively assumed that after controlling for differences in patient characteristics (i.e., age, gender, melanoma staging, ECOG status, LDH level, brain metastatic and subsequent ipilimumab use), the PPS is the same among all immunotherapies including nivolumab, ipilimumab and the Regimen. Similar PPS for nivolumab and ipilimumab were estimated in the previous nivolumab monotherapy submission[154], which supports the assumption of similar or improved PPS for nivolumab compared to ipilimumab. UK clinicians also support a conservative assumption of similar PPS projections for all immunotherapies including the Regimen.[3] Please see Section 4.13 for more details on the rationale, assumptions, methods and results of the analysis.

Patient level data were not available for the BRAF inhibitor comparisons. For BRAF mutation-positive patients only, survival with dabrafenib and vemurafenib was therefore modelled based upon parametric curves fitted on trial-based empirical OS and PFS using digitised data, which were used to derive the proportions of patients in the progression-free, progressed and death states in each Markov cycle using the area under the curve method (see Section 5.3.3 for detailed parametric curves fitted for OS and PFS for BRAF inhibitors). This method was used as data were not available for TTP, PPS and PrePS. In the model base case, the same survival efficacies (OS and PFS) are assumed for dabrafenib and vemurafenib based on the NICE appraisal for dabrafenib (TA321[60]), which concluded that “It was likely that dabrafenib and vemurafenib did not differ in clinical effectiveness and that it

would not be unreasonable to assume that they have similar effect". The safety, drug price and resource use are still modelled separately for dabrafenib and vemurafenib. For comparability, patient characteristics based on the BRAF inhibitor trials were applied to the covariate-adjusted models from the indirect comparison analysis to estimate TTP, PPS and PrePS, and thus, the OS and PFS, for nivolumab and ipilimumab for the BRAF mutation-positive patient subgroup. A standard mixed treatment comparison between dabrafenib/vemurafenib with immunotherapies (e.g. ipilimumab) using published aggregate data is not recommended, as discussed and accepted in the recent nivolumab monotherapy (ID845[154]) and ipilimumab (TA319[55]) NICE appraisals, with the main reasons being:

- Non proportional hazards between BRAF inhibitors and immunotherapies due to their differing mechanisms of action.
- High levels of crossover and subsequent ipilimumab use in the BRAF inhibitor trials.[67, 68, 133]

The survival methods outlined above are applied within the first 3 years of the model for all treatments in the base case. The 3-year cut-off was chosen because: a) the maximum follow-up period for the CheckMate 067 trial is around 18 months, and therefore, long-term extrapolation of TTP and PrePS and subsequently OS (which is estimated conditional on progression in the state-transition model) for the Regimen and ipilimumab are subject to greater uncertainty; b) recent published long-term pooled ipilimumab study showed a plateau in the OS beginning around Year 3[11] and this is assumed for immunotherapies including the Regimen and ipilimumab from Year 3 onwards. Given the uncertainty and methodological difficulty of extrapolating trial-based parametric curves beyond the trial follow-up period, alternative sources for long-term survival are used for the extrapolation of long-term OS for all treatment arms. These include the use of melanoma registry data[170] (from Year 3 onwards for BRAF inhibitors in the base case), long-term ipilimumab OS data[11] (from Year 3 onwards for the Regimen and ipilimumab in the base case), and general UK population mortality as background mortality.

For TTP, the KM data were used for the first 84 days due to the trial protocol effect where the first tumour assessments were performed at week 7 in CheckMate 067 (Section 4.13). For PrePS, although parametric curves were fitted, the curves did not pass visual validity check when compared with observed data, potentially due to the trial protocol effect and small number of events for PrePS compared to TTP. Therefore, similar to TTP, the KM data were used for PrePS in the base case (Section 4.13).

Structure for modelling utility

Utility analysis based on EQ-5D data collection in the CheckMate 067 trial was used in the model base case (see Section 5.4.4 for detailed utility analysis). Utilities were estimated for the progression-free and progressed health states.

Time to death based utilities have been used together with progression status based utilities in the recent nivolumab monotherapy (ID845[154]) and have also been used alone in the recent NICE appraisal for ipilimumab (TA319[55]). However, it is not possible to estimate time to death based utilities using data from CheckMate 067 trial because overall survival data is not available (i.e. timing of death unknown). The utilities used in these two previous submissions are tested in scenario analyses.

Differences in utilities among different treatment arms in CheckMate 067 (i.e. the Regimen, nivolumab and ipilimumab) were also estimated using EQ-5D data collected in the trial and these were used to model the utility impacts of AEs for the treatments included in the model.

Structure for modelling resource use

Resource use in many oncology models is calculated based on progression status. For example, the recent ipilimumab NICE appraisal (TA319[55]) mainly used resource use inputs

from the Oxford Outcomes study[171], which focused on resource use patterns for traditional chemotherapies and used progression status to gather one-off or follow-up resource use for advanced melanoma patients. However, based upon UK clinical expert input[2], the level of resource use in UK clinical practice with immunotherapies has now become more closely related to the time from treatment initiation rather than progression status. There is a trend of decreasing resource use further from treatment initiation.[2] Therefore, after consulting with clinical experts[2], four health states (see description above and Figure 2) were defined to better capture the resource use associated with the current routine management of melanoma in the UK using immunotherapies. Based on these health states, one-off costs are defined for treatment initiation and end of life care, and per week follow-up costs are defined for the first year, second year, and third year onwards after treatment initiation, and for the last 12 weeks before death (palliative care). The same structure was used and accepted in the previous nivolumab monotherapy NICE appraisal (ID845[154]).

Structure for modelling drug cost

The expected marketing authorisation for the Regimen is likely to recommend that 'treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient'.[166] Two health states were therefore defined within the model – on treatment and off treatment – to better calculate the nivolumab drug cost in the Regimen arm, because the timing of treatment discontinuation may not be aligned with the health states defined above (e.g. progression). Individual patient level data from trial CheckMate 067 were used to fit a covariate-adjusted time on treatment (TOT) curve that is used to estimate the proportion of patients on and off treatment for nivolumab in the Regimen arm. Furthermore, a maximum treatment duration of 2 years is assumed in the model, the justification for which is discussed in detail in Section 5.2.3. The same structure and assumption were used in the previous nivolumab monotherapy NICE appraisal (ID845[154]).

Patients have a maximum on treatment period of 4 doses for ipilimumab in both the Regimen and ipilimumab arms. The on treatment period for patients in the BRAF inhibitor treatment arms is defined based on the progression free health state in line with the license.

Modelling subsequent anti-cancer therapies

The cost of active subsequent anti-cancer therapies which may be used in UK clinical practice were included within the model based upon usage in the CheckMate 067 trial. These consisted of ipilimumab, dabrafenib, vemurafenib and pembrolizumab; other subsequent anti-cancer therapies were not explicitly modelled (Section 5.5.5).

Table 47 summarises the key features of the de novo analysis.

Table 47: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	40 years	Lifetime horizon for the advanced melanoma patient population considered appropriate as per TA319
Cycle length	1 week (7 days)	Deemed to offer sufficient resolution to model patterns of treatment administration and disease progression
Half-cycle correction	Yes	NICE Guide to the Methods of Technology Appraisals, 2013[172]
Were health effects measured in QALYs; if not, what was used?	Yes	

Factor	Chosen values	Justification
Discount of 3.5% for utilities and costs	Yes	
Perspective (NHS/PSS)	Yes	
Key: PSS, personal social services; QALYs, quality-adjusted life years.		

5.2.3 Intervention technology and comparators

Table 48 summarises the dosing regimen and continuation rules for nivolumab and comparators.

Table 48: Dosing regimen and continuation rules applied in the model

Treatment	Dosing regimen	Justification	Continuation rules as per SmPC	Continuation rules implemented in the model	Justification implementation in the model
Nivolumab (first 4 doses in the Regimen arm)	1mg/kg, every 3 weeks by IV	SmPC[166]	The marketing authorisation recommends that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.	Parametric curves fitted using observed time on treatment data from CheckMate 067 trial	In line with expected SmPC and the use of CheckMate 067 trial data
Nivolumab (after first 4 doses in the Regimen arm)	3mg/kg, every 2 weeks by IV	SmPC[166]	The marketing authorisation recommends that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.	Parametric curves fitted using observed time on treatment data from CheckMate 067 trial	In line with expected SmPC and the use of CheckMate 067 trial data
				Maximum 2 years	Clinical opinion and likely clinical practice consistent with advice received for nivolumab monotherapy
Ipilimumab	3mg/kg, every 3 weeks by IV	SmPC[9]	SmPC states that patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions.	Four doses	In line with SmPC
Dabrafenib	150mg twice daily, oral	SmPC[59]	SmPC states that treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.	Until progression	In line with SmPC and UK clinical practice
Vemurafenib	960mg twice daily, oral	SmPC[57]	SmPC states that treatment should continue until disease progression or the development of unacceptable toxicity.	Until progression	
Key: IV, intravenous infusion; SmPC, summary of product characteristics.					

The Regimen

It is expected that in line with the nivolumab monotherapy SmPC, the updated SmPC including the Regimen will state that nivolumab should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.[166] As stated in Section 4, treatment duration in CheckMate 067 was defined using similar criteria, with some patients taken off nivolumab treatment prior to progression (RECIST defined) due to toxicity or patient preference, while other patients (those considered to be still benefiting from nivolumab treatment by their physician) were treated beyond RECIST assessed progression. Parametric curves fit to the TOT data from the trial are therefore used in the model (Section Sections 5.3.4 and 5.3.5).

As discussed in Section 2 UK clinical expert opinion has confirmed that treating until progression is not necessarily a realistic approach in UK clinical practice and that it would be reasonable to assume a maximum treatment duration of 2 years in clinical practice in England instead. The TOT data from CheckMate 067 showed that only 27.9% of patients were still on nivolumab therapy within the Regimen arm at 18 months. The treatment continuation rule for nivolumab was tested in a range of scenario analyses including 75%, 50%, 25% and 0% of "on treatment" patients discontinuing treatment at 2 years, and setting the maximum treatment duration to 3, 4, 5 years and infinity (i.e. no maximum treatment duration).

As data from the CheckMate 067 trial and UK clinical expert opinion indicate no loss of response upon early discontinuation of therapy, it is assumed that when patients discontinue nivolumab their treatment effect is maintained.

Comparator treatments

Table 49 shows the detailed dosing for ipilimumab used in the model. The proportion of patients receiving doses 1 to 4 in the Regimen and ipilimumab arms is based on the patient level data from CheckMate 067.

Table 49: Ipilimumab detailed dosing

	% of patients receiving dose				Mean doses received	Sample size
	Dose 1	Dose 2	Dose 3	Dose 4		
Ipilimumab arm	100.0%	[redacted]	[redacted]	[redacted]	[redacted]	311
the Regimen arm	100.0%	[redacted]	[redacted]	[redacted]	[redacted]	313

For dabrafenib and vemurafenib, a simplified assumption was made in the model that treatment will continue until progression. This assumption maintains consistency between these comparators and is broadly in line with their respective SmPCs and clinical practice, where some patients may discontinue treatment before progression due to toxicity, and others may continue treatment after progression.

5.3 Clinical parameters and variables

5.3.1 Clinical evidence

Table 50 summarises the key sources of clinical evidence that were used to populate the model. The NICE DSU model selection algorithm was used to select the most appropriate structure for all fitted parametric curves.[173]

Table 50: Sources of key clinical evidence used to populate the model

Clinical evidence	Brief description	Use in the model
CheckMate 067	Pivotal Phase III trial in treatment naïve advanced melanoma patients that investigates the efficacy of nivolumab 3mg/kg (n=316) compared with ipilimumab 3mg/kg (n=315) and nivolumab 1mg/kg + ipilimumab 3mg/kg (n=314)	• Patient level data were used to fit TTP and PrePS parametric curves for the Regimen and ipilimumab • Patient level data in the Regimen arm were used to fit TOT parametric curves for nivolumab • EQ-5D data were used for trial-based utility analysis for the Regimen and ipilimumab • Used for modelling AEs for the Regimen and ipilimumab • Patient characteristics from the trial were used to represent BRAF mutation-negative patients in the model, and to populate covariate-adjusted TTP, PPS, PrePS and TOT parametric curves
CheckMate 069	Pivotal Phase II trial in treatment naïve advanced melanoma patients that that investigates the efficacy of nivolumab 1mg/kg + ipilimumab 3mg/kg (n=94) compared with ipilimumab 3mg/kg (n=46)	• Validation of outcomes for OS for the Regimen and ipilimumab
CheckMate 066	Pivotal Phase III trial in treatment naïve BRAF mutation-negative advanced melanoma patients that investigates the efficacy of nivolumab 3mg/kg (n=210) compared with DTIC (n=208)	• Patient level data in the nivolumab arm (pooled with patient level data in the ipilimumab arm in the MDX010-020 trial) were used to fit PPS parametric curves for the Regimen and ipilimumab
MDX010-20	Pivotal Phase III trial in previously-treated advanced melanoma patients that investigates the efficacy of ipilimumab 3mg/kg (n=540 in two arms [ipilimumab and ipilimumab + GP100]) compared with GP100 (n=136) Trial used by ipilimumab NICE appraisals at all lines of therapy (TA268[56], TA319[55])	• Patient level data in the ipilimumab arm (pooled with patient level data in the nivolumab arm in the CheckMate 066 trial) were used to fit PPS parametric curves for the Regimen and ipilimumab

Clinical evidence	Brief description	Use in the model
BRIM-3	Pivotal Phase III trial in previously untreated BRAF mutative-positive advanced melanoma patients that investigates the efficacy vemurafenib (n=337) compared with DTIC (n=338)	• Published OS and PFS KM curves were digitised and used to fit parametric curves for BRAF inhibitors (vemurafenib and dabrafenib) • Patient characteristics from the trial were used to represent BRAF mutation-positive patients in the model, and to populate covariate-adjusted TTP, PPS, PrePS and TOT parametric curves for the Regimen and ipilimumab • Used for modelling adverse events for vemurafenib
BREAK-3	Pivotal Phase III trial in previously untreated BRAF mutative-positive advanced melanoma patients that investigates the efficacy dabrafenib (n=187) compared with DTIC (n=63)	• Indirect comparison to vemurafenib presented in TA321[60] was used in a scenario analysis to the assumption of equal efficacy for vemurafenib and dabrafenib • Used for modelling AEs for dabrafenib
Long-term registry OS[170]	Long-term OS (up to 15 years) for different stages of melanoma based on registry from AJCC (n=1158 for Stage IV melanoma)	• Used to model long-term OS from Year 3 onwards for BRAF inhibitors
Pooled long-term OS of ipilimumab[11]	Pooled analysis of long-term survival data (up to 10 years) from Phase II and Phase III trials of ipilimumab in advanced melanoma (n=1,861 from 12 studies)	• Used to model survival from Year 3 onwards for the Regimen and ipilimumab
General population mortality	Latest England general population mortality by single year of age	• Used to supplement long-term registry OS from AJCC as the AJCC reports melanoma-specific mortality • Used to set the minimum threshold of age-matching mortality rates for modelled patients in all treatment arms
Key: AJCC, American Joint Committee on Cancer; AE, adverse events; kg, kilogram; m, metre; OS, overall survival; PFS, progression free survival; PPS, post-progression survival; PrePS, pre-progression survival; TOT, time on treatment; TTP, time to progression.		

5.3.2 Progression free survival and overall survival – BRAF mutation-negative

As stated previously, for BRAF mutation-negative patients, the modelled PFS and OS for the Regimen and the comparator ipilimumab is calculated within the model using covariate-adjusted parametric curves fitted for TTP, PPS and PrePS using patient characteristics based on CheckMate 067 for the first 3 years for the Regimen and ipilimumab, and registry OS and long-term pooled ipilimumab OS from Year 3 onwards. General population mortality is also used to set the minimum mortality rate for each model cycle.

Patient characteristics

Table 51 shows the patient characteristics used in the base case model for BRAF mutation-negative analysis based on the BRAF mutation-negative patient population in CheckMate 067 (n=647)[10] and details how they are used in the model.

Table 51: Patient characteristics in the base case model – BRAF mutation-negative

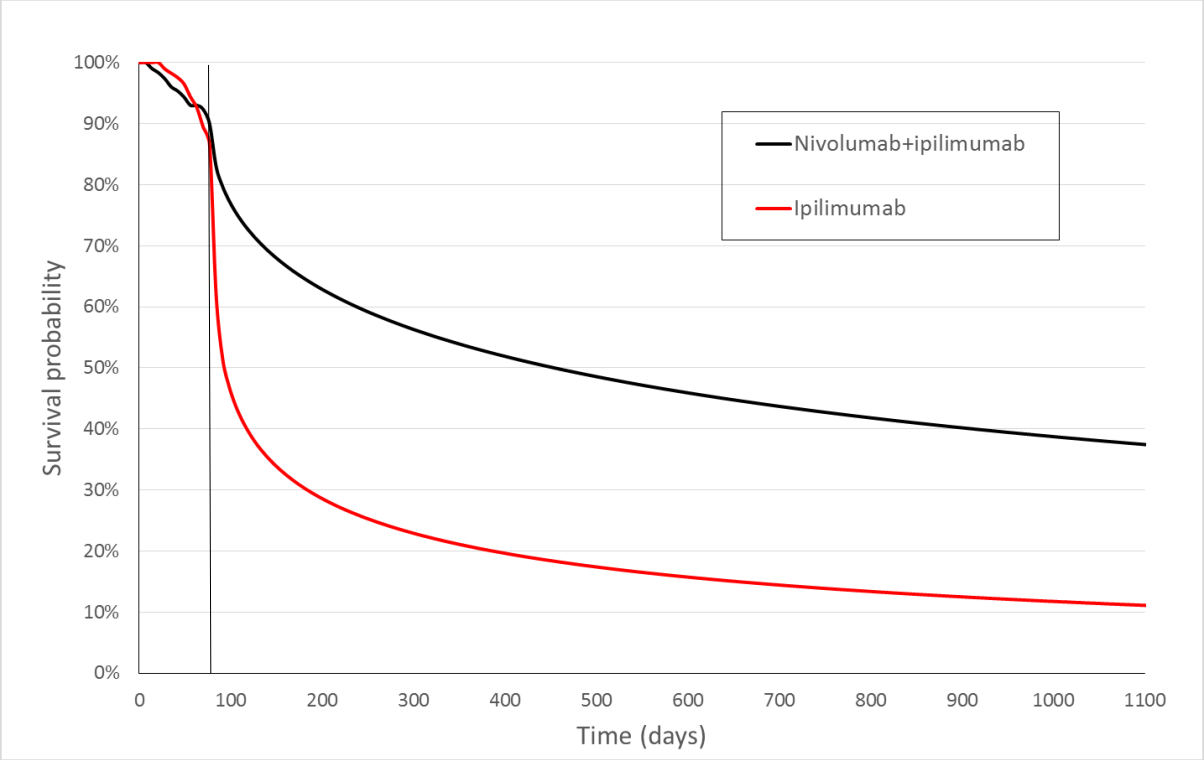
	BRAF mutation-negative[10]	**Use in the model**
Mean age	62	Starting age in the model
% male	66.2%	TTP, PrePS, TOT
% under 65	53.3%	TTP, PrePS, TOT
Mean weight (kg)	79.6	Drug dosing
% stage M1c	59.2%	TTP, PrePS, TOT
ECOG status = 0	70.4%	TTP, PrePS, TOT
% elevated LDH (>ULN)	38.4%	TTP, PrePS, TOT
% with brain metastases	3.9%	TTP, PrePS, TOT

Key: ECOG, Eastern Cooperative Oncology Group; kg, kilogram; LDH, lactate dehydrogenase; m, metre; PPS, post-progression survival; PrePS, pre-progression survival; TOT, time on treatment; TTP, time to progression; ULN, upper limit of the normal range.

Time to progression

As discussed in Section 4.13, time to progression is modelled using KM data for the first 84 days, and fitted parametric curves post 84 days. Among the six parametric curves fitted, the log-normal curve is chosen for the base case based on the NICE DSU guidance[173] (see Section 4.13 for detailed results of the parametric curves fitted and the choice of the base case curve). Other types of curves were tested as scenario analyses. Figure 45 shows the final modelled time to progression for BRAF mutation-negative patients combining the KM data for the first 84 days and parametric curves post 84 days. Patient characteristics shown in Table 51 are applied to the log-normal covariate-adjusted TTP and to the observed KM TTP data in the first 84 days to account for bias resulting from different patient characterises among treatment arms.

Figure 45: Time to progression in the base case model for BRAF mutation-negative analysis over 3 years



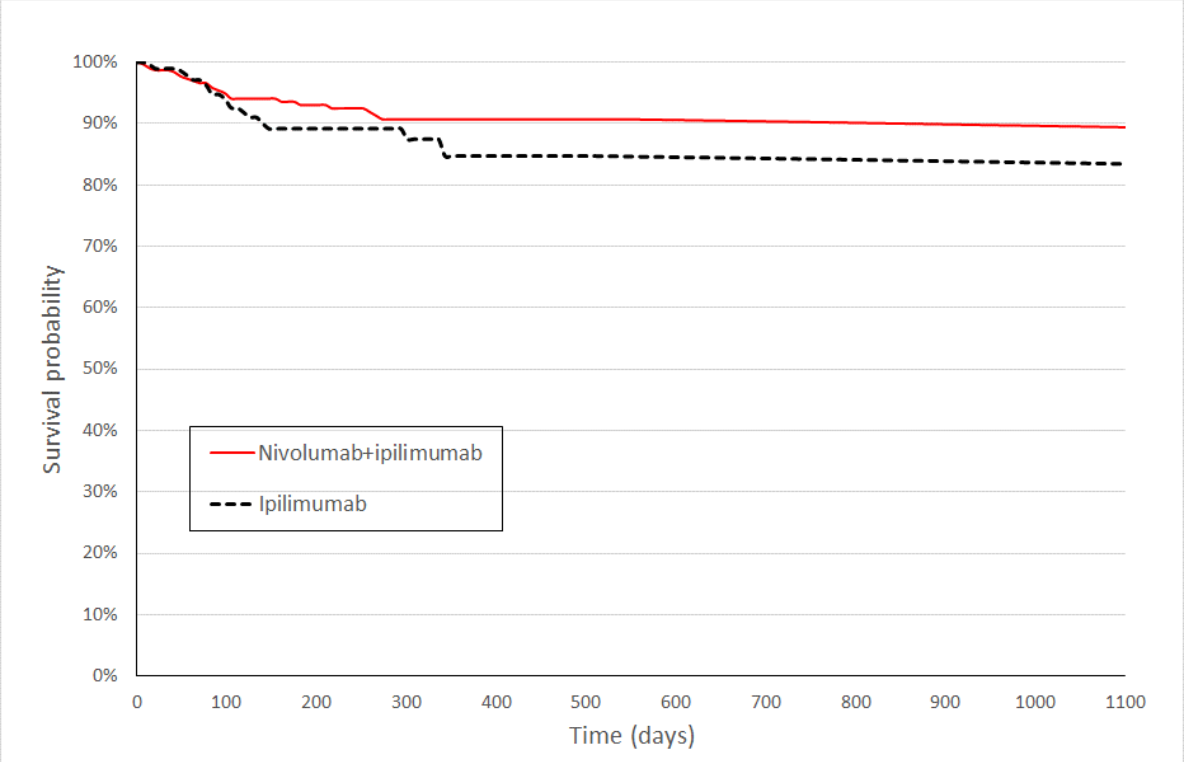
Pre-progression survival

Six parametric curves were fitted for PrePS, but none of the standard parametric curves provided a good visual fit to observed data (Section 4.13). Therefore, similar to the method for TTP pre-84 days, PrePS is modelled using available KM data in the base case (Section 4.13). The longest follow-up for observed PrePS data in the CheckMate 067 trial is 1.5 years and no deaths were observed on the Regimen arm after 271 days (343 days for ipilimumab arm); therefore, mortality rates based on the UK life tables (i.e. general population mortality) were used for PrePS after the last observed KM data and before switching to long-term OS at Year 3.

Figure 46 shows the final modelled pre-progression survival for BRAF mutation-negative patients after applying the patient characteristics shown in Table 51. The figure shows that PrePS for the Regimen is higher than ipilimumab in the first 1.5 years based on observed KM data from CheckMate 067.

It should be noted that the sensitivity of the model to assumptions around PrePS is limited due to the low number of events experienced, and the majority of patients within the trials die following observed progression events.

Figure 46: Pre-progression survival in the base case model for BRAF mutation-negative analysis

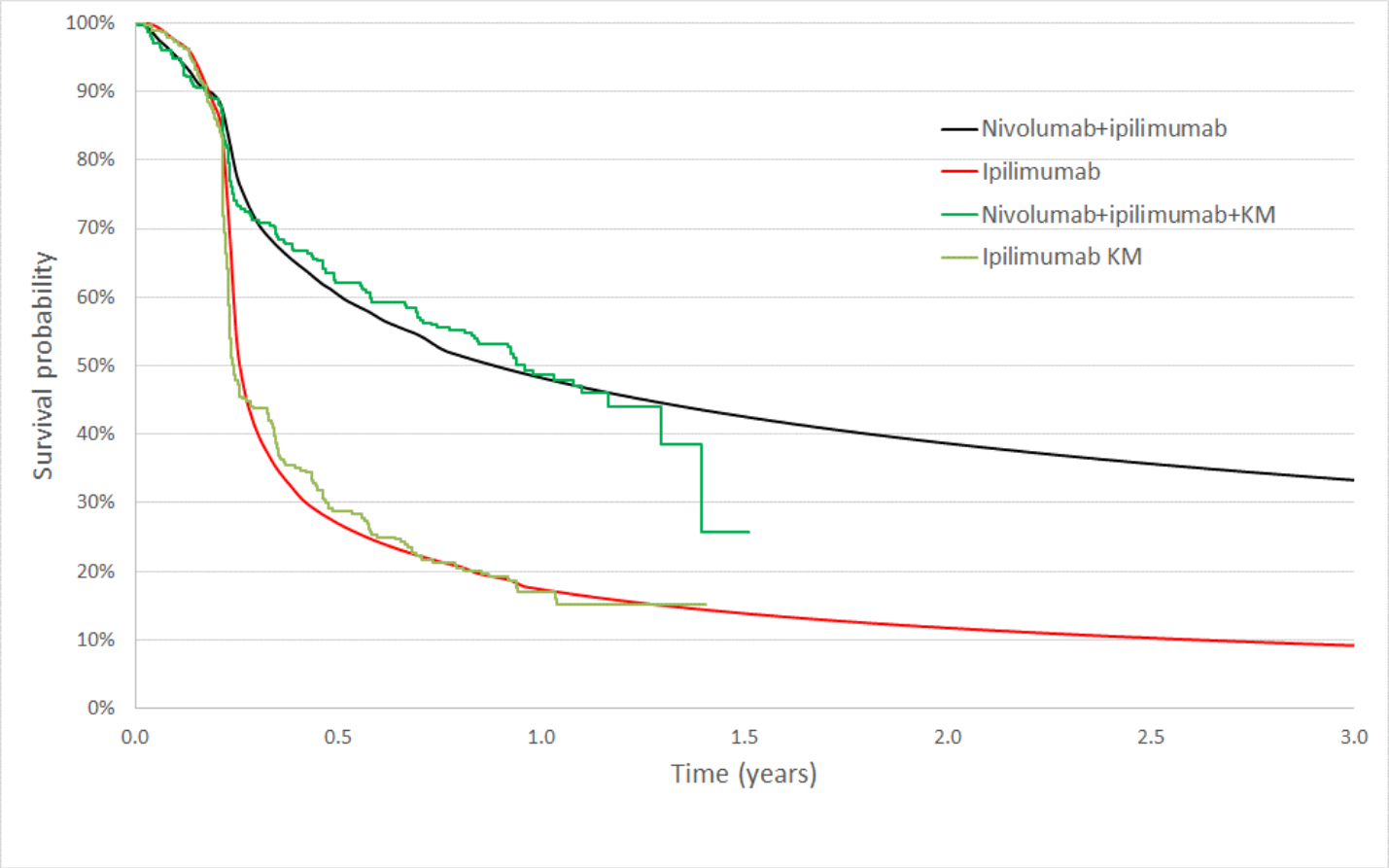


Progression free survival

Final modelled PFS for the Regimen and ipilimumab for the BRAF mutation-negative analysis for the first 3 years and the corresponding KM data from CheckMate 067 trial are presented in Figure 47. The final modelled PFS combines TTP (as shown in Figure 45) and PrePS (as shown in Figure 46) and fits well with the KM data as expected because the covariate adjusted TTP and PrePS are fitted using CheckMate 067 data and patient characteristics from CheckMate 067 are used. The difference between observed PFS and model estimated PFS around 1.5 years for the Regimen arm (i.e., the drop in the tail of the observed PFS KM data) is due to the small number of patients still at risk within the KM data.

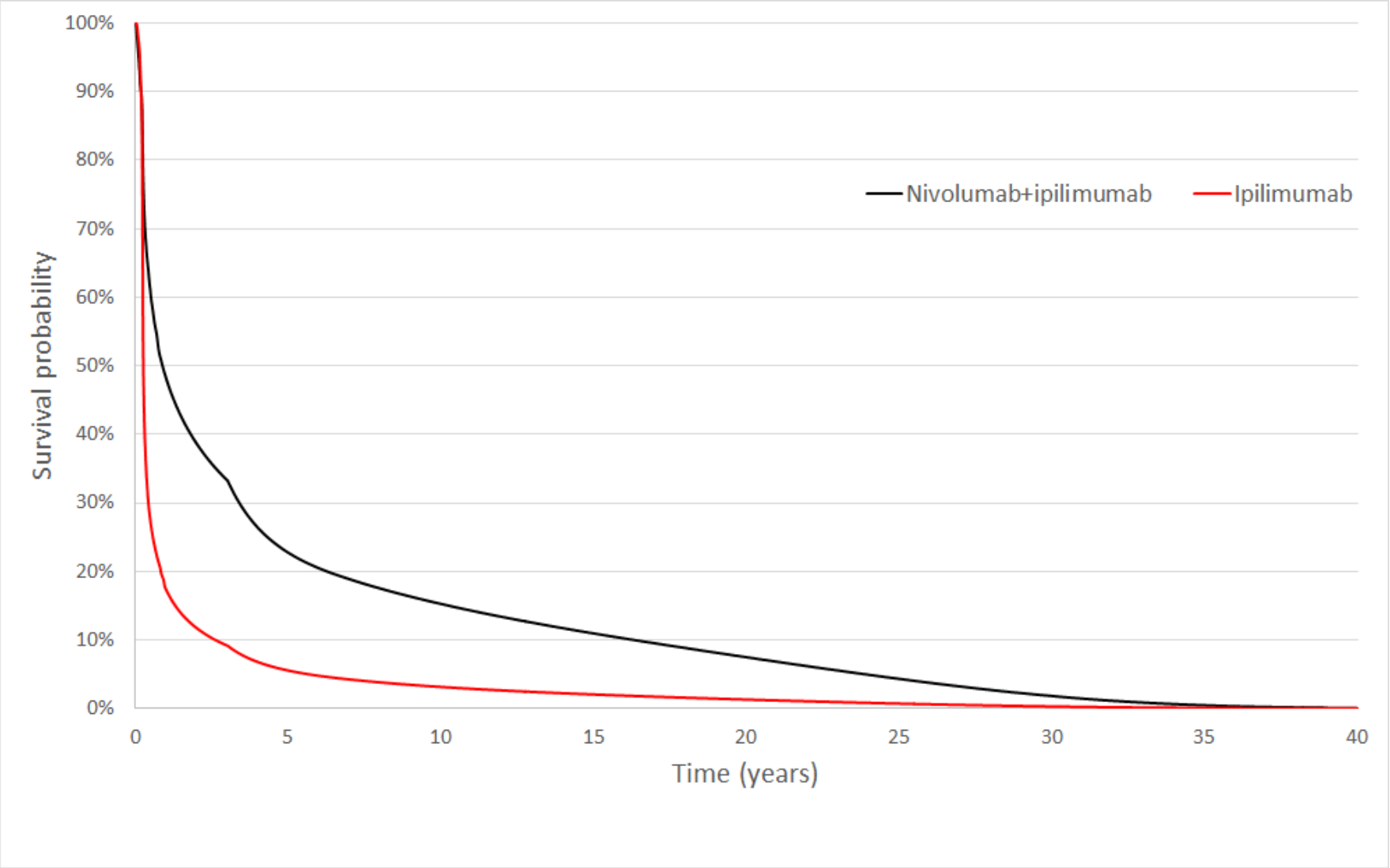
Final modelled PFS for the Regimen and ipilimumab for the BRAF mutation-negative analysis over a lifetime horizon are presented in Figure 48.

Figure 47: Final PFS in the base case model for BRAF mutation-negative analysis for the first 3 years



No. at risk					
Time (year)	0	0.5	1	1.5	2
Nivolumab+ipilimumab	313	173	69	2	0
Ipilimumab	309	76	28	0	

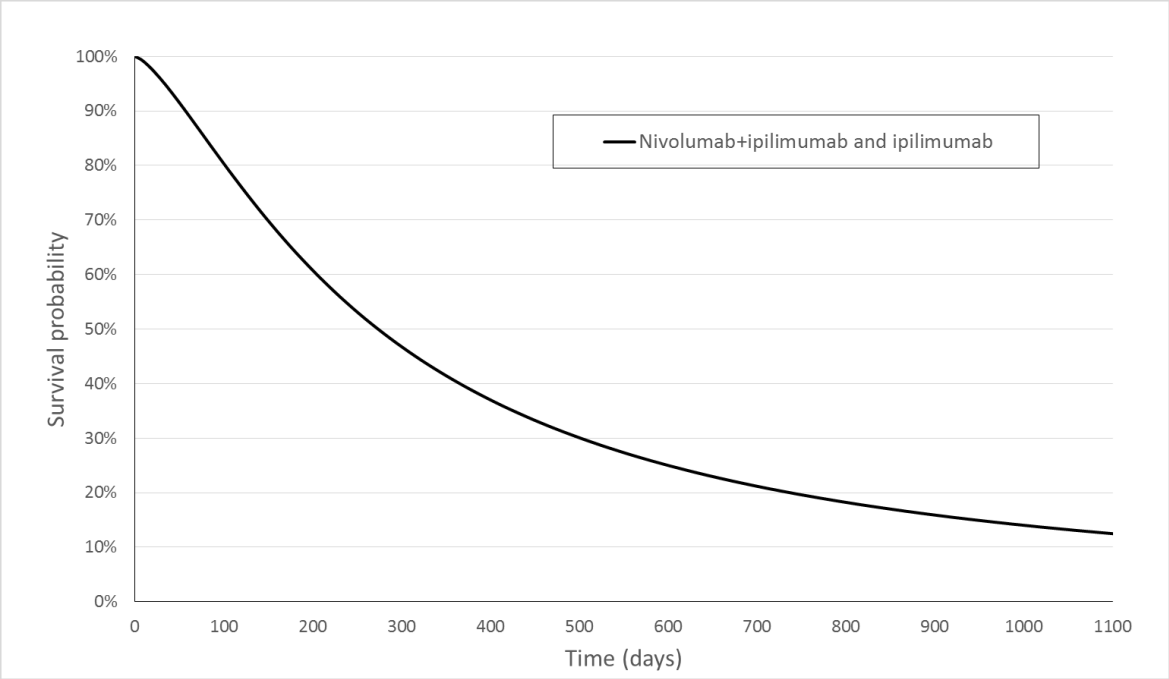
Figure 48: Final PFS in the base case model for BRAF mutation-negative analysis



Post-progression survival

Among the six parametric curves fitted, the log-logistic curve is chosen for the base case based on the NICE DSU guidance[173] (see Section 4.13 for detailed discussion). Other types of curves were tested as scenario analyses. Figure 49 shows the final modelled post-progression survival for BRAF mutation-negative patients after applying the patient characteristics shown in Table 51. It is conservatively assumed that PPS is the same for all immunotherapies, including nivolumab, ipilimumab, and the Regimen, after controlling for the patient characteristics.

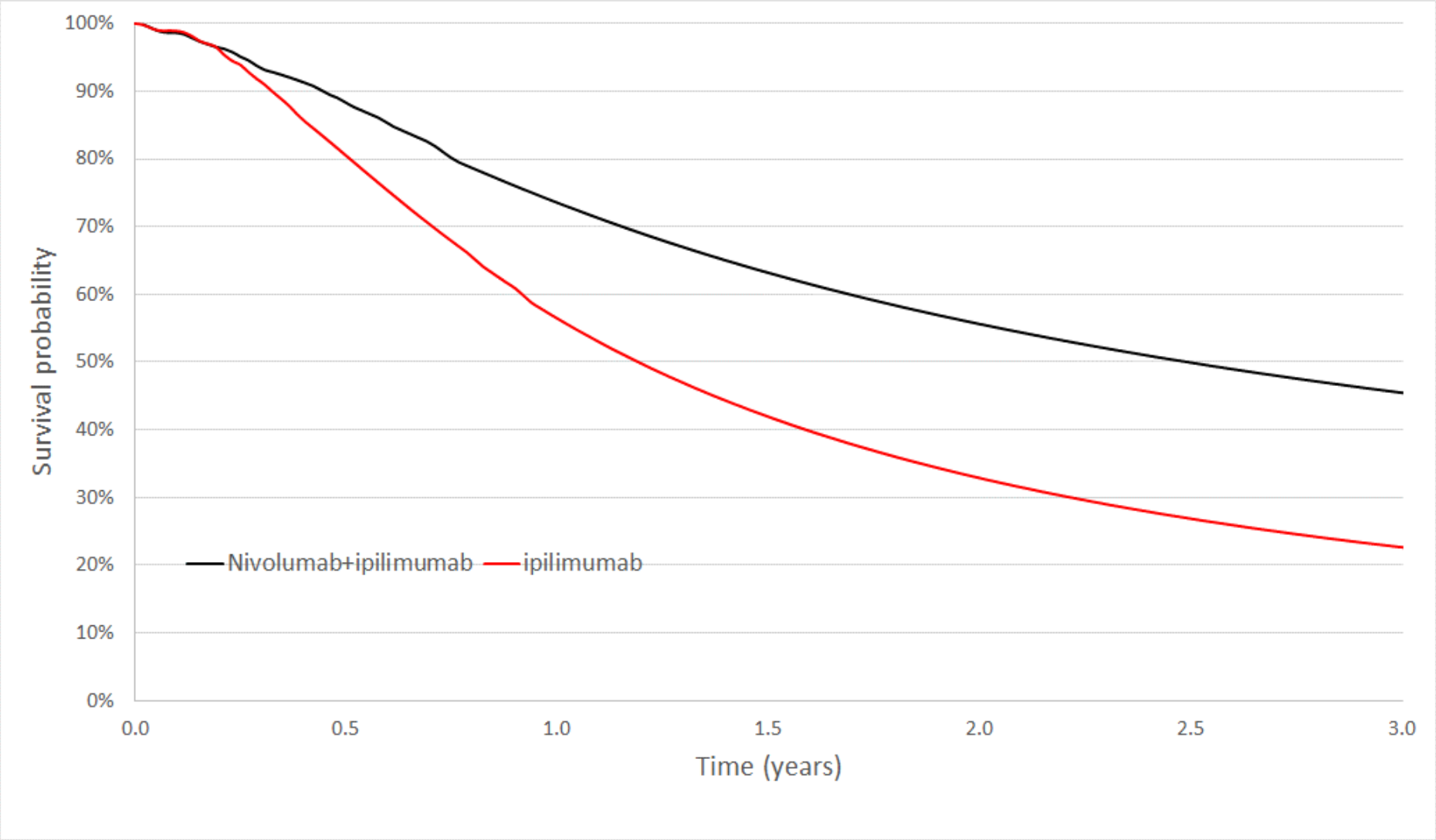
Figure 49: Post-progression survival in the base case model for BRAF mutation-negative analysis over 3 years



Overall survival for the first 3 years

The modelled OS for BRAF mutation-negative patients for the first 3 years is presented in Figure 50, which combines the TTP, PPS, and PrePS shown in Figure 45, Figure 49 and Figure 46, respectively.

Figure 50: Overall survival in the base case model for BRAF mutation-negative analysis for the first 3 years



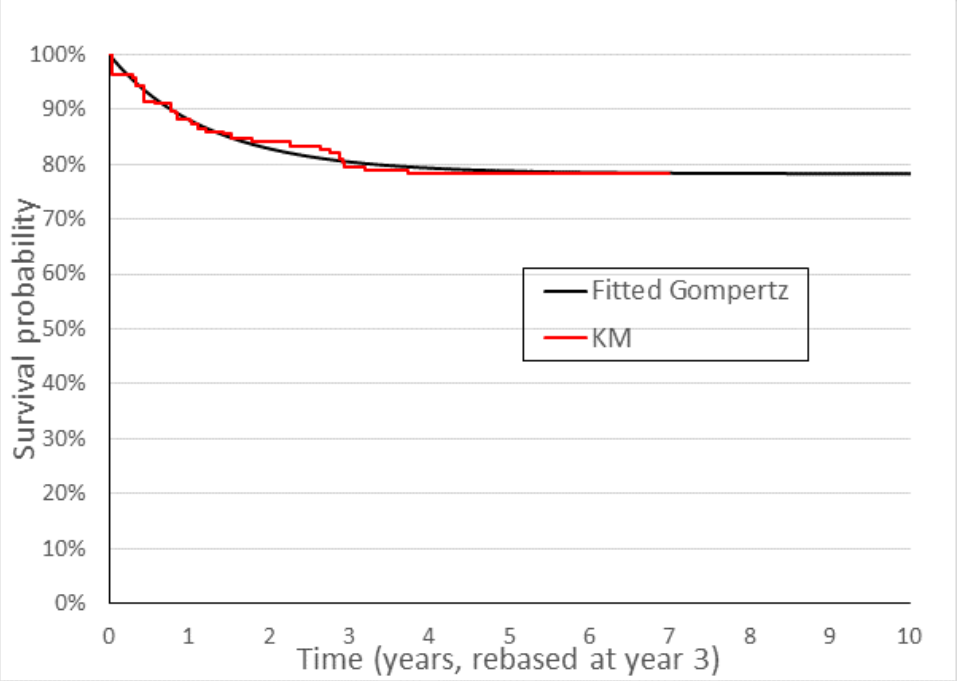
Long-term overall survival

To avoid extrapolating long-term OS from fitted parametric curves based on short follow-up trial data, and to use comparable long-term survival across treatment arms, two sources of evidence were used to model long-term survival for BRAF mutation-negative patients:

- Pooled ipilimumab long-term OS[11] for the Regimen and ipilimumab from Year 3 onwards. The pooled analysis showed a plateau in the OS curve beginning around Year 3 using pooled ipilimumab trials with follow-up up to 10 years. The long-term OS is also assumed to be applicable to long-term OS for the Regimen due to similarity of mechanism of action (both are immunotherapies); this was considered a reasonable and potentially conservative assumption based on clinical opinion.[3]
- Life tables for England (2012-2014) reported by the Office for National Statistics[174] as background mortality.

The pooled ipilimumab long-term survival data reported by Schadendorf et al[11] were digitised and rebased at 3 years to fit different types of parametric curves. Based on AIC and BIC goodness of fit statistics, the Gompertz curve was used in the base case (Figure 51). Other curve fits are tested in scenario analyses. Please refer to Appendix 9 for curve fit parameters and goodness of fit statistics.

Figure 51: KM and fitted base case OS (rebased at 3 years) using long-term pooled ipilimumab data

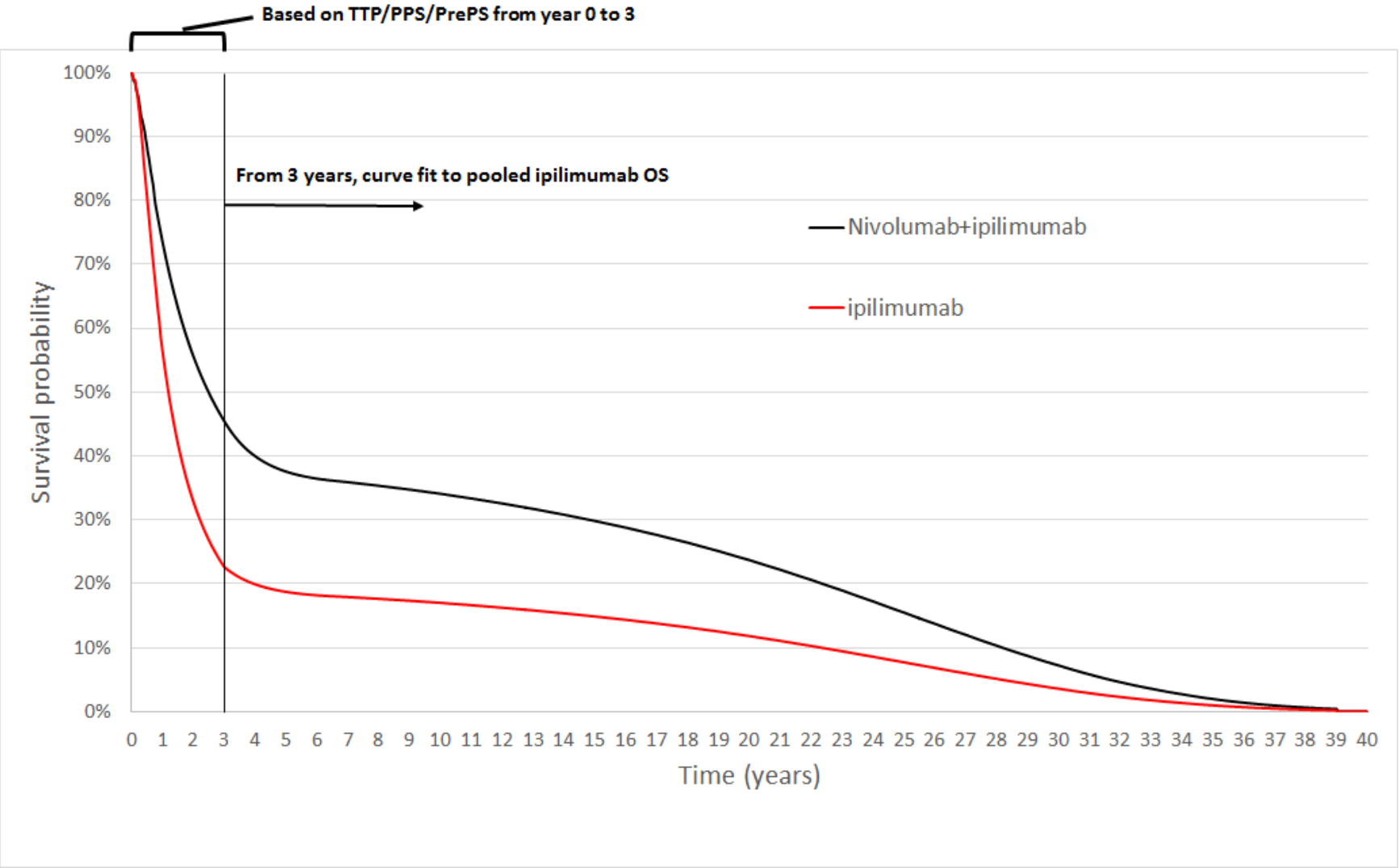


The general population mortality was also used to set the minimum threshold mortality rates for modelled patients in all treatment arms. This is based on the latest Life Tables for England (2011-2013)[174], as a weighted average of male and female mortality risks using the gender distribution of participants of the CheckMate 067 trial.

Final overall survival

The final modelled OS for BRAF mutation-negative patients, combining short-term trial-based estimates, long-term OS from pooled ipilimumab estimates over 40 years, is presented in Figure 52.

Figure 52: Final overall survival in the base case model for BRAF mutation-negative analysis over life time (40 years)



5.3.3 Progression free survival and overall survival – BRAF mutation-positive

The comparators for the BRAF mutation-positive analysis include dabrafenib, vemurafenib and ipilimumab. For the Regimen and ipilimumab, the same method used for the BRAF mutation-negative analysis was used to estimate PFS and OS, i.e. covariate-adjusted parametric curves or KM data for TTP, PPS and PrePS for the first 3 years; and long-term pooled ipilimumab OS from Year 3 onwards. The only difference is that patient characteristics are now based on the vemurafenib arm of the BRIM-3 trial to reflect BRAF mutation-positive patients and to maintain comparability with the PFS and OS used for the dabrafenib and vemurafenib arms (see Table 52).

Table 52: Patient characteristics in the base case model – BRAF mutation-positive

	BRAF mutation-positive[67]	**Use in the model**
Mean age	56	Starting age in the model
% male	59.0%	TTP, PPS, PrePS, TOT
% under 65	100%	TTP, PPS, PrePS, TOT
Mean weight (kg)	79.6[a]	Drug dosing
% stage M1c	66.0%	TTP, PPS, PrePS, TOT
ECOG status = 0	68.0%	TTP, PPS, PrePS, TOT
% elevated LDH (>ULN)	58.0%	TTP, PPS, PrePS, TOT
% with brain metastases	0%	TTP, PPS, PrePS, TOT

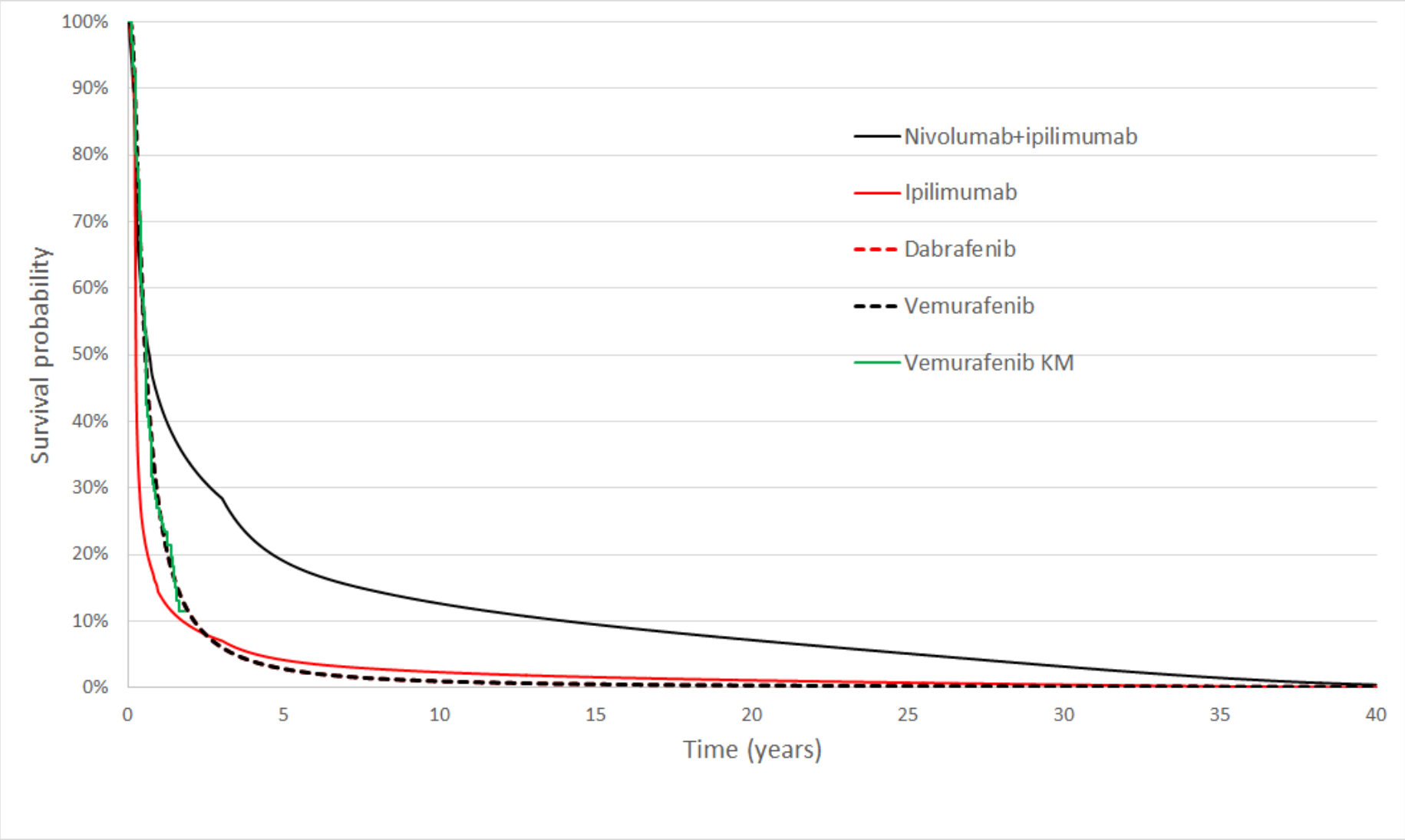
Key: ECOG, Eastern Cooperative Oncology Group; kg, kilogram; LDH, lactate dehydrogenase; m, metre; PPS, post-progression survival; PrePS, pre-progression survival; TOT, time on treatment; TTP, time to progression; ULN, upper limit of the normal range.

Based upon the NICE recommendation for dabrafenib[60] in the base case, it was assumed that dabrafenib and vemurafenib have the same efficacy for PFS and OS (Section 4.13). Due to the much larger sample size of the vemurafenib BRIM-3 trial (n=675) compared with the dabrafenib BREAK-3 trial (n=250), the PFS and OS reported for the BRIM-3 trial by McArthur et al[133] were selected to represent the PFS and OS for both dabrafenib and vemurafenib. Reported KM data were digitised to fit different types of parametric curves.

Progression free survival

The final modelled PFS for the Regimen and its comparators for BRAF mutation-positive patients over the lifetime horizon is presented in Figure 53: Final PFS in the base case model for BRAF mutation-positive analysis. For the Regimen and ipilimumab, the final PFS combines TTP and PrePS based on BRIM-3 trial patient characteristics. For dabrafenib and vemurafenib, it is assumed that the two BRAF inhibitors have the same PFS, and the KM data from vemurafenib BRIM-3 trial were used to fit parametric curves. Based on AIC and BIC goodness of fit statistics, the Generalised Gamma curve was used in the base case (Figure 53). Figure 53 also shows the KM data for vemurafenib for comparison and validation. The figure shows that modelled PFS fits well to the KM data. Other parametric curve fits are tested in scenario analysis. Please refer to Appendix 9 for curve fit parameters and goodness of fit statistics. Alternative PFS for BRAF inhibitors based on dabrafenib was also tested in scenario analysis. The modelled PFS for all treatment arms shown in Figure 53 also uses the modelled OS as the upper threshold for PFS.

Figure 53: Final PFS in the base case model for BRAF mutation-positive analysis

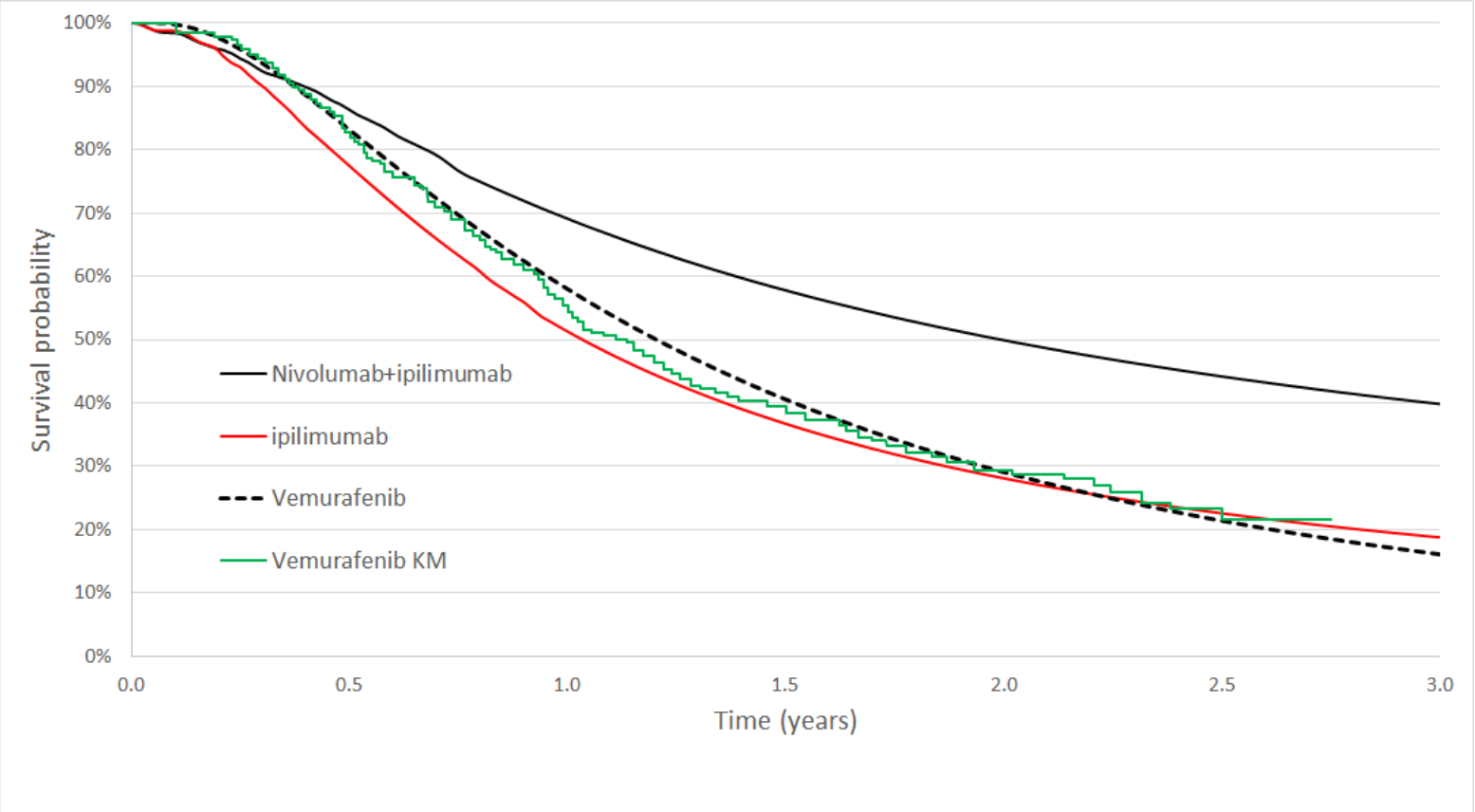


Dabrafenib and vemurafenib overall survival for the first 3 years

The modelled OS for BRAF mutation-positive patients for the first 3 years for the Regimen and ipilimumab is presented in Figure 54, which combines TTP, PPS, and PrePS using patient characteristics from the vemurafenib arm in the BRIM-3 trial.

For dabrafenib and vemurafenib, it is assumed that the two BRAF inhibitors have the same OS, and the KM data from vemurafenib BRIM-3 trial were used to fit parametric curves. Based on AIC and BIC goodness of fit statistics, the log-normal curve was used in the base case (Figure 54). Figure 54 also shows the KM data for vemurafenib for comparison and validation. The fitted OS fits well with the KM data. Other parametric curve fits are tested in scenario analysis. Please refer to Appendix 9 for curve fit parameters and goodness of fit statistics.

Figure 54: Overall survival in the base case model for BRAF mutation-positive analysis for the first 3 years



No. at risk

Time (year)	0	0.5	1	1.5	2	2.5	3
Vemurafenib	337	280	186	133	98	30	0

Long-term overall survival

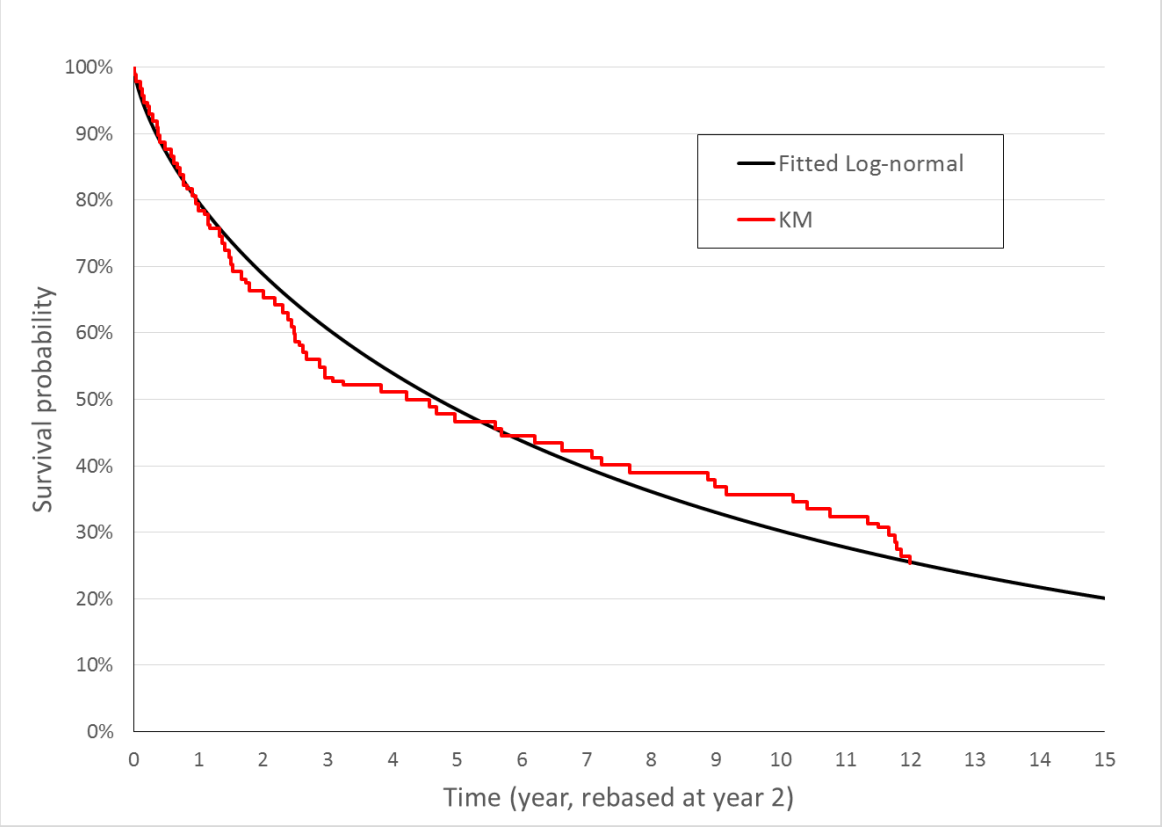
To avoid extrapolating long-term OS from fitted parametric curves based on short follow-up trial data, and to use comparable long-term survival across treatment arms, three sources of evidence were used to model long-term survival for BRAF mutation-positive patients:

- Melanoma registry OS by the AJCC[170] for the BRAF inhibitors' arm from Year 3 onwards. This is because no OS trial data exist for the BRAF inhibitors after 3 years.
- Pooled ipilimumab long-term OS[11] for the Regimen and ipilimumab from Year 3 onwards, which is the same evidence used for long-term overall survival for BRAF mutation-negative patients (see Section 5.3.2).
- Life tables for England (2012-2014) reported by the Office for National Statistics[174] to supplement AJCC registry OS and used as background mortality.

The AJCC registry survival data for Stage IV reported by Balch et al[170] was used as the melanoma registry OS because it provides data with the longest follow-up period, 15 years. Reported KM data were digitised and rebased at 3 years to fit different types of parametric curves. Based on AIC and BIC goodness of fit statistics, the log-normal curve was used in the base case (Figure 55). Other curve fits are tested in scenario analyses. Please refer to Appendix 9 for curve fit parameters and goodness of fit statistics.

As the AJCC registry data records only melanoma-specific mortality rates, additional age-specific background survival rates were applied. These were taken from Life Tables for England (2011-2013)[174], as a weighted average of male and female mortality risks using the gender distribution of participants of the BRIM-3 trial. The general population mortality was also used to set the minimum threshold mortality rates for modelled patients in all treatment arms.

Figure 55: KM and fitted base case OS (rebased at 3 years) using registry data



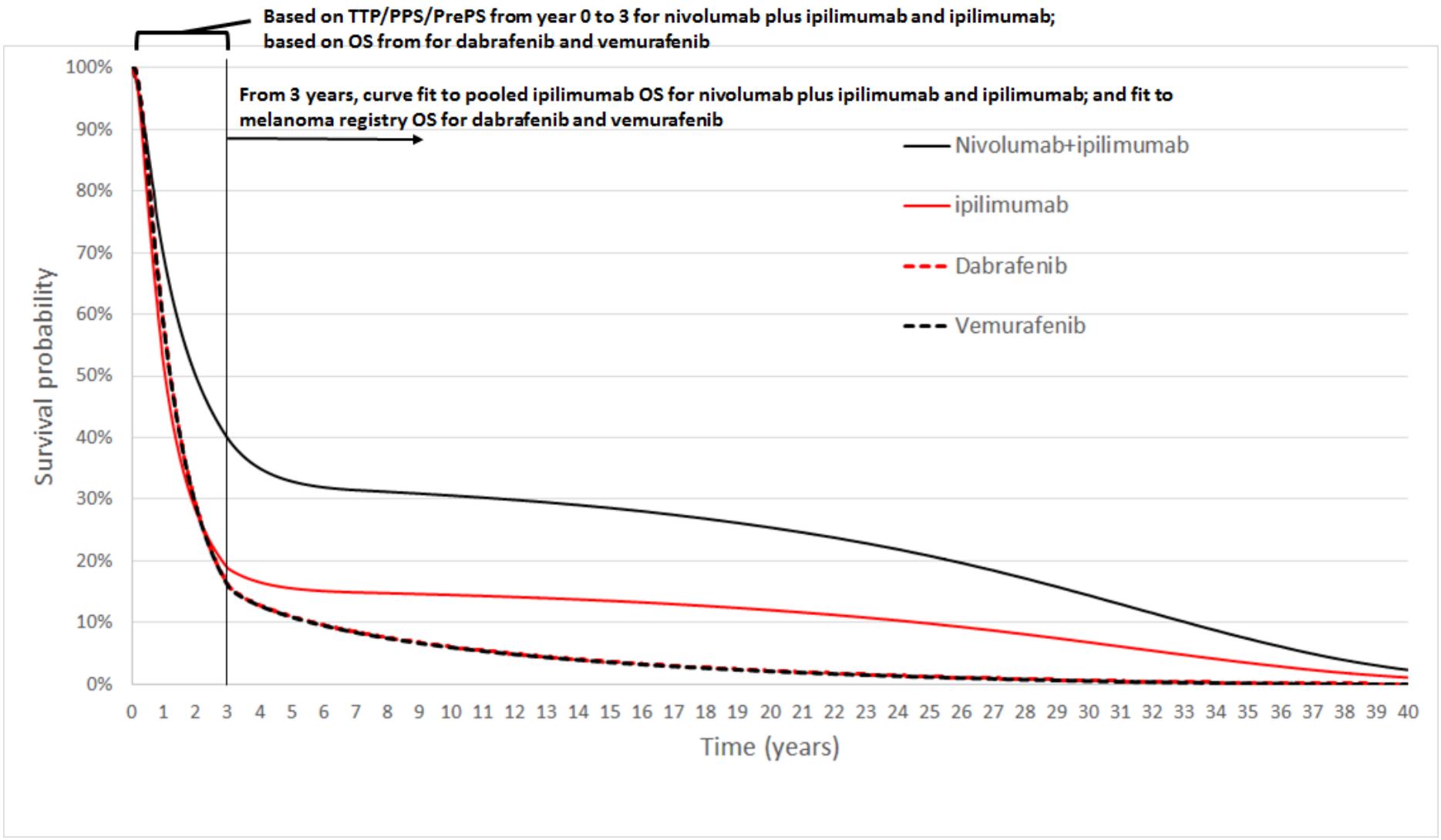
For the Regimen and ipilimumab, the same method used for BRAF mutation-negative patients for these two treatments was used, i.e. pooled ipilimumab long-term survival used from Year 3 onwards (Figure 51), and general population mortality used as background mortality.

For dabrafenib and vemurafenib, melanoma registry survival was used from Year 3 onwards (Figure 53) and general population mortality was used as background mortality. This assumption is supported by the most recent data cuts for vemurafenib[133] (BRIM-3 trial data cut-off on 1 February 2012) and dabrafenib[114] (BREAK-3 trial data cut-on in January 2014) (Section 4.13). Whilst BRAF inhibitors have demonstrated short-term survival benefits, the long-term survival benefit for BRAF inhibitors appears to be similar to chemotherapies based upon these most recently available data using intention-to-treat analysis.

Final overall survival

The final modelled OS for BRAF mutation-positive patients, combining short-term trial-based estimates, long-term OS from registry or pooled ipilimumab estimates, and the general population, over 40 years, is presented in Figure 56.

Figure 56: Final overall survival in the base case model for BRAF mutation-positive analysis over life time (40 years)

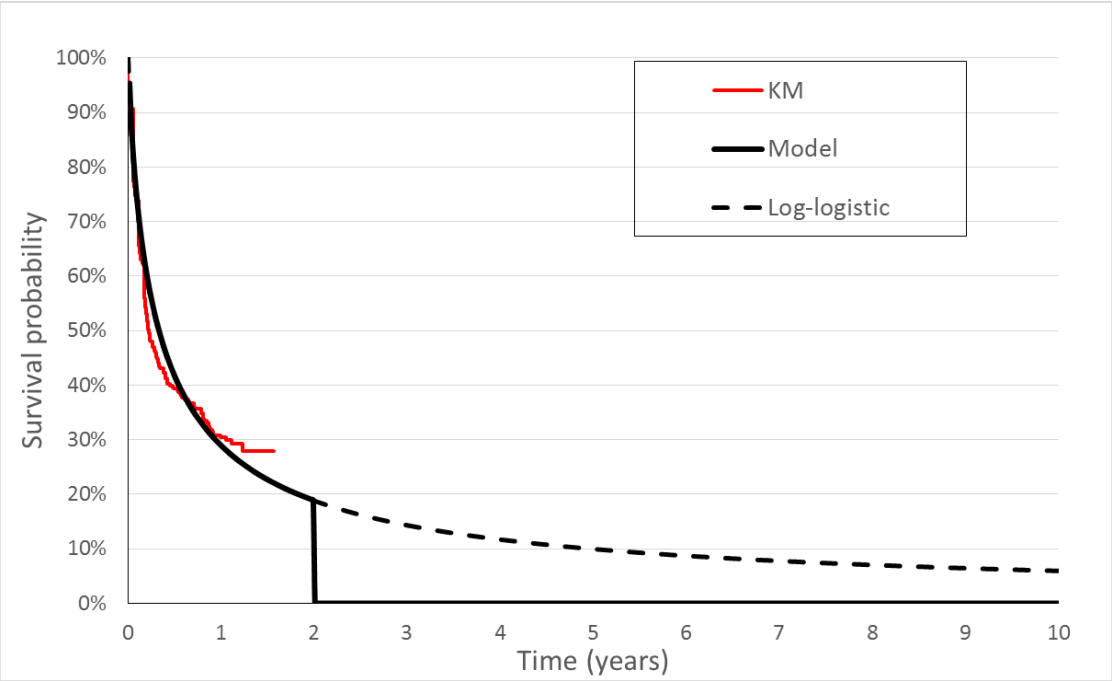


5.3.4 *Time on treatment (nivolumab in the Regimen arm) – BRAF mutation-negative*

TOT patient level data for nivolumab in the Regimen arm from CheckMate 067 trial are used to fit different types of parametric curves. Based on AIC and BIC goodness of fit statistics and clinical validity, the log-logistic curve was used in the base case as it has the lowest AIC/BIC scores and has plausible prediction at the tail (Figure 57). Figure 57 also shows the KM data for comparison and validation. Other parametric curve fits were tested in the scenario analysis. Please refer to Appendix 9 for curve fit parameters and goodness of fit statistics.

The final modelled nivolumab TOT for BRAF mutation-negative patients shown in Figure 57 have also used the OS as upper thresholds and a maximum treatment duration of 2 years in line with expected clinical practice (Section 4 for detailed discussion).

Figure 57: Final TOT in the base case model for BRAF mutation-negative analysis



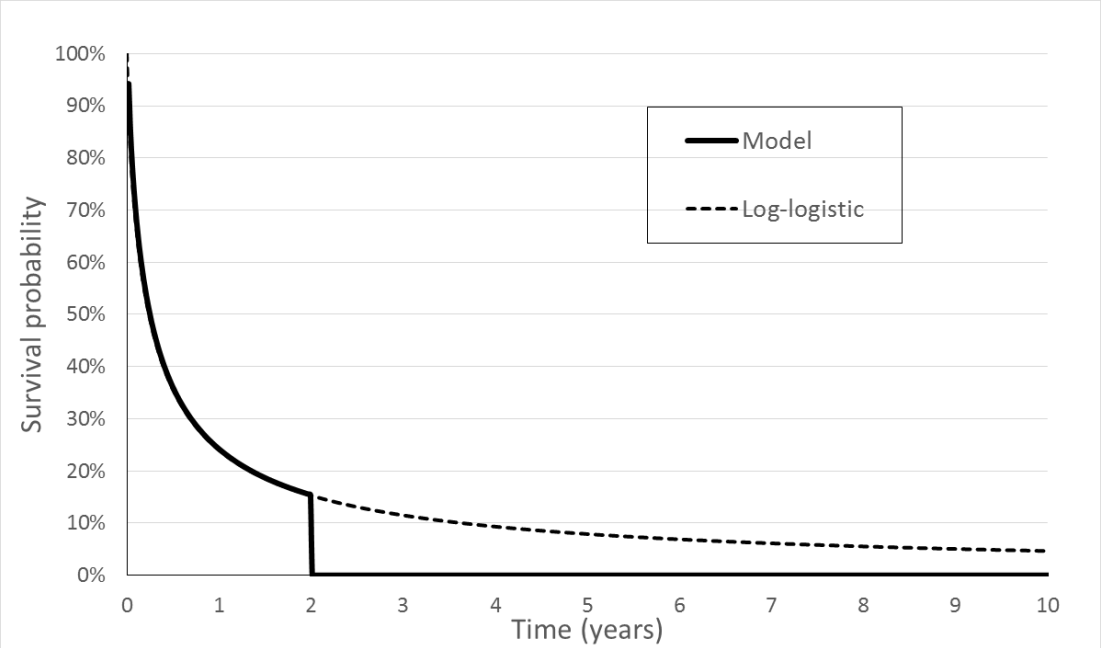
No. at risk

Time (year)	0	0.5	1	1.5	2
Nivolumab	313	123	88	21	0

5.3.5 *Time on treatment (nivolumab in the Regimen arm) – BRAF mutation-positive*

The final modelled nivolumab TOT for BRAF mutation-positive patients is shown in Figure 58. The only difference compared to BRAF mutation-negative patients is that patient characteristics are based on the vemurafenib arm of BRIM-3.

Figure 58: Final TOT in the base case model for BRAF mutation-positive analysis



5.3.6 Safety

Regimen and ipilimumab

In line with the recent nivolumab monotherapy NICE submission[154] and based on clinical expert opinion[2, 3], three categories drug-related AEs are captured within the model which are any grade of endocrine disorder, Grade 2 or high diarrhoea and other Grade 3 or higher drug-related AEs, and with no restriction on the minimum proportion of patients experiencing an AE. The inclusion of all Grade 3+ AEs without setting a minimum cut-off threshold would capture a much wider range of outcomes than the safety modelling included in previous NICE submissions in this disease area (a usual cut-off of 3% or more of patients experiencing the AE were used in previous submissions).

Patient-level AE data from CheckMate 067 were used to calculate the proportion of patients in the Regimen and ipilimumab arms that experience drug-related endocrine disorders (any grade), diarrhoea (Grade 2+) and other AEs (Grade 3+), with no restriction on the minimum proportion of patients experiencing an AE (Table 53).

Clinical expert opinion suggested that majority of the costs associated with AEs for the treatment of advanced melanoma would be the hospitalisation costs for the treatment of AEs. [2, 3] Therefore, as part of the patient level data analysis, the recorded hospitalisation (measured by hospital bed days) used for treating AEs is summarised and presented in Table 53 for the Regimen and ipilimumab arms. The proportions of patient requiring outpatient visits presented in Table 53 are based on the following assumptions from the Oxford Outcome study[171] used in the recent nivolumab monotherapy and ipilimumab NICE appraisals (ID845[154] and TA319[55]): 25% of patients having endocrine disorders require outpatient visits, 19.2% for diarrhoea and 17.2% for other AEs.

Table 53: Summary of adverse event analysis using patient level data from the CheckMate 067 trial and aggregate data from BREAK-3 and BRIM-3 trials

	The Regimen	Ipilimumab	Dabrafenib (BREAK-3 trial)	Vemurafenib (BRIM-3 trial)
Patient numbers for AE analysis	313	311	187	336
Endocrine disorder (any grade)				
% of patients	30.0%	11.3%	0%[a]	0%[a]
% of patients hospitalised	8.6%	2.6%	0%[b]	0%[b]
Total hospitalisation days	194	43	0	0
Mean hospitalisation days per patient (hospitalised patients)	7.2	5.4	5.4[c]	5.4[c]
Mean hospitalisation days per patient (all safety patients)	0.6	0.1	0	0
% of patients requiring outpatient visits	7.7%	2.9%	0%	0%
Diarrhoea (Grade 2+)				
% of patients	24.6%	18.6%	0%[a]	5.5%
% of patients hospitalised	10.5%	7.4%	0%[b]	2.2%[b]
Total hospitalisation days	411	351	0	112
Mean hospitalisation days per patient (hospitalised patients)	12.5	15.3	15.3[c]	15.3[c]
Mean hospitalisation days per patient (all safety patients)	1.3	1.1	0	0.3
% of patients requiring outpatient visits	4.7%	3.6%	0%	1.1%
Other AEs (Grade 3+)				
% of patients	49.5%	27.0%	32.0%	44.5%
% of patients hospitalised	25.6%	14.8%	17.5%[b]	24.4%[b]
Total hospitalisation days	1,051	537	383	956
Mean hospitalisation days per patient (hospitalised patients)	13.1	11.7	11.7[c]	11.7[c]
Mean hospitalisation days per patient (all safety patients)	3.4	1.7	2.0	2.8
% of patients requiring outpatient visits	8.5%	4.6%	5.5%	7.6%

Notes: [a], based on conservative assumption because no published data is identified; [b], estimated by apply the relative ratio (% of patient hospitalised vs % of patient) for the ipilimumab arm; [c], assumed to be the same for the ipilimumab arm.

Dabrafenib and vemurafenib

Patient-level AE data were not available for dabrafenib or vemurafenib from the CheckMate studies. To maintain comparability and consistency, published results from the dabrafenib arm of the BREAK-3 trial and the vemurafenib arm of the BRIM-3 trial were used to derive the most plausible estimates of the proportions of patients expected to experience an endocrine disorder (any grade), diarrhoea (Grade 2+) and other AEs (Grade 3+) for the dabrafenib and vemurafenib arms. The expected proportions of patients being hospitalised

for the dabrafenib and vemurafenib treatment arms are then calculated by applying the relative ratios derived from the patient level AE data for ipilimumab in CheckMate 067 trial. The number of hospitalisation days per hospitalised patient for dabrafenib and vemurafenib are assumed to be the same for patients in the ipilimumab arm. The comparable estimates for the dabrafenib and vemurafenib arms are also shown in Table 53.

The use of aggregate published data may not be ideal for estimating AEs for BRAF inhibitors due to different mechanisms of action of immunotherapy (the Regimen and ipilimumab) and BRAF inhibitors (e.g. common AEs for BRAF inhibitors include cutaneous carcinomas, nausea and fatigue, which are grouped into other AEs in this method). However, the same classification of AEs (endocrine disorder, diarrhoea and other AEs) used for patient-level CheckMate 067 trial analysis was used for BRAF inhibitors as the most robust approach to estimating comparative safety across relevant interventions. This represents a conservative comparison versus BRAF inhibitors as the most emphasis is placed on the AEs associated with immunotherapies.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

In the CheckMate 067 trial, HRQL was assessed using the EQ-5D, which is consistent with the NICE reference case. On-study assessments of EQ-5D were scheduled during week 1 and week 5 of the first 2 treatment cycles and for on study assessments up to 6 months. After 6 months the on study EQ-5D assessments occurred during week 1 of the treatment cycle only. During the follow-up phase (when the decision to discontinue a subject from study therapy is made i.e., no further treatment with study therapy) EQ-5D assessments continued to be taken every three months for the next 12 months, and then every six months thereafter. A total of 5,244 visits involving 827 study patients where the EQ-5D was administered were included in a statistical analysis to derive the utilities used in the model.

5.4.2 Health-related quality-of-life studies

Systematic literature search

Three separate systematic reviews were conducted to identify utility and HRQL studies for advanced melanoma. The first systematic review was conducted in May 2013 for the NICE STA TA319.[55] Two updates to this systematic review were conducted using the same methods and process as the first review (apart from the span of the search period) in November 2014 for the nivolumab monotherapy NICE submission (ID845)[154] and then in October 2015 for this submission to identify more recent literature. A precise search strategy was used including terms for HRQL and melanoma; see Appendix 10 for details.

To ensure that the literature was comprehensively reviewed, a wide range of databases were searched in May 2013 for the first systematic review and in November 2014 and October 2015 for the two updates. These included: MEDLINE, EMBASE, ECONLIT, NHS EED, CDSR, HTA, DARE and CINAHL. In addition to the formal electronic searches, reference lists of included quality of life studies identified were hand searched and scanned for additional publications of relevance to the research question.

Having identified studies from a wide range of databases, the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem. Table 54 shows the eligibility criteria for assessing the relevance of different studies. The papers that, after a detailed review of the title and abstract, appeared to meet the eligibility criteria were obtained for a secondary review. This secondary review involved the entire article being assessed according to the criteria outlined in Table 54.

Table 54: Eligibility criteria for utility and HRQL studies

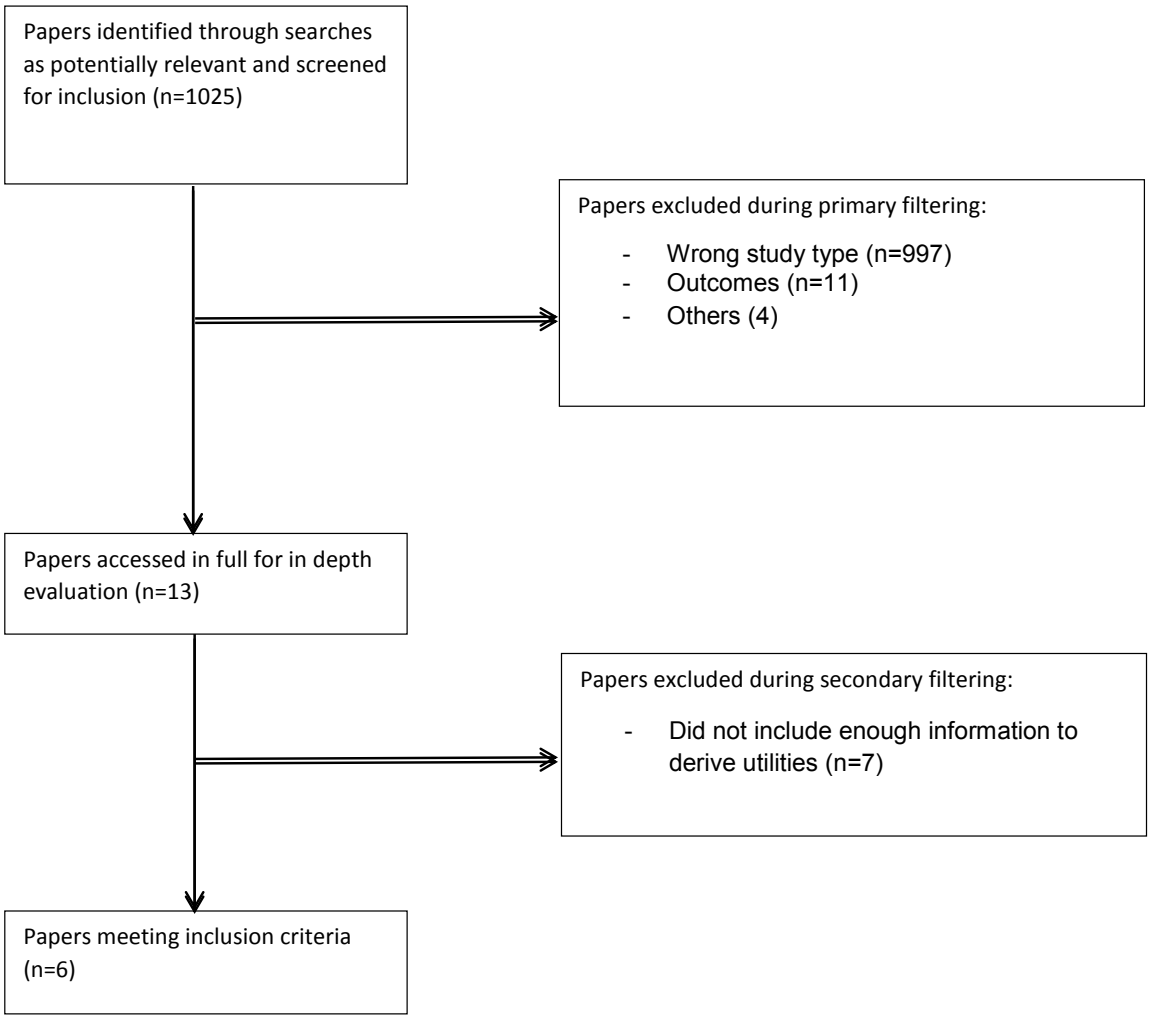
Inclusion criteria		
Category	**Inclusion criteria**	**Rationale**
Study type	Studies reporting utilities or HRQL data	The aim of the review was to identify relevant utility data
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant population
Interventions	No restriction to intervention	To allow all relevant papers to be identified
Comparators	No restriction to comparators	To allow all relevant papers to be identified
Outcomes	Any reported measurement in the form of utilities was included; and utility values mapped from a measure of HRQL	The aim of the review was to identify relevant utility studies
Exclusion criteria		
Category	**Exclusion criteria**	**Rationale**
Publication year	Studies before 1970	The earliest melanoma trial was published in 1972
Language	Non-English language literature	Time and resource required for translation
Publication type	Letters, editorials and review studies	Primary study articles are required

Identification of relevant studies

For the latest systematic review update performed in October 2015, as illustrated in Figure 59, a large proportion of the initially identified papers failed to meet the eligibility criteria during the primary filtering (Table 54). The main reason for exclusion was on the basis of type of study (997 out of 1025 papers). Other papers were excluded on the basis of outcomes reported. Altogether 13 papers were retained for further consideration after the first filtering.

During secondary filtering, seven papers were excluded because they did not report utilities or had HQRL outcomes that could not be mapped to utility values. This left six studies that met all the inclusion criteria following both primary and secondary filtering.

Figure 59: Identification of utility and HRQL studies relevant to the decision problem



Overview of relevant studies

Among the six studies identified in the latest systematic review update, two are primary utility studies.[94, 175] Both studies used European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EQ-5D data collected in nivolumab clinical trials to derive utilities for the progression-free and post-progression health states. The remaining four studies are secondary cost-effectiveness studies using utilities from previously published articles.[176-179] Both studies identified in the previous systematic review update are primary utility studies.[42, 180] They used the EORTC QLQ-C30 and applied a validated mapping algorithm for deriving utilities.

Thirteen studies were included from the first systematic review that reported relevant HRQL data. Seven of the studies directly measure quality of life. Beusterien et al. (2009)[181] and Hogg et al. (2010)[65] measure utilities and utility decrement for eight toxicity states in members of the general public. Dixon et al. (2006) [182] and King et al. (2011)[183] measure utilities in the melanoma population. Askew et al. (2011) [184] validate a technique for mapping Functional Assessment of Cancer Therapy - Melanoma to EQ-5D utilities, and both studies by Batty et al. (2011, 2012)[185, 186] compare several mapping techniques. The six remaining studies are cost-effectiveness studies using utilities from published articles.

Table 55 summarises the characteristics of these included utility and HRQL studies. Appendix 11 presents the detailed results of the studies identified in the three systematic literature reviews.

Table 55: Characteristics of the utility and HRQL studies

Systematic review	Reference	Location (patients)	Population	Study type	Utilities included
Systematic review update (October 2015)	Abernethy et al., 2015[94]	Global	Patients with naïve advanced melanoma	Primary: EORTC QLQC30 and EQ-5D questionnaire was used during the CheckMate 069.	Progression-free survival, post-progression
	Long et al., 2015[175]	Global	Patients with naïve advanced melanoma	Primary: EORTC QLQC30 and EQ-5D questionnaire was used during the CheckMate 066.	Progression-free survival, post-progression
	Delea et al., 2014[176]	Not specified	Patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	Secondary: cost-effectiveness paper primarily using utilities (EQ-5D) from BREAK-3 trial data	Progression-free survival, post-progression
	Li et al., 2015[177]	USA	Patients with metastatic melanoma, compared with a single-site BRAF V600 mutation test	Secondary: cost-effectiveness paper primarily using Beusterien et al, 2009[181]	Progression-free survival, post-progression
	Matter et al., 2015[178]	USA	Patients with metastatic melanoma	Secondary: cost-effectiveness paper primarily using Amdahl et al., 2014[187] and Beusterien et al, 2009[181]	Progression-free survival, post-progression
	Shih et al., 2015[179]	USA	Patients with metastatic melanoma	Secondary: cost-effectiveness paper primarily using Beusterien et al, 2009[181]	Progression-free survival, progression
Systematic review update (November 2014)	Porter et al. 2014[180]	Global (111 sites in Africa, Australia, Europe, North America and South America)	Previously untreated patients with unresectable malignant melanoma	Primary: EORTC QLQ-C30 responses were mapped to a generic, preference-based measure (EORTC-8D) using the mapping algorithm developed by Rowen et al., 2011[188]	Pre-progression, post-progression and time to death

Systematic review	Reference	Location (patients)	Population	Study type	Utilities included
	Hatswell et al. 2014[42]	Global (125 sites in Africa, Europe, North America and South America)	Previously treated unresectable advanced melanoma, at Stage III or IV	Primary: generating EORTC-8D utilities from the EORTC QLQ-C30 results using the mapping algorithm developed by Rowen et al., 2011[188]	Pre-progression, post-progression and time to death
First systematic review (May 2013)	Askew et al. 2011[184]	USA	Melanoma Stages I/II, III, IV	Primary: mapping study for FACT-M to EQ-5D	Stage I/II, Stage III, Stage IV, active treatments and surveillance
	Barzey et al. 2013[189]	USA	Pre-treated advanced melanoma	Secondary: cost-effectiveness paper primarily using utilities by Beusterien et al., 2009[181]	Complete/partial response, stable disease, progressive disease, death, inpatient treatment, outpatient treatment
	Batty et al. 2011[185]	Global (125 sites in Africa, Europe, North America and South America)	Previously treated advanced melanoma	Primary: comparison of mapping techniques (SF-6D and EORTC-8D)	Progression free and post-progression
	Batty et al. 2012[186]	Global (125 sites in Africa, Europe, North America and South America)	Previously treated advanced melanoma & general population	Primary: comparing patient (EORTC-8D) and general-population utilities	Progression free and post-progression with different treatments, and utilities for different times before death
	Beusterien et al. 2009[181]	UK and Australia	General public evaluating outcomes for advanced melanoma	Primary: HRQL outcomes study	Partial response, stable disease, progressive disease and best supportive care. Also utility decrement for 8 toxicity states included
	Cormier et al. 2007[190]	USA	Previously treated, metastatic melanoma	Secondary: cost-effectiveness paper primarily using utilities by Kilbridge et al., 2001[191]	NED, NED with NED treatment, salvage LR, salvage DR, LR, DR
	Dixon et al. 2006[182]	UK	Malignant melanoma	Primary: cost-effectiveness study also measuring HRQL	Follow-up after interferon-alpha treatment. Years 1-5.

Systematic review	Reference	Location (patients)	Population	Study type	Utilities included
	Hirst et al. 2012[192]	Australia	No melanoma, and different stages of melanoma	Secondary: cost-effectiveness analysis paper using utilities published by Bendeck et al. 2004, Kilbridge et al., 2001, Stratton et al., 2000 and Morton et al., 2009[191, 193-195]	Melanoma in situ, melanoma Stages I, II, III and IV. For all stages utilities are given for 'at diagnosis' and for 'stable disease'
	Hogg et al. 2010[65]	Canada	General public	Primary: HRQL outcomes study	Partial response, stable disease, progressive disease and best supportive care. Also utility decrement for 8 toxicity states included
	King et al. 2011[183]	USA	Melanoma	Primary: HRQL outcomes study	Stages I, II, III and IV disease. New diagnoses and established diagnoses
	Lee et al. 2012[196]	UK	Previously treated, metastatic melanoma	Secondary: cost-effectiveness paper primarily using utilities from MDX010-20 trial	Ipilimumab and best supportive care
	Losina et al. 2007[197]	USA	Melanoma	Secondary: Cost-effectiveness paper primarily using utilities by Chen et al., 2004[195]	Stages I/II and Stages III/IV
	Mooney et al. 1997[198]	USA	Melanoma	Secondary: Cost-effectiveness paper using utilities published by Hillner et al., 1992 and Wong et al., 1995[199, 200]	Complete remission and metastatic melanoma

Key: DR, distant recurrence; EORTC QLQ, the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, The EuroQol five dimensions questionnaire; FACT-M, Functional Assessment of Cancer Therapy - Melanoma; HRQL, Health-related quality of life; LR, local recurrence; NED, no evidence of disease.

5.4.3 Adverse reactions

The impacts of AEs on HRQL are captured in the model by applying treatment arm specific utility decrements estimated from the statistical model based on patient level EQ-5D data collected in the CheckMate 067 trial (see Table 56). The same statistical model was also used for the estimation of utilities for progression-free and progressed health states.

5.4.4 Health-related quality-of-life data used in cost-effectiveness analysis

There are three arms in the CheckMate 067 trial: the Regimen, ipilimumab and nivolumab; and EQ-5D data from all treatment arms were used for the statistical analysis with key covariates including baseline EQ-5D (i.e. EQ-5D utilities observed at baseline / randomisation), progression status (progression free as the reference category) and treatment arms (two separate covariates to represent the Regimen arm and ipilimumab arm respectively with nivolumab arm as the reference category). Nivolumab was included within the quality of life model as this is recognised as a considerably less toxic treatment for patients compared to ipilimumab therefore including this treatment arm allowed a more accurate baseline utility to be estimated to use for comparisons to BRAF inhibitors.

The utility impacts of the Regimen and ipilimumab treatment arms (relative to the nivolumab arm) are captured by the estimated coefficients of the two covariates representing the Regimen and ipilimumab treatment arms. It is assumed in this analysis that these estimated treatment arm specific utilities (after controlling for baseline EQ-5D and progression status) reflect the utility impacts of different AE profiles of different treatment arms.

Table 56 presents the final chosen statistical model fitted using EQ-5D data collected in the CheckMate 067 trial. Utilities were produced using a mixed effects to account for the correlation of utility observations within patient. Detailed methods and procedure used for fitting the statistical model are presented in Appendix 12.

Table 56: Statistical model results using EQ-5D data from CheckMate 067

	Coefficient	95% confidence interval	p-value
Intercept	0.4259	(0.3787, 0.4732)	<.0001
Post-progression	-0.03291	(-0.04577, -0.02005)	<.0001
Baseline EQ-5D	0.4765	(0.4239, 0.5292)	<.0001
Treatment: ipilimumab	-0.03136	(-0.059, -0.00372)	0.0262
Treatment: the Regimen	-0.03373	(-0.06121, -0.00626)	0.0161
Sample size: 5,244 EQ-5D observations from 827 patients; Baseline EQ-5D = 0.7754.			

The estimated utility decrements for the Regimen and ipilimumab arms are -0.03373 and -0.03136 and respectively with nivolumab arm being the reference arm (see Table 56) which implies that patients treated with the Regimen and ipilimumab have worse utility due to AEs compared with patients treated with nivolumab (after controlling for baseline utility and progression status) and that patients treated with the Regimen have worse utility compared to patients treated with ipilimumab due to AEs.

For dabrafenib and vemurafenib, a conservative assumption was made to assume the utility impacts of AEs for dabrafenib and vemurafenib are comparable with the nivolumab arm, i.e., a decrement of 0 is applied for dabrafenib and vemurafenib and patients treated with dabrafenib and vemurafenib have better utility compared to patients treated with the

Regimen and ipilimumab. This is a simplifying assumption consistent with the calculations made for the nivolumab monotherapy submission based upon adverse event rates and disutilities for specified adverse event types which showed similar utility decrements for nivolumab and BRAF inhibitors.

In the economic model, these utility decrements were applied to the patients who are on treatments (and therefore susceptible to drug-related AEs) in each corresponding treatment arm.

The utilities of the progression-free and progressed health states derived from the statistical model (see Table 56) were used for all treatment arms. As expected, being post progression is associated with decreased utility values (estimated mean coefficients are -0.03292) with the final mean utility values for progression-free and progressed health states being 0.7954 and 0.7625 when the baseline EQ-5D value of 0.7754 was used for the calculation (i.e. 0.7954 = 0.4259 + 0.4765 x 0.7754 and 0.7625 = 0.4259 + 0.4765 x 0.7754 – 0.03291).

Table 57 summarises the utilities used in the base case model including the utilities for different health states defined by progression status, and utility decrements for AEs for different treatment arms.

Utilities used in the recent nivolumab monotherapy and ipilimumab NICE appraisals[55, 154] were tested in a scenario analysis.

Table 57: Summary of utility values for cost-effectiveness analysis

	Utility value	Uncertainty in the model	Reference in submission	Justification
Utility values for health states defined by progression status				
Progression free	0.7954	Sampling using variance-covariance matrices assuming multivariate-normal distribution	Section 5.4	Based on statistical models fitted using EQ-5D data collected in CheckMate 067 trial
Progressed	0.7625			
Utility decrements for adverse events				
The Regimen	-0.03373	Sampling using variance-covariance matrices assuming multivariate-normal distribution	Section 5.4	Based on statistical models fitted using EQ-5D data collected in CheckMate 067 trial
Ipilimumab	-0.03136			
Dabrafenib	0	Fixed		Conservative assumption
Vemurafenib	0	Fixed		

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

Systematic literature search

Similar to the utility and HRQL studies, three separate systematic reviews were conducted to identify costs and resource studies for advanced melanoma. The first systematic review was conducted in May 2013 for the NICE STA TA319.[55] Two updates to this systematic review

were conducted using the same methods and process as the first review (apart from the span of the search period) in November 2014 for the nivolumab monotherapy NICE submission (ID845)[154] and then in October 2015 for this submission to identify more recent literature. A precise search strategy was used that included terms for costs, resource use and melanoma; see Appendix 10 for details.

To ensure that the literature was comprehensively reviewed, a wide range of databases were searched in May 2013 for the first systematic review and in November 2014 and in October 2015 for the two systematic review updates. These included MEDLINE, EMBASE, ECONLIT, NHS EED, CDSR, HTA, DARE and CINAHL. In addition to the formal electronic searches, reference lists of included cost and resource use studies identified, were hand searched and scanned for additional publications of relevance to the research question.

After identifying the studies, the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem. Table 58 shows the inclusion criteria for assessing the relevance of different studies.

The papers, which after a detailed review of the title and abstract, appeared to meet the inclusion criteria, were obtained for a secondary review. This secondary review involved the entire article being assessed according to the criteria outlined in Table 58.

Table 58: Eligibility criteria for cost and resource use studies and rationale for each criterion

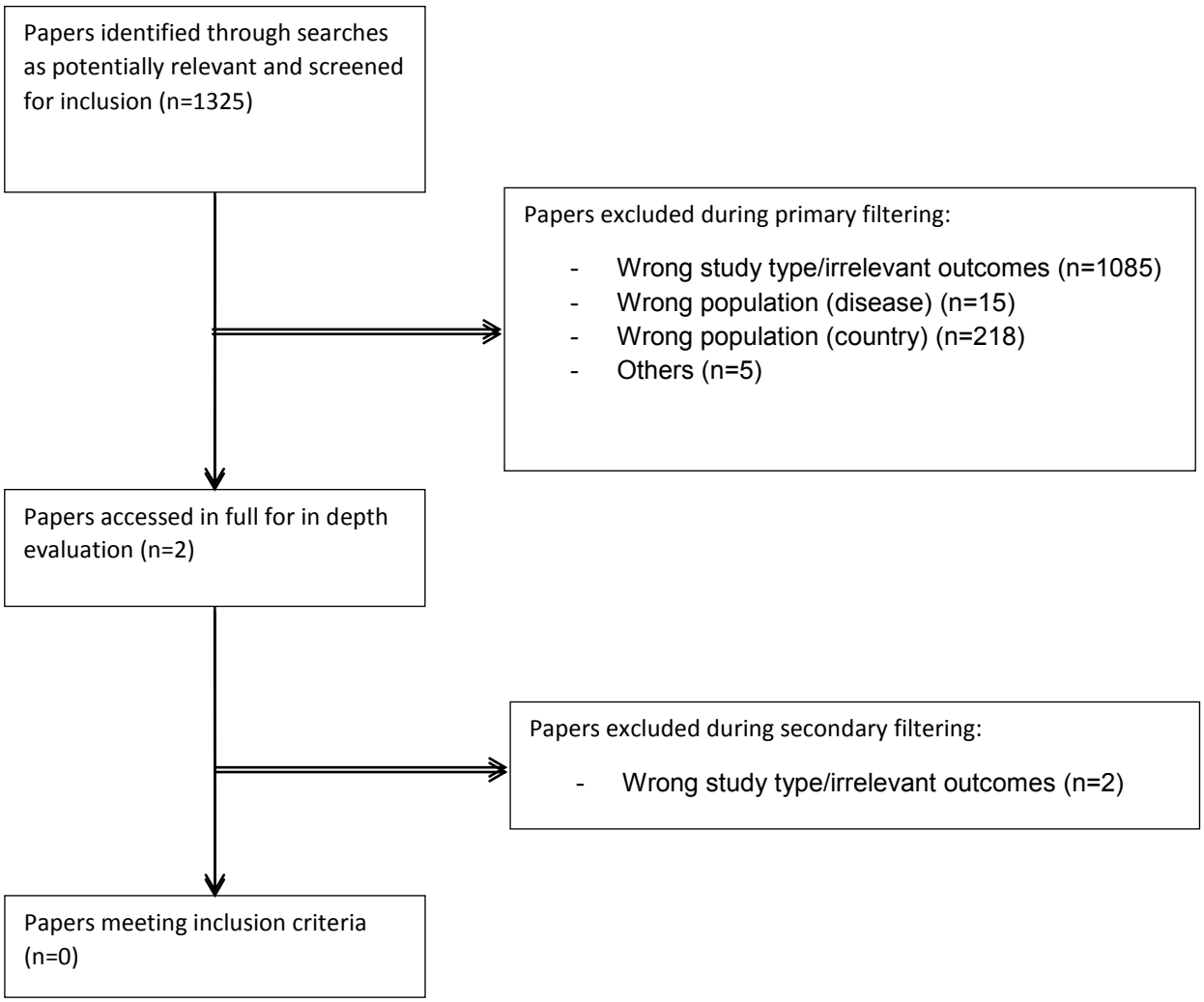
Inclusion criteria		
Category	Inclusion criteria	Rationale
Study type	Studies reporting costs and resource use	The aim of the review was to identify relevant costs and use of resources
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population
Interventions	There was no restriction to intervention	To allow all relevant evidence to be identified
Comparators	There was no restriction to comparators	To allow all relevant evidence to be identified
Outcomes	Studies reporting the resource use and costs associated with the treatment and ongoing management of advanced melanoma	The aim of the review was to identify relevant costs and data about resource use
Country of study	UK and Ireland	Costs and use of resources from a UK or Irish perspective were required
Exclusion criteria		
Category	Exclusion criteria	Rationale
Publication year	Studies before 1970	The earliest melanoma trial was published in 1972
Language	Non-English language literature	Time and resource required for translation and relevance to UK setting
Publication type	Letters, editorials and review studies	Primary study articles are required

Identification of relevant studies

For the latest systematic review update performed in October 2015, as illustrated in Figure 60, the majority of the papers identified failed to meet the eligibility criteria during the first filtering. Of 1325 identified papers, 1085 were excluded based on study type and outcomes. Other papers were excluded based on patient population. Two papers were retained for further consideration after the first filtering.

During secondary filtering, both papers were excluded on the basis of type of study. Therefore, following both primary and secondary screening, no paper met all the eligibility criteria.

Figure 60: Identification of cost and resource use studies relevant to the decision problem in the second systematic review



Overview of relevant studies

Although the latest update of the systematic review did not identify any relevant study, three studies were identified in the previous systematic review update (performed in November 2014) which all reported drug cost: one cost-analysis study[42] and two structured abstracts[201, 202]. Furthermore, five studies were identified in the first systematic review (performed in May 2013) which are economic impact and cost-effectiveness analyses[182, 196, 203] or cost and resource utilisation studies[52, 204]. These five studies reported a wide range of costs and resource use data, including costs for drugs, inpatient/outpatient, GP/nurse, palliative and terminal care, and indirect costs.

Table 59 presents the key characteristics of the studies included in the original systematic review and the previous update. Appendix 13 provides the full results for these two systematic reviews.

None of the available studies report on the costs or resource use associated with disease management for newly available immunotherapies or BRAF inhibitors.

Table 59: Characteristics of the costs and resource use studies identified

Systematic review	Reference	Country	Population	Study type	Resource use and costs included
Systematic review update (November 2014)	Hatswell et al. 2014[42]	UK	Metastatic melanoma	Cost analysis	Costs for drugs
	NIHR et al. 2013[201]	UK	Malignant melanoma	Summary safety, efficacy or effectiveness of new drugs	Costs for drugs
	NIHR et al. 2013[202]	UK	Advanced melanoma	Summary safety, efficacy or effectiveness of new drugs	Costs for drugs
First systematic review (May 2013)	Dixon et al. 2006[182]	UK	Malignant melanoma	Cost-effectiveness analysis	Inpatient costs, outpatient costs, GP, costs, nurse visit costs and interferon costs for two groups (observation and interferon)
	Johnston et al. 2012[203]	UK, Italy and France	Advanced melanoma	Economic impact	Hospitalisation and outpatient costs, use of hospital and hospice
	Lee et al. 2012[196]	UK	Previously treated metastatic melanoma	Cost-effectiveness analysis	Costs for drugs, treatment, palliative and terminal care
	Lorigan et al. 2010[204]	UK	Advanced melanoma	Healthcare resource utilisation study	Hospitalisation rates and duration of hospitalisation
	Morris et al. 2009[52]	UK	Malignant melanoma	Cost analysis	Costs of GP consultations, inpatient care, day cases, and outpatient attendances. NHS costs, patient costs and indirect costs

5.5.2 Intervention and comparators' costs and resource use

The unit drug costs of the treatments are based on the list price for nivolumab, ipilimumab and BRAF inhibitors (Table 60). In a scenario analysis, known and assumed patient access scheme (PAS) discounts are used (Table 60). The drug cost of pembrolizumab based on list price is also presented in Table 60 as this is used for the calculation of costs for subsequent treatments.

Table 60: Unit drug costs

Drug	Concentration	Vial volume	Dose per vial/pack (mg/MU)	Price per vial/pack (no PAS) – base case	Price per vial/pack (with PAS) – scenario analysis	Source for price with no PAS
Nivolumab	10mg/ml	4ml	40	£439.00	n/a	BMS
		10ml	100	£1,097.00	n/a	BMS
Ipilimumab	5mg/ml	10ml	50	£3,750.00	[redacted]	MIMS November 2015
		40ml	200	£15,000.00	[redacted]	MIMS November 2015
Dabrafenib	50mg	28 tablets	1400	£933.33	[redacted]	MIMS November 2015
	75mg	28 tablets	2100	£1,400.00	[redacted]	MIMS November 2015
Vemurafenib	240mg	56 tablets	13440	£1,750.00	[redacted]	MIMS November 2015
Pembrolizumab[c]	1mg/ml	50ml	50	£1,315.00	[redacted]	MIMS November 2015

[redacted];
[c], only used for the calculation of cost of subsequent therapy;
[redacted]

The dosing regimen for each treatment is presented in Table 48. For the Regimen and ipilimumab, dosing based on the method of moments using patient weight data is applied to estimate the mean number of vials required in the base case using UK patient-level weight data from trials CheckMate 067, CheckMate 066, CheckMate 037 and CA184-024. The method assumes a log-normal distribution for body weight and calculates the proportion of patients requiring each possible number of vials based upon the log-normal distribution derived from the individual patient weights. This calculation is an accurate method of accounting for wastage, assuming that no vial sharing occurs. The method has been used in the recent ipilimumab NICE appraisal (TA319[55]). Table 61 shows the total dose required and the drug costs for each administration for the base case and with PAS.

Table 61: Dose required and drug costs for each administration

Drug	Dosing regimen	Dose per admin	Vials per admin[a]	Drug cost per admin (without PAS)	Drug cost per admin (with PAS)
Nivolumab (first 4 doses in the Regimen arm)	1mg/kg, every 3 weeks by IV	80mg	[redacted]	£1,082 per IV	n/a
Nivolumab (after first 4 doses in the Regimen arm)	3mg/kg, every 2 weeks by IV	239mg	[redacted]	£2,840 per IV	n/a
Ipilimumab	3 mg/kg	239mg	[redacted]	£19,786 per IV	[redacted]
Dabrafenib	300mg, daily oral	300mg		£200 per day	[redacted]
Vemurafenib	1920mg, daily oral	1920mg		£250 per day	[redacted]
Pembrolizumab[b]	2mg/kg, every 3 weeks by IV	159mg	[redacted]	£4,843 per IV	n/a
Note: [a], mean vials calculated for nivolumab and ipilimumab using method of moment; [b], only used for the calculation of cost of subsequent therapy.					

Dose interruption was included within the model using data from the CheckMate 067 trial for the Regimen and ipilimumab and incorporated into the model per administered cycle. These analyses showed that, on average, 90.2% of patients on nivolumab within the Regimen received their expected doses and the mean number of doses received was [redacted] and [redacted] for ipilimumab within the Regimen and ipilimumab monotherapy respectively.

Administration costs for all chemotherapies are taken from NHS reference costs with all treatments assumed to be given in a day case setting. A one-off cost is included for BRAF inhibitors as oral chemotherapy at treatment initiation. Furthermore, a complete metabolic panel laboratory test cost is added to the ipilimumab and nivolumab administration costs based on test requirements in the product SmPCs.[55] The administration cost assumptions for ipilimumab and vemurafenib are the same as those within the previous ipilimumab NICE submission.[55] The summary of administration costs used within the model is shown in Table 62.

Table 62: Unit costs for each type of administration

Resource use element	Unit cost	Source
Complex parenteral chemotherapy - 1st attendance	£329.32	NHS Reference costs 2014/2015 SB13Z
Exclusively oral chemotherapy	£192.32	NHS Reference costs 2014/2015 SB11Z
Laboratory tests – complete metabolic panel	£1.19	NHS Reference costs 2014/2015 DAPS04

5.5.3 Health-state unit costs and resource use

As discussed in Section 5.2 resource use is modelled in the same manner to the recent submission for nivolumab monotherapy by dividing the patient's lifetime into the following health states: first year after treatment initiation, second year after treatment initiation, third and subsequent years after treatment initiation, 12 weeks before death (palliative care), and death. Consequently, two one-off costs (treatment initiation and end of life) and four per cycle based costs are estimated.

All health state resource use quantities and frequencies included within the model are the same as those included in the recent submission for nivolumab monotherapy, mainly based on the MELODY study described in an Oxford Outcomes report[205] and UK clinical opinion, and these assumptions have been regarded as appropriate by the ERG of the nivolumab monotherapy appraisal.[154] The unit costs and health inflation index have been updated based on the latest NHS reference costs for 2014/15[206] and the latest Personal Social Services Research Unit (PSSRU) report for 2015[207].

Table 63 presents the detailed resource use estimates for the one-off treatment initiation and end of life costs.

Table 64 presents the detailed resource use estimates for the cycle costs for the first, second, third and subsequent years after treatment initiation and for palliative care. Table 65 summarises the resource use for the defined health states used in the economic model. **Table 63: One-off resource use for treatment initiation and end of life**

Resource use item	Unit cost	Treatment initiation – one off		End of life care – one off		Sources
		% Patients	Resource use number	% Patients	Resource use number	
Outpatient						
Medical oncologist outpatient visit	£158.54	81.0%	3.6			NHS Referen Oncology (To
Radiation oncologist outpatient visit	£134.48	6.0%	2.3			NHS Referen Previously Ra code 800)
General practitioner visit	£38.00	4.0%	2.0			PSSRU 2014 costs
Palliative care physician outpatient visit	£96.80	1.3%	1.0			NHS Referen total for SD04
Psychologist outpatient visit	£138.00	0.5%	1.0			PSSRU 2014 hour visit ass
Plastic surgeon outpatient visit	£92.69	2.0%	1.5			NHS Referen (Total OPAT
Inpatient (resource use and unit cost measured by days)						
Oncology/general ward – inpatient	£302.97	6.0%	2.8			NHS Ref cos for elective a HRGs. Weigh
Terminal care						
Hospice stay	£6,337.20			23.1%	1.0	Improving Ch Dewar, the K
Laboratory tests						
Complete blood count	£3.01	100.0%	1.2			NHS Referen (TOC currenc

Resource use item	Unit cost	Treatment initiation – one off		End of life care – one off		Sources
		% Patients	Resource use number	% Patients	Resource use number	
Complete metabolic panel	£1.19	100.0%	1.2			NHS Referen biochemistry
Lactate dehydrogenase	£1.19	100.0%	1.2			NHS Referen biochemistry
Radiological examinations						
CT scan (any)	£96.57	100.0%	1.0			NHS Referen RD20A/RD21
MRI of brain	£141.06	14.5%	1.0			NHS Referen RD01A/RD02
PET scan	£517.00	5.0%	1.0			NHS Referen Emission Tor RN07A (Tota
Bone scintigraphy	£188.77	16.8%	1.0			NHS Referen Scan of two c RN15A (Tota
Echography	£55.39	4.5%	1.0			NHS Referen RA23Z/RA24
Chest x-ray	£102.03	17.5%	1.0			NHS Referen Fluoroscopy 20 minutes R

Table 64: Cycle resource use for patients in the pre-palliative care and palliative periods

Resource use item	Unit cost	Pre-palliative care period						Palliative care period		Sources (unit cost)
		Year 1		Year 2		Year 3 and beyond				
		% Patients	Monthly resource use	% Patients	Monthly resource use	% Patients	Monthly resource use	% Patients	Monthly resource use	
Outpatient										
Medical oncologist outpatient visit	£158.54	79.3%	1.9	39.6%	1.9	23.8%	1.9	62.3%	0.9	NHS Reference costs 2014/2015 Medical Oncology (Total OPATT service code 370)
Radiation oncologist outpatient visit	£134.48	6.0%	1.0	3.0%	1.0	1.8%	1.0	7.0%	1.5	NHS Reference costs 2014/2015 Clinical Oncology Previously Radiotherapy (Total OPATT service code 800)
General practitioner visit	£38.00	4.0%	2.0	2.0%	2.0	1.2%	2.0	78.5%	1.9	PSSRU 2014: pg195 without qual. with indirect costs
Palliative care physician outpatient visit	£96.80							23.0%	1.2	NHS Reference costs 2013/2014 Weight Ave of total for SD04A and SD05A
Psychologist outpatient visit	£138.00							3.5%	3.0	PSSRU 2014: pg183 per hour of client contact. 1 hour visit assumed
Plastic surgeon outpatient visit	£92.69	2.0%	1.5	1.0%	1.5	0.6%	1.5			NHS Reference costs 2014/2015 Plastic Surgery (Total OPATT service code 160)
Nurse visit	£37.26	12.5%	1.0	6.3%	1.0	3.8%	1.0			NHS Reference costs 2014/2015 District Nurse, Adult, Face to face (TOC currency code N02AF)
Inpatient (resource use and unit cost measured by days)										
Oncology/general ward – inpatient	£302.97	5.0%	1.3	2.5%	1.3	1.5%	1.3	13.0%	3.6	NHS Ref costs 2014/2015 Ave of excess bed days for elective and non-elective inpatients for all HRGs. Weighted by activity.
Palliative care unit – inpatient	£180.05							24.5%	4.0	NHS Reference costs 2014/2015 Ave of total for SD01A and SD03A
Home care										
Palliative care physician – home care	£124.00							21.8%	1.0	PSSRU 2014: pg111 Outpatient - non medical specialist palliative care attendance (adults and children)
Palliative care nurse – home care	£78.67							61.0%	1.4	NHS Reference costs 2014/2015 Specialist Nursing, Palliative/Respite Care, Adult, Face to face (TOC currency code N21AF)
Home aide visits	£153.00							25.5%	7.3	PSSRU 2014: pg111 Outpatient - medical specialist palliative care attendance (adults and children)

Resource use item	Unit cost	Pre-palliative care period						Palliative care period		Sources (unit cost)
		Year 1		Year 2		Year 3 and beyond				
		% Patients	Monthly resource use	% Patients	Monthly resource use	% Patients	Monthly resource use	% Patients	Monthly resource use	
Laboratory tests										
Complete blood count	£3.01	100.0%	1.3	50.0%	1.3	30.0%	1.3			NHS Reference costs 2014/2015 Haematology (TOC currency code DAPS05)
Complete metabolic panel	£1.19	95.0%	1.3	47.5%	1.3	28.5%	1.3			NHS Reference costs 2014/2015 Clinical biochemistry (TOC currency code DAPS04)
Lactate dehydrogenase	£1.19	95.0%	1.3	47.5%	1.3	28.5%	1.3			NHS Reference costs 2014/2015 Clinical biochemistry (TOC currency code DAPS04)
Radiological examinations										
CT scan (any)	£96.57	100.0%	1.0	50.0%	1.0	30.0%	1.0	3.8%	1.0	NHS Reference costs 2014/2015 Ave of total for RD20A/RD21A/RD22Z
MRI of brain	£141.06	18.0%	0.3	9.0%	0.3	5.4%	0.3	1.3%	1.0	NHS Reference costs 2014/2015 Ave of total for RD01A/RD02A/RD03Z
PET scan	£517.00	0.0%	0.4	0.0%	0.4	0.0%	0.4			NHS Reference costs 2014/2015. Positron Emission Tomography (PET), 19 years and over RN07A (Total HRG)
Bone scintigraphy	£188.77	1.0%	0.3	0.5%	0.3	0.3%	0.3			NHS Reference costs 2014/2015 Nuclear Bone Scan of two or three phases, 19 years and over RN15A (Total HRG)
Echography	£55.39	9.0%	0.3	4.5%	0.3	2.7%	0.3			NHS Reference costs 2014/2015 Ave of total for RA23Z/RA24Z/RA25Z/RA26Z/RA27Z
Chest x-ray	£102.03	27.5%	1.1	13.8%	1.1	8.3%	1.1	1.3%	1.0	NHS Reference costs 2014/2015 Contrast Fluoroscopy Procedures with duration of less than 20 minutes RA16Z (Total HRG)
Pain control										
Morphine – Oral	£10.88							51.0%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014
Morphine – IV	£118.00							22.0%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014
Morphine – Transdermal patch	£40.31							15.0%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014
NSAIDs (Ibuprofen)	£0.75							47.5%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014
Other – Paracetamol	£4.60							36.0%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014

Table 65: List of health states and associated costs in the economic model

Defined health states	Value
Treatment initiation – one off	£740.77
Year 1 (per week)	£96.80
Year 2 (per week)	£48.40
Year 3 and beyond (per week)	£29.04
Palliative care period – 12 weeks before death (per week)	£217.16
End of life care – one off	£1,463.89

5.5.4 Adverse reaction unit costs and resource use

As discussed in Section 5.3.8 resource use for treating AEs is based on patient-level CheckMate 067 trial data analysis and considered for endocrine disorder (any grade), diarrhoea (Grade 2+) and other AEs (Grade 3+) and split into costs for hospitalisation and outpatient visits. The unit cost for hospital days and outpatient visits and sources are presented in Table 66.

Table 66: Unit costs used for AEs

Items	Value	Reference
Hospital stay for endocrine disorders (day)	£255.35	NHS ref cost 2014/15 (Other Endocrine Disorders with CC Score 4+ (KA08A)(Non elective excess bed days)
Hospital stay for other AEs (day)	£295.80	NHS ref cost 2014/15 (Non Elective Inpatients - Excess Bed Days (NEL_XS)
Unit cost for outpatient visit (endocrine disorder)	£413.17	Oxford Outcomes[205]
Unit cost for outpatient visit (diarrhoea)	£575.98	
Unit cost for outpatient visit (other AEs)	£348.75	

The unit costs are applied to the number of hospital days and outpatient visits for each treatment arm (Table 53), and a final per patient (accounting for patients who do not have AEs) average AE cost is calculated for each treatment arm and is used in the model (Table 67).

For simplicity, treatment arm specific per patient AE resource use is applied at the start of the model, and then periodically for patients who are still on treatment, where the cycle to apply the decrement is determined by the mean follow-up of the CheckMate 067 trial which is 54 weeks.

Table 67: Summary of per patient AE costs in the economic model

	the Regimen	Ipilimumab	Dabrafenib	Vemurafenib
Hospitalisation costs – endocrine disorder (any grade)	£158.27	£35.31	£0.00	£0.00
Hospitalisation costs – diarrhoea (Grade 2+)	£388.42	£333.85	£0.00	£98.46
Hospitalisation costs – other AEs (Grade 3+)	£993.25	£510.76	£605.13	£841.50
Hospitalisation costs – subtotal	**£1,539.93**	**£879.91**	**£605.13**	**£939.96**
Outpatient costs – endocrine disorder (any grade)	£31.62	£11.85	£0.00	£0.00
Outpatient costs – diarrhoea (Grade 2+)	£27.21	£20.62	£0.00	£6.08
Outpatient costs – other AEs (Grade 3+)	£29.66	£16.18	£19.17	£26.65
Outpatient costs – subtotal	**£88.48**	**£48.65**	**£19.17**	**£32.74**
Total cost	**£1,628.42**	**£928.56**	**£624.29**	**£972.70**

5.5.5 Miscellaneous unit costs and resource use

The costs of subsequent treatments of ipilimumab, dabrafenib, vemurafenib and pembrolizumab were captured by the model. Table 68 shows the proportions of patients using these subsequent treatments for each treatment arm, based on patient level data from CheckMate 067 trial for the Regimen and ipilimumab arms, and from BRIM-3 trial for dabrafenib and vemurafenib arms.

Table 68: Proportions of patients using selected subsequent treatments

Treatment arms (by BRAF status)	Subsequent treatments			
	Ipilimumab	Dabrafenib	Vemurafenib	Pembrolizumab
BRAF mutation-negative				
After the Regimen	4.7%	0.9%	0.0%	4.7%
After ipilimumab	1.8%	0.9%	0.9%	34.4%
BRAF mutation-positive				
After the Regimen	3.0%	19.8%	11.9%	1.0%
After ipilimumab	1.0%	36.1%	27.8%	17.5%
After dabrafenib	22.0%	0.0%	0.0%	0.0%
After vemurafenib	22.0%	0.0%	0.0%	0.0%

Table 69 shows the calculations of the one-off costs for subsequent use of ipilimumab, dabrafenib, vemurafenib and pembrolizumab, based on list price and estimated mean

duration of subsequent treatment of these drugs. These one-off costs were applied to the patients who discontinue treatments in the model and the estimated proportions of patients using each drug as subsequent treatment (see Table 68). The mean number of ipilimumab doses used for previously treated patients is 3.3 which was based on the NICE TA268.[56] The mean duration of treatment was assumed to be 7 months for vemurafenib based on the costing template from NICE TA269.[58] The same treatment duration was used for dabrafenib due to absence of alternative data. The mean number of pembrolizumab doses was assumed to be 13.3 which was based on the reported mean life years of 0.762 in the pre-progression state for previously treated patients in the pembrolizumab arm in NICE TA357.[6]

Table 69: One-off cost for subsequent use of ipilimumab, dabrafenib, vemurafenib and pembrolizumab (based on list price)

Resource use element	Value	Sources
Ipilimumab		
Mean duration (doses)	[redacted]	NICE TA268[56]
Drug cost	[redacted]	See Table 61
Administrative cost	£1,091	See Table 62
Adverse event cost	£929	See Table 67
Total	[redacted]	
Dabrafenib		
Mean duration (day)	213.1	Assumed same as vemurafenib
Drug cost	£42,612	See Table 61
Administrative cost	£192	See Table 62
Adverse event cost	£624	See Table 67
Total	£43,429	
Vemurafenib		
Mean duration (day)	213.1	NICE TA269[58]
Drug cost	£53,266	See Table 61
Administrative cost	£192	See Table 62
Adverse event cost	£973	See Table 67
Total	£54,431	
Pembrolizumab		
Mean duration (doses)	13.3	NICE TA357[6]
Drug cost	£64,180	See Table 61
Administrative cost	£4,380	See Table 62
Adverse event cost	£624	Assumed same as dabrafenib
Total	£69,184	

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base case de novo analysis inputs

Table 70 summarises the key inputs for the base case model. A full list of model inputs and the values used (mean and measurement of uncertainty) can be found in the "Parameters" sheet in the submitted Excel model.

Table 70: Summary of variables applied in the base case economic model

Variable	Mean base case value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model setting			
Discount rate - costs	3.5%	Fixed	
Discount rate - QALYs	3.5%	Fixed	
Patient characteristics			
BRAF mutation-negative	See Table 51	Fixed	See Table 51 in Section 5.3.2 and Table 52 in Section 5.3.3
BRAF mutation-positive	See Table 52	Fixed	
Parametric survival curves based on indirect comparison			
TTP the Regimen and ipilimumab	See Figure 45	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Section 5.3.2
PPS the Regimen and ipilimumab	See Figure 49		
PrePS the Regimen and ipilimumab	See Figure 46		
Parametric survival curves for BRAF inhibitors			
OS - vemurafenib	See Figure 54	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Section 5.3.3
PFS - vemurafenib	See Figure 53		See Section 5.3.3
OS HR dabrafenib vs vemurafenib	1	Fixed	See Section 5.3.3
PFS HR dabrafenib vs vemurafenib	1	Fixed	
Parametric survival curves for long-term survival			
Registry survival (rebase at Year 3)	See Figure 55	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Section 5.3.2
Pooled ipilimumab survival (rebase at Year 3)	See Figure 51		See Section 5.3.3
Parametric survival curve for TOT			
TOT nivolumab – BRAF mutation-negative	See Figure 57	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Section 5.3.4
TOT – BRAF mutation-positive	See Figure 58		See Section 5.3.5

Variable	Mean base case value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Utilities			
Progression free	0.7954	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Table 57 in Section 5.4.4.
Progressed	0.7625		
Drug dosing and costs			
Patient weight (kg)	79.6	SE=0.77 (Normal)	Section 5.3.2, 5.3.3 and 5.5.2
Drug cost of nivolumab (first 4 doses in the Regimen arm)	£1,082.37	Fixed	See Table 61 in Section 5.5.2
Drug cost of nivolumab (after first 4 doses in the Regimen arm)	£2,840.49	Fixed	
Drug cost of ipilimumab per IV	[redacted]	Fixed	
Drug cost of dabrafenib per day	£200.00	Fixed	
Drug cost of vemurafenib per day	£250.00	Fixed	
Administration cost of IV	£330.51	SE assumed to be 20% of mean (Normal)	See Table 62 in Section 5.5.2
Administration cost of oral chemotherapy (one off)	£192.32		
Resource use and costs			
Treatment initiation - one off	£740.77	SE assumed to be 20% of mean (Normal)	See Table 65 in Section 5.5.3
Year 1 (per week)	£96.80		
Year 2 (per week)	£48.40		
Year 3 and beyond (per week)	£29.04		
Palliative care period (per week)	£217.16		
End of life care - one off	£1,463.89		
Length of palliative care period (weeks)	12	Fixed	Section 5.5.3
Other costs			
Subsequent ipilimumab treatment (one-off)	[redacted]	Within model calculation	See Table 69 in Section 5.5.5
Subsequent dabrafenib treatment (one-off)	£43,428.96		
Subsequent vemurafenib treatment (one-off)	£54,430.64		
Subsequent pembrolizumab treatment (one-off)	£69,184.28		

Variable	Mean base case value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Adverse events (rates, costs, utility decrements)			
AE costs for the Regimen	£1,628.42	SE assumed to be 20% of mean (Normal)	See Table 67 in Section 5.5.4
AE costs for ipilimumab	£928.56		
AE costs for dabrafenib	£624.29		
AE costs for vemurafenib	£972.7		
AE utility decrement for nivolumab and ipilimumab	-0.03373	SE assumed to be 20% of mean (Beta)	See Table 57 in Section 5.4.4
AE utility decrement for ipilimumab	-0.03136		
AE utility decrement for dabrafenib	0	Fixed	
AE utility decrement for vemurafenib	0		
Mean safety follow-up period	54	Fixed	See Section 5.5.4
Key: AE, adverse event; CI, confidence interval; DTIC, dacarbazine; OS, overall survival; PFS, progression free survival; PPS, post-progression survival; SE: standard error; TOT, time on treatment; TTP, time to progression.			

Assumptions

The de novo economic model used a range of assumptions on the model structure and model inputs on efficacy and safety, drug costs, resource use and HRQL. These assumptions and the rationales have been described throughout the cost effectiveness section. Among these, the most important model assumptions are summarised below:

- The assumptions that underpin the patient-level indirect treatment comparison using CheckMate 067, CheckMate 066 and the MDX010-20 trials for deriving comparative efficacy of nivolumab and ipilimumab in terms of TTP, PPS and PrePS (see detail in Section 4.13).
- The extremely conservative assumption of equal PPS for all immunotherapy (see detail in Section 4.13)
- The assumptions that underpin the comparison to BRAF inhibitors (dabrafenib and vemurafenib) and immunotherapies (see Section 4.13).
- The assumptions for extrapolation of OS using melanoma registry data for BRAF inhibitors and pooled ipilimumab long-term OS for the Regimen and ipilimumab from Year 3 onwards (see Section 5.3.2).
- The pragmatic treatment continuation rule of setting a maximum treatment period of 2 years for nivolumab (see Section 5.3.2).

5.7 Base-case results

5.7.1 Base case incremental cost-effectiveness analysis results

Table 71 and Table 72 present the base case incremental cost-effectiveness results for BRAF mutation-negative and BRAF mutation-positive patients, respectively, at NHS list price as requested by NICE. However, these results cannot be relied upon for decision-making since ipilimumab, dabrafenib and vemurafenib have been recommended by NICE on the basis that the manufacturers provide these drugs to the NHS with a confidential discount via their respective PAS's. Therefore, the costs for the comparators presented in Table 71 and Table 72 do not represent the true costs to the NHS, and consequently, the incremental cost and incremental cost-effectiveness ratios (ICERs) of the Regimen will be underestimated compared to these drugs.

[redacted] In both the base case and PAS-assumed base case, no PAS is assumed for nivolumab in the Regimen arm.

The Regimen is cost-effective at a willingness to pay threshold of £30,000 in both the BRAF mutation-negative and BRAF mutation-positive populations.

Table 71: Base case results – BRAF mutation-negative (drug prices based on list price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
Ipilimumab	[redacted]	3.77	2.90						
The Regimen	[redacted]	6.55	5.09	£22,826	2.79	2.19	£10,433		£10,433

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

Table 72: Base case results – BRAF mutation-positive (drug prices based on list price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
Dabrafenib	[redacted]	2.24	1.74						
Vemurafenib	[redacted]	2.24	1.74	£19,070	0.00	0.00	Same QALYs	Dominated	Excluded due to dominance
Ipilimumab	[redacted]	3.38	2.59	£25,161	1.13	0.85	£29,597	Extended dominated	Excluded due to dominance
The Regimen	[redacted]	6.26	4.85	£35,085	4.02	3.11	£11,284		£11,284

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Notes: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

[redacted]

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									
[redacted]									
[redacted]									

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

5.7.2 Clinical outcomes from the model

Table 75 summaries the estimated key clinical results from the model and compares the model results with the clinical trial result. It shows that the model results are comparable with the corresponding clinical data. Modelled long-term OS for ipilimumab at Year 10 for BRAF mutation-positive patients is slightly lower than what was reported in the pooled ipilimumab analysis.[11] This is potentially due to the very small number of patients at risk at Year 10 in the pooled analysis.

Table 75: Summary of model results compared with clinical data

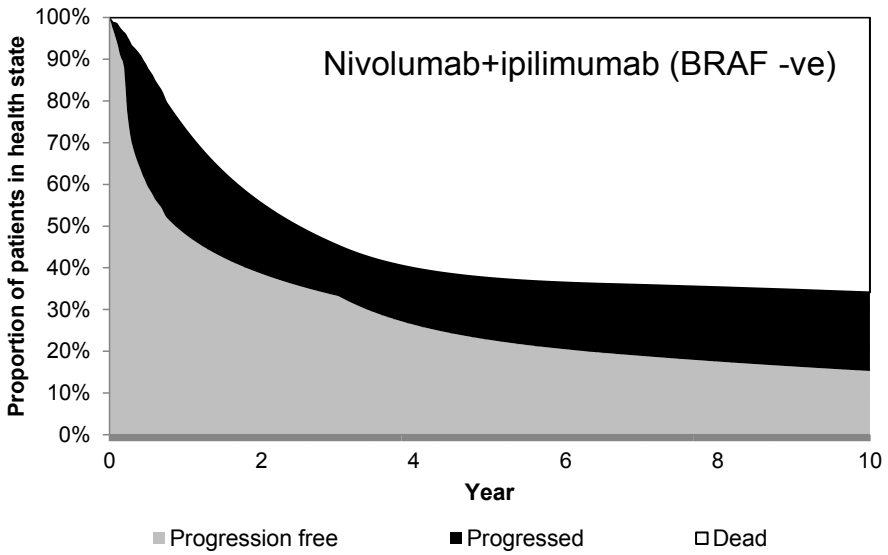
Outcome	Clinical trial result	Model result
BRAF mutation-negative short-term results (trial results based on CheckMate 067 and CheckMate 069)		
OS at Month 6 for the Regimen (CheckMate 069)	83.1%	88.3%
OS at Year 1 for the Regimen (CheckMate 069)	73.4%	73.6%
PFS at Month 6 for the Regimen (CheckMate 067)	62.1%	60.4%
PFS at Month 6 for ipilimumab (CheckMate 067)	28.8%	27.0%
PFS at Year 1 for the Regimen (CheckMate 067)	48.7%	48.3%
PFS at Year 1 for ipilimumab (CheckMate 067)	16.9%	17.4%
BRAF mutation-positive short-term results (trial results based on BRIM-3)		
OS at Month 18 for vemurafenib – BRAF mutation-positive	39%	40.7%
PFS at Month 18 for vemurafenib – BRAF mutation-positive	14%	16.3%
Long-term results (clinical results based on pooled ipilimumab analysis)[11]		
OS at Year 3 for ipilimumab	22%	22.7% and 17.7%[a]
OS at Year 10 for ipilimumab	18%	17.0% and 13.6% [a]

Key: OS, overall survival; PFS, progression free survival.

Notes: [a], model results for BRAF mutation-negative and BRAF mutation-positive patients, respectively.

Figure 61 and Figure 62 present the modelled Markov trace for each treatment arm for BRAF mutation-negative and BRAF mutation-positive patients, respectively.

Figure 61: Markov trace for BRAF mutation-negative analysis



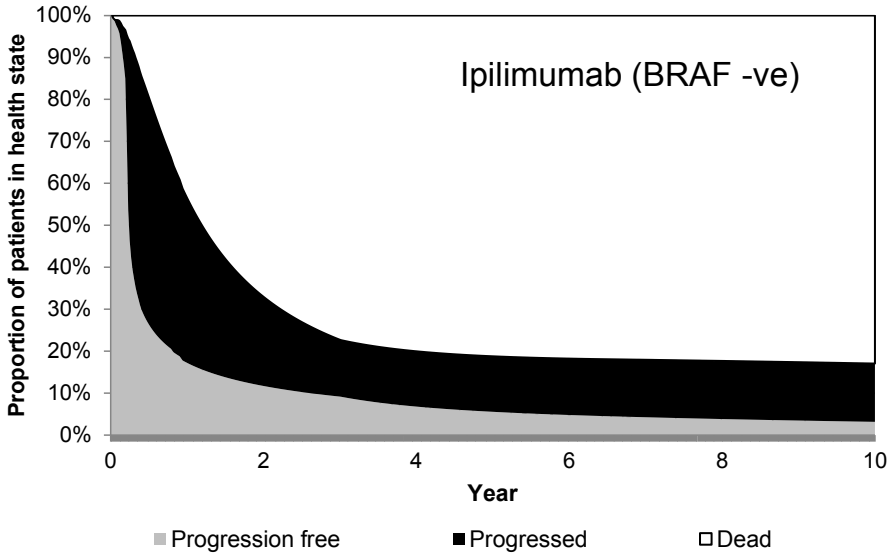
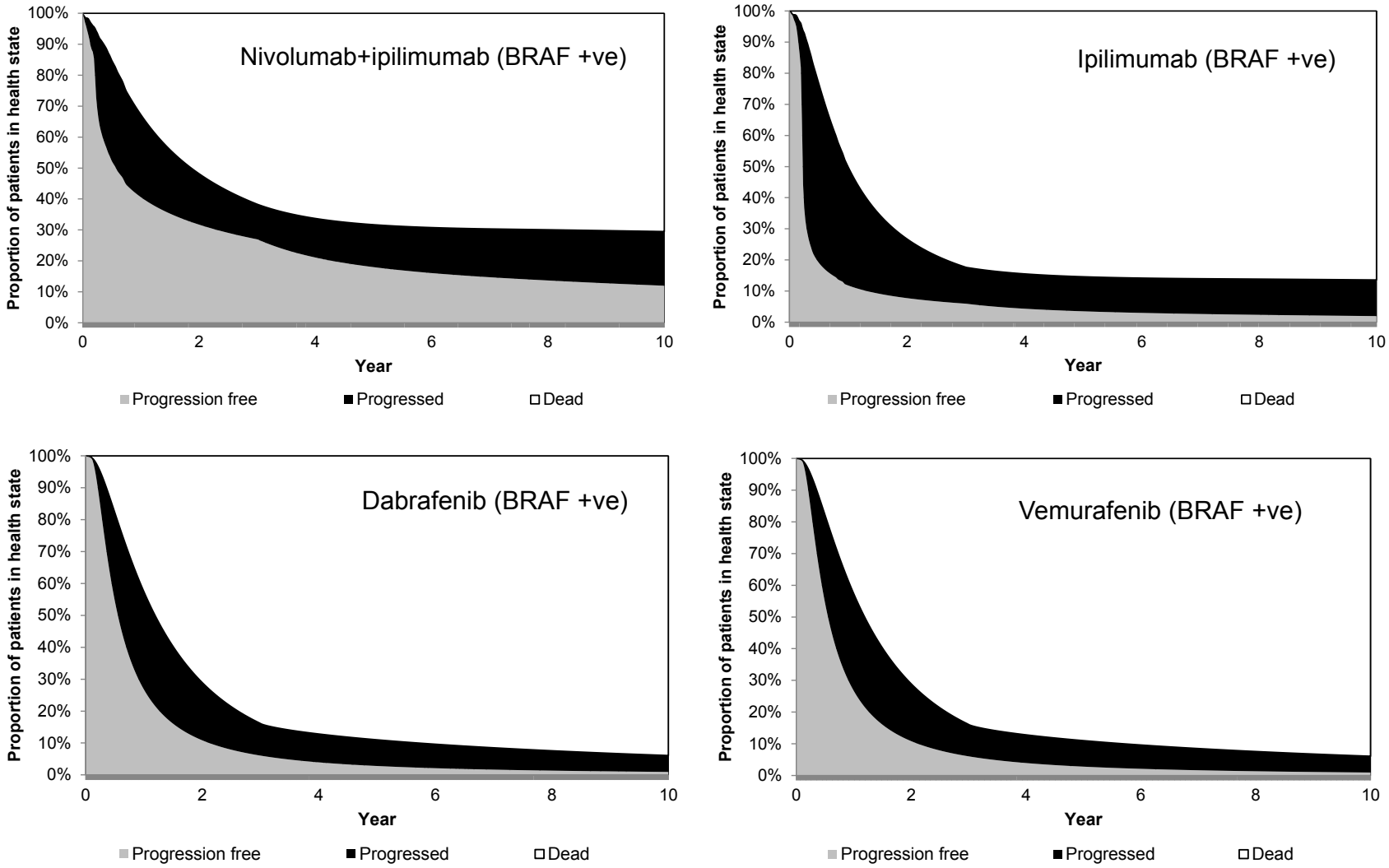


Figure 62: Markov trace for BRAF mutation-positive analysis



5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Table 76 and Table 77 present the disaggregated QALY gains by health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively. Table 78 and Table 79 present the disaggregated life year gains by health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively.

Table 80 and Table 81 present the disaggregated costs by cost category and health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively, in the base case with list drug costs. Table 82 and Table 83 present the disaggregated costs by cost category health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the PAS-based base case. The results show the Regimen is more costly than ipilimumab and BRAF inhibitors with respect to drug cost, drug administration cost and pre-palliative care costs; and less costly than ipilimumab with respect to subsequent treatment costs.

Table 76: Summary of QALY gain by health state – BRAF mutation-negative

Health state	QALY – the Regimen	QALY - ipilimumab	Absolute increment (vs ipilimumab)	% increment (vs ipilimumab)
Progression free	2.753	0.863	1.891	69%
Progressed	2.358	2.045	0.313	13%
Disutility due to AE	-0.023	-0.007	-0.016	69%
Total QALYs	**5.089**	**2.901**	**2.188**	**43%**
Key: AE, adverse event; DTIC, dacarbazine; QALY, quality-adjusted life year.				

Table 77: Summary of QALY gain by health state – BRAF mutation-positive

Health state	QALY – the Regimen	QALY - ipi	QALY - dab	QALY – vem	Absolute inc (vs ipi)	Absolute inc (vs dab)	Absolute inc (vs vem)	% inc (vs ipi)	% inc (vs dab)	% inc (vs vem)
Progression free	2.345	0.637	0.807	0.807	1.708	1.537	1.537	73%	66%	66%
Progressed	2.528	1.964	0.936	0.936	0.564	1.592	1.592	22%	63%	63%
Disutility due to AE	-0.020	-0.007	0.000	0.000	-0.013	-0.020	-0.020	64%	100%	100%
Total QALYs	**4.852**	**2.593**	**1.743**	**1.743**	**2.259**	**3.109**	**3.109**	**47%**	**64%**	**64%**
Key: dab, dabrafenib; inc, incremental; ipi, ipilimumab; nivo, nivolumab; QALY, quality-adjusted life year; vem, vemurafenib.										

Table 78: Summary of LY gain by health state – BRAF mutation-negative

Health state	LY - the Regimen	LY - ipilimumab	Absolute increment (vs ipilimumab)	% increment (vs ipilimumab)
Progression free	3.462	1.085	2.377	69%
Progressed	3.093	2.682	0.411	13%
Total LYs	**6.554**	**3.767**	**2.788**	**43%**
Key: DTIC, dacarbazine; LY, life year.				

Table 79: Summary of LY gain by health state – BRAF mutation-positive

Health state	LY - nivo	LY - ipi	LY - dab	LY – vem	Absolute inc (vs ipi)	Absolute inc (vs dab)	Absolute inc (vs vem)	% inc (vs ipi)	% inc (vs dab)	% inc (vs vem)
Progression free	2.948	0.801	1.015	1.015	2.147	1.933	1.933	73%	66%	66%
Progressed	3.315	2.576	1.228	1.228	0.740	2.087	2.087	22%	63%	63%
Total LYs	**6.263**	**3.376**	**2.243**	**2.243**	**2.887**	**4.020**	**4.020**	**46%**	**64%**	**64%**
Key: dab, dabrafenib; inc, incremental; ipi, ipilimumab; LY, life year; nivo, nivolumab; vem, vemurafenib.										

Table 80: Summary of costs by health state – BRAF mutation-negative (base case)

Health state	Cost – the Regimen	Costs - ipilimumab	Absolute increment (vs ipilimumab)	% increment (vs ipilimumab)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment initiation	[redacted]	[redacted]	[redacted]	[redacted]
Pre-palliative care	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Key: AE, adverse event; DTIC, dacarbazine.				

Table 81: Summary of costs by health state – BRAF mutation-positive (base case)

Health state	Cost – the Regimen	Cost – ipilimumab	Cost – dabrafenib	Cost – vemurafenib	Absolute increment (vs ipilimumab)	Absolute increment (vs dabrafenib)	Absolute increment (vs vemurafenib)	% increment (vs ipilimumab)	% increment (vs dabrafenib)	% increment (vs vemurafenib)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment initiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; PAS, patient access scheme.

Table 82: Summary of costs by health state – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)

Health state	Cost – the Regimen	Costs - ipilimumab	Absolute increment (vs ipilimumab)	% increment (vs ipilimumab)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment initiation	[redacted]	[redacted]	[redacted]	[redacted]
Pre-palliative care	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; DTIC, dacarbazine.

Table 83: Summary of costs by health state – BRAF mutation-positive (assuming PAS drug prices for comparator treatments)

Health state	Cost - nivolumab	Cost - ipilimumab	Cost - dabrafenib	Cost – vemurafenib	Absolute increment (vs ipilimumab)	Absolute increment (vs dabrafenib)	Absolute increment (vs vemurafenib)	% increment (vs ipilimumab)	% increment (vs dabrafenib)	% increment (vs vemurafenib)
Drug costs										
Drug admin costs										
Subsequent treatment costs										
Treatment initiation										
Pre-palliative care										
Palliative care										
End of life care										
AE costs										
Total costs										

Key: AE, adverse event; PAS, patient access scheme.

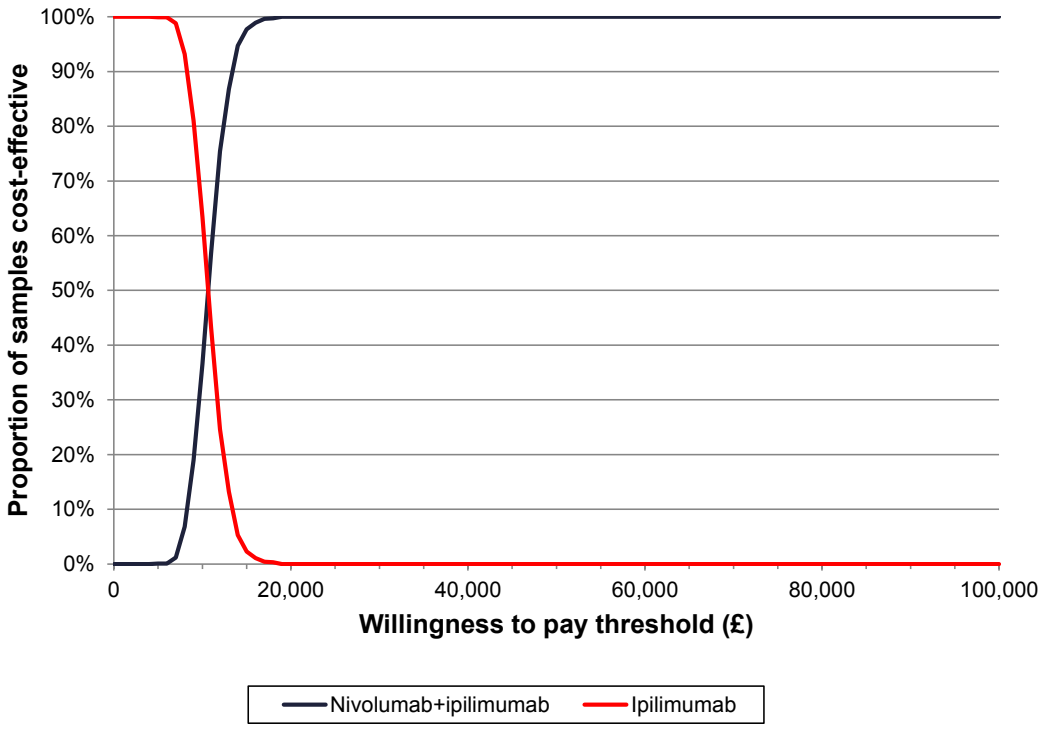
5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Figure 67 and Figure 68 present probabilistic sensitivity analysis (PSA) scatter plots (the Regimen vs its comparators) for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the base case. Figure 69 and Figure 70 present PSA scatter plots (the Regimen vs its comparators) for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the PAS-based base case. Each PSA scatter plot is drawn based on the result of 1,000 PSA runs.

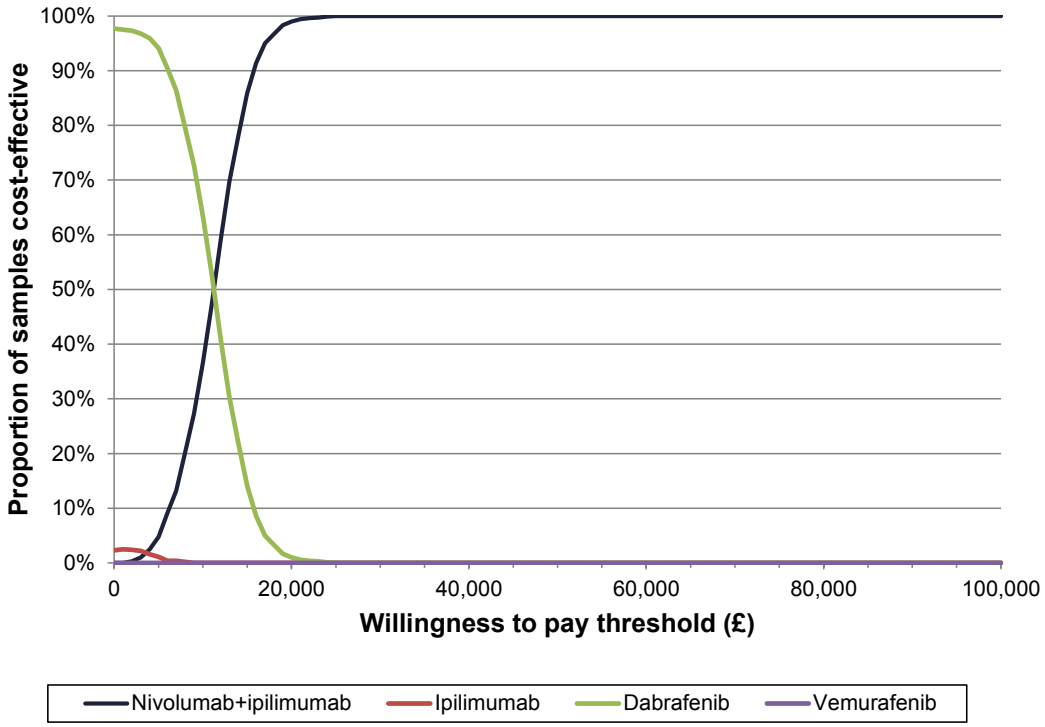
Figure 63 and Figure 64 present the cost-effectiveness acceptability curves (CEACs) for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the base case. The probabilities of the Regimen being most cost effective are 100% and 100% for willingness to pay (WTP) thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-negative patients. The probabilities of the Regimen being most cost effective are 100% and 100% for WTP thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-positive patients. Figure 65 and Figure 66 present the CEACs for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the PAS-based base case. The probabilities of the Regimen being most cost effective are 100% and 100% for WTP thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-negative patients. The probabilities of the Regimen being most cost effective are 100% and 100% for WTP thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-positive patients.

Figure 63: Cost-effectiveness acceptability curve – BRAF mutation-negative (base case)



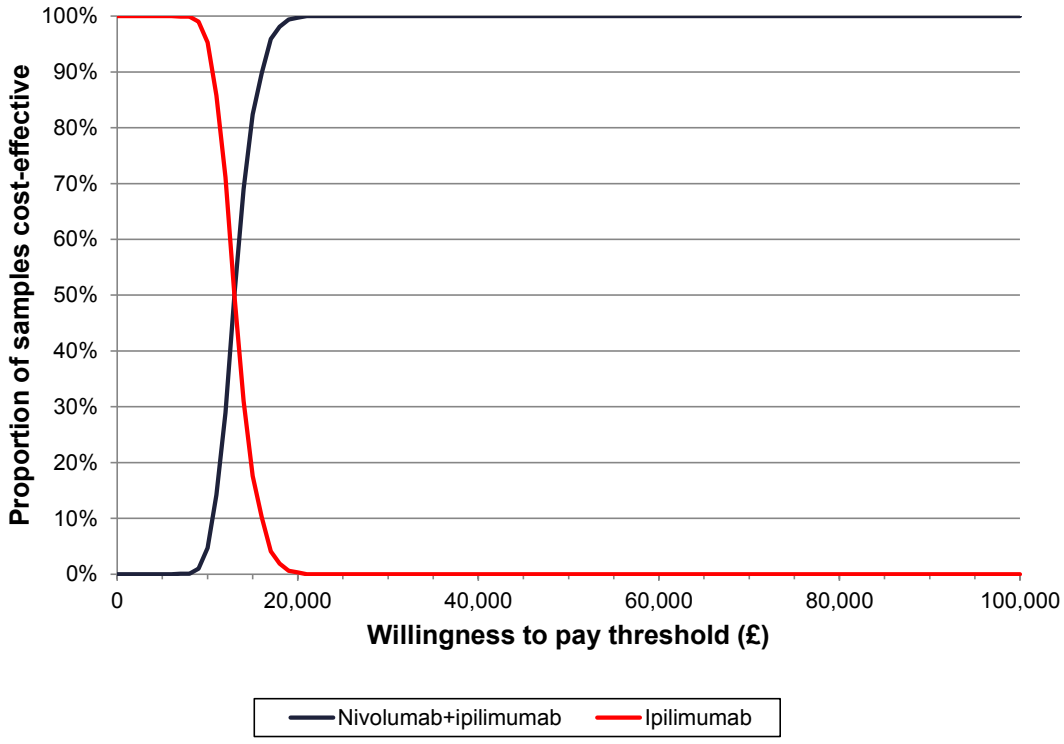
Key: WTP, willingness to pay.

Figure 64: Cost-effectiveness acceptability curve – BRAF mutation-positive (base case)



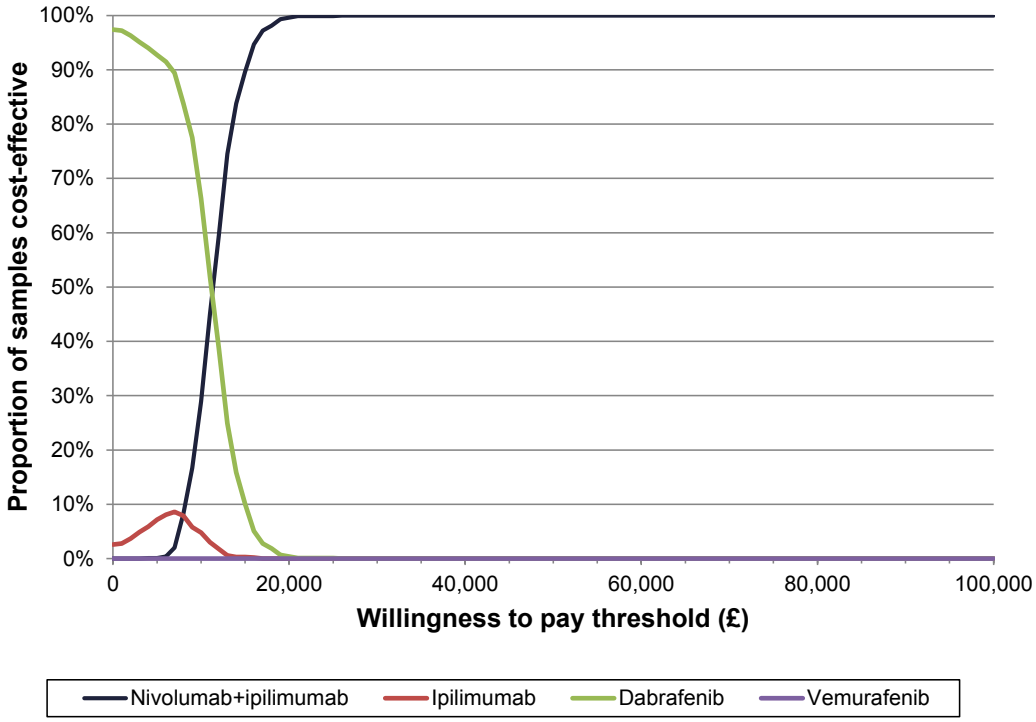
Key: WTP, willingness to pay.

Figure 65: Cost-effectiveness acceptability curve – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)



Key: PAS, patient access scheme; WTP, willingness to pay.

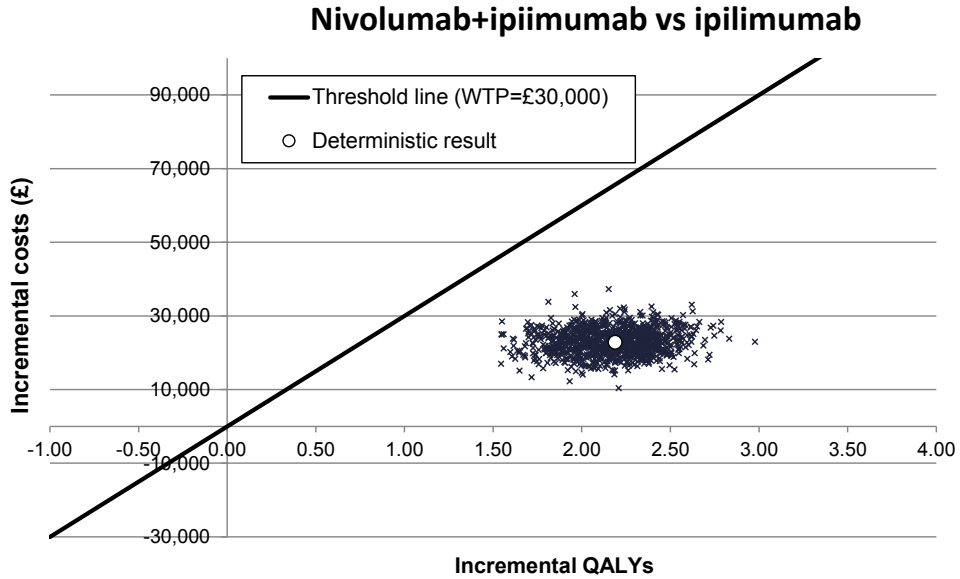
Figure 66: Cost-effectiveness acceptability curve – BRAF mutation-positive assuming PAS drug prices for comparator treatments)



Key: PAS, patient access scheme; WTP, willingness to pay.

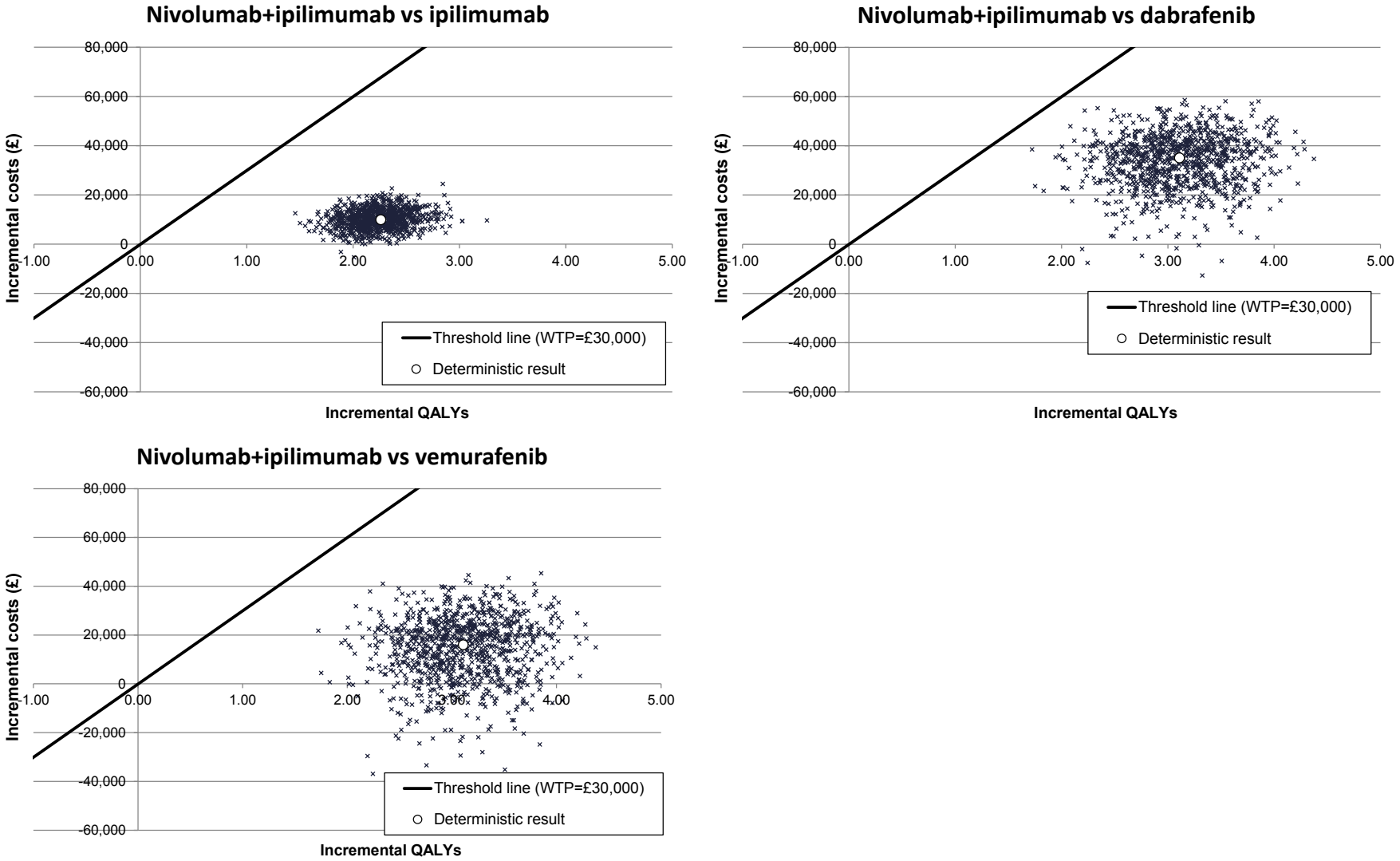
Table 84 and Table 85 present the mean model results based on PSA (1,000 runs) and compare the PSA results with the deterministic results for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the base case. Table 86 and Table 87 present the same results for the PAS-based base case. The results show that the results of the probabilistic analysis are similar to those of the deterministic analysis.

Figure 67: PSA scatter plots of the Regimen vs its comparators – BRAF mutation-negative (base case)



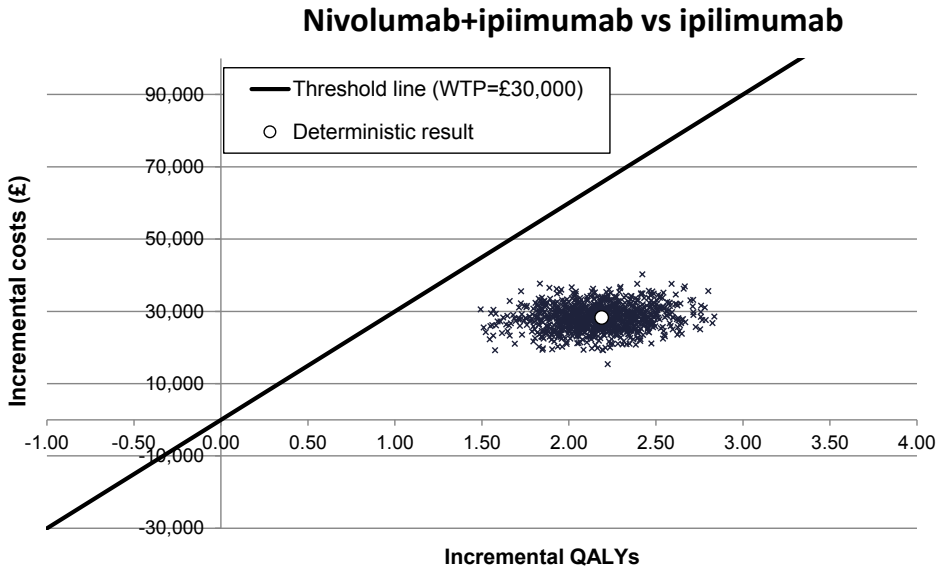
Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 68: PSA scatter plots of the Regimen vs its comparators – BRAF mutation-positive (base case)



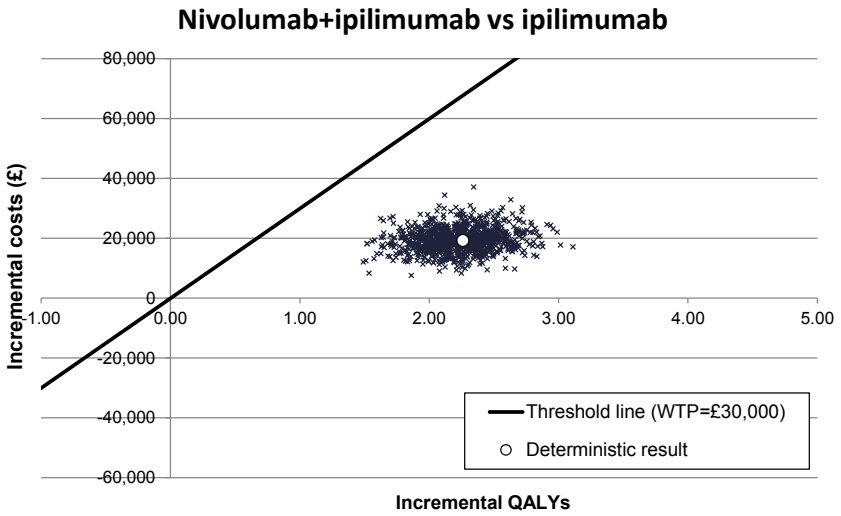
Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

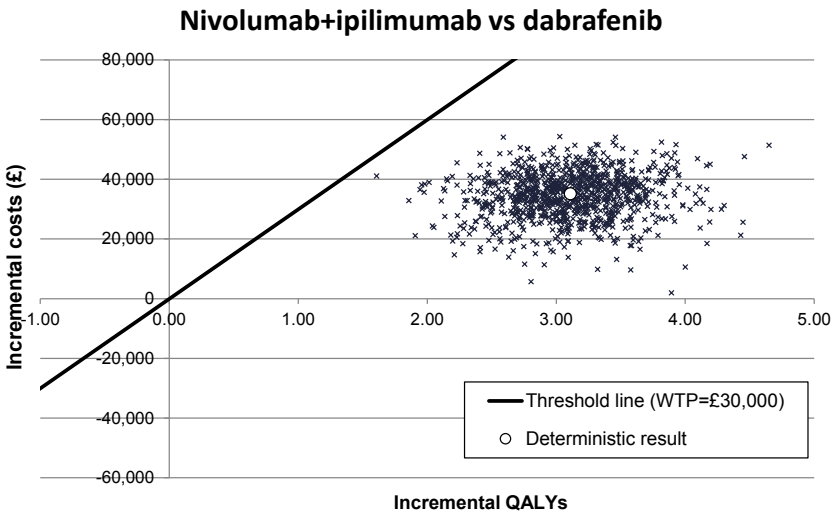
Figure 69: PSA scatter plots of the Regimen vs its comparators – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)

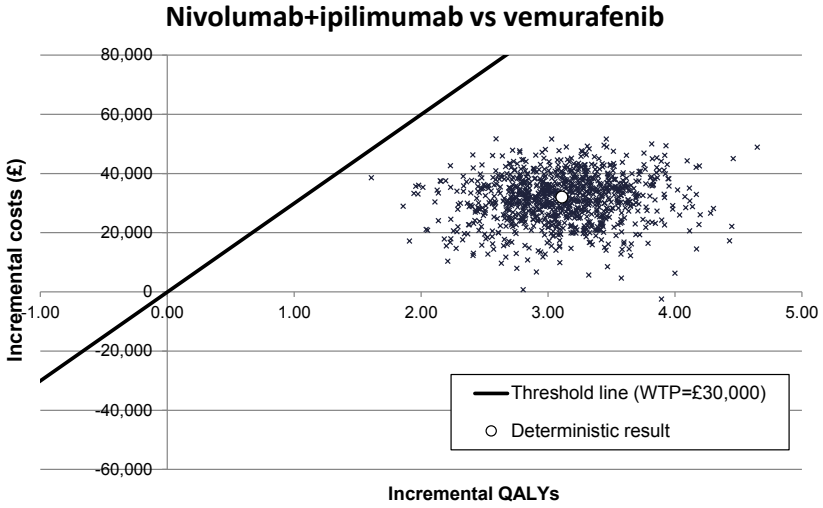


Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 70: PSA scatter plots of the Regimen vs its comparators – BRAF mutation-positive (assuming PAS drug prices for comparator treatments)







Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Table 84: Mean results of PSA (1,000 runs) and comparison with deterministic results – BRAF mutation-negative (base case)

Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)		Dominance		ICER (£) incremental (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
Ipilimumab	[redacted]	[redacted]	2.91	2.90						
The Regimen	[redacted]	[redacted]	5.07	5.09	£10,654	£10,433			£10,654	£10,433

Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 85: Mean results of PSA (1,000 runs) and comparison with deterministic results – BRAF mutation-positive (base case)

Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)		Dominance		ICER (£) incremental (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
Ipilimumab	[redacted]	[redacted]	1.743	1.74						
The Regimen	[redacted]	[redacted]	1.743	1.74	Same QALYs	Same QALYs	Dominated	Dominated	Excluded due to dominance	Excluded due to dominance
Dabrafenib	[redacted]	[redacted]	2.608	2.59	£27,314	£29,597	Extended dominated	Extended dominated	Excluded due to dominance	Excluded due to dominance
Vemurafenib	[redacted]	[redacted]	4.842	4.85	£10,909	£11,284			£10,909	£11,284

Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 86: Mean results of PSA (1,000 runs) and comparison with deterministic results – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)

Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)		Dominance		ICER (£) incremental (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The Regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 87: Mean results of PSA (1,000 runs) and comparison with deterministic results – BRAF mutation-positive (assuming PAS drug prices for comparator treatments)

Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)		Dominance		ICER (£) incremental (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The Regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

5.8.2 Deterministic sensitivity analysis

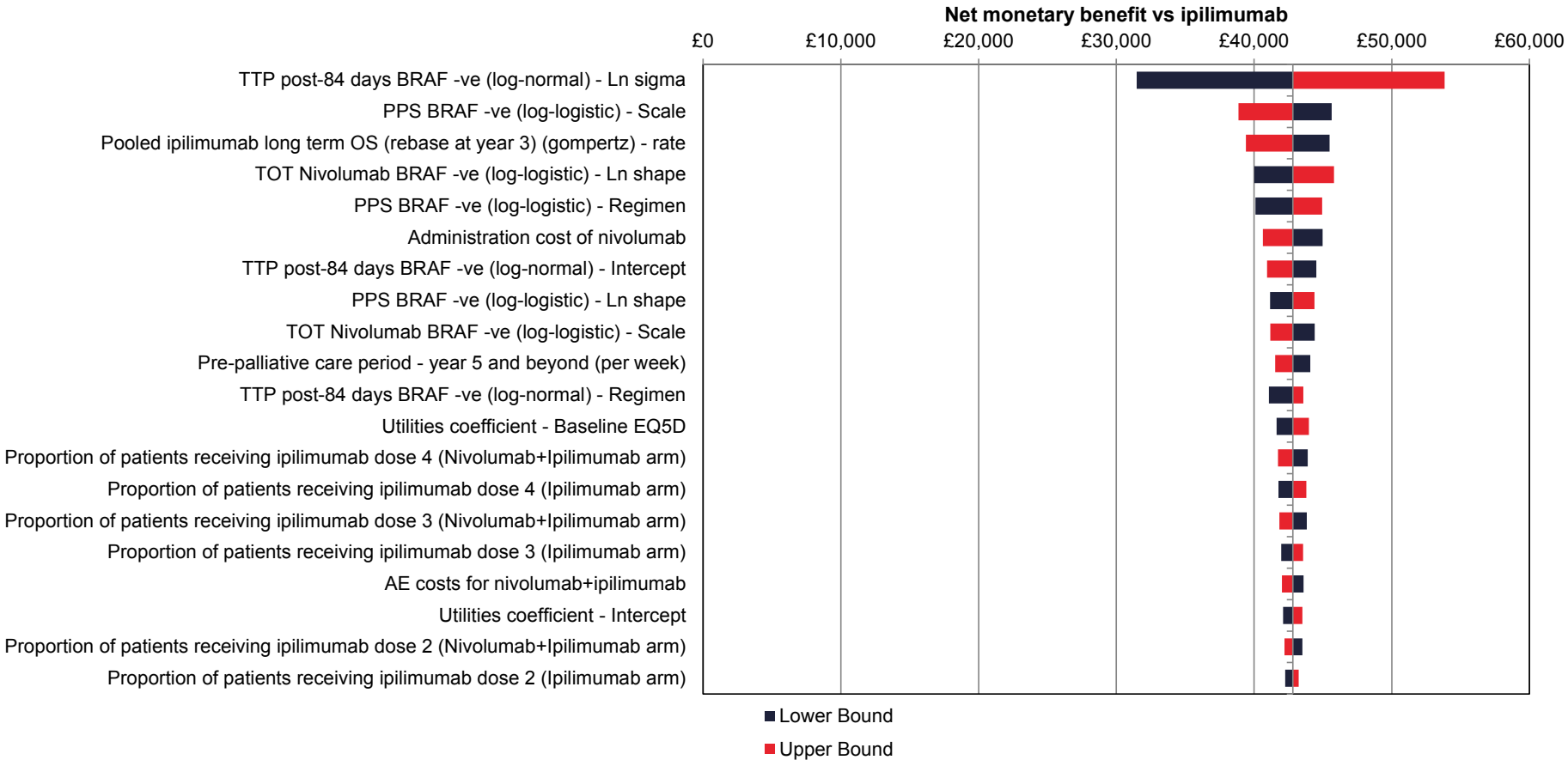
Figure 71 and Figure 72 present tornado diagrams from the deterministic one-way sensitivity analyses (OWSA), illustrating the effect on the net benefit per patient of treatment with the Regimen of varying the 20 most influential parameters between their upper and lower bounds, for BRAF mutation-negative and BRAF mutation-positive patients, respectively. Net benefit has been chosen as the results are easier to interpret in cases where one drug dominates another. The assumed WTP threshold for a QALY used in the net benefit calculation is £30,000. The same analysis was performed for the PAS-assumed base case, and the results were similar and shown in Appendix 14.

The deterministic OWSA showed that the model results are most sensitive to the parameters defining the key fitted parametric curves including TTP, PPS, long-term OS, OS/PFS for vemurafenib and TOT, parameters for defining utilities and administrative cost for IV therapies.

5.8.3 Scenario analysis

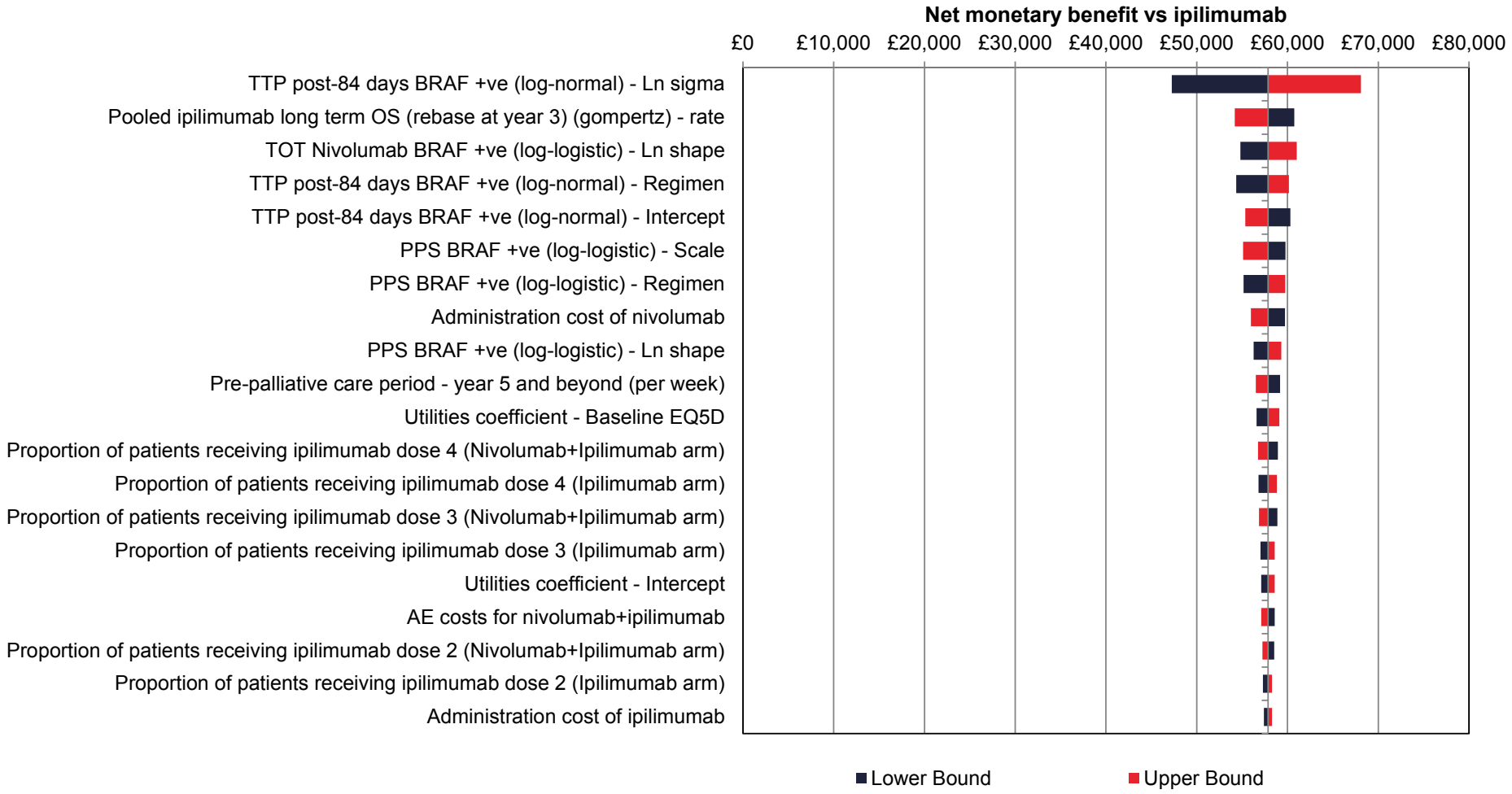
Table 88 and Table 89 present the scenario analysis performed for BRAF mutation-negative and BRAF mutation-positive patients, respectively, with the base case and PAS-assumed base case results shown in different columns.

Figure 71: Tornado diagram containing 20 most influential parameters – BRAF mutation-negative (base case)

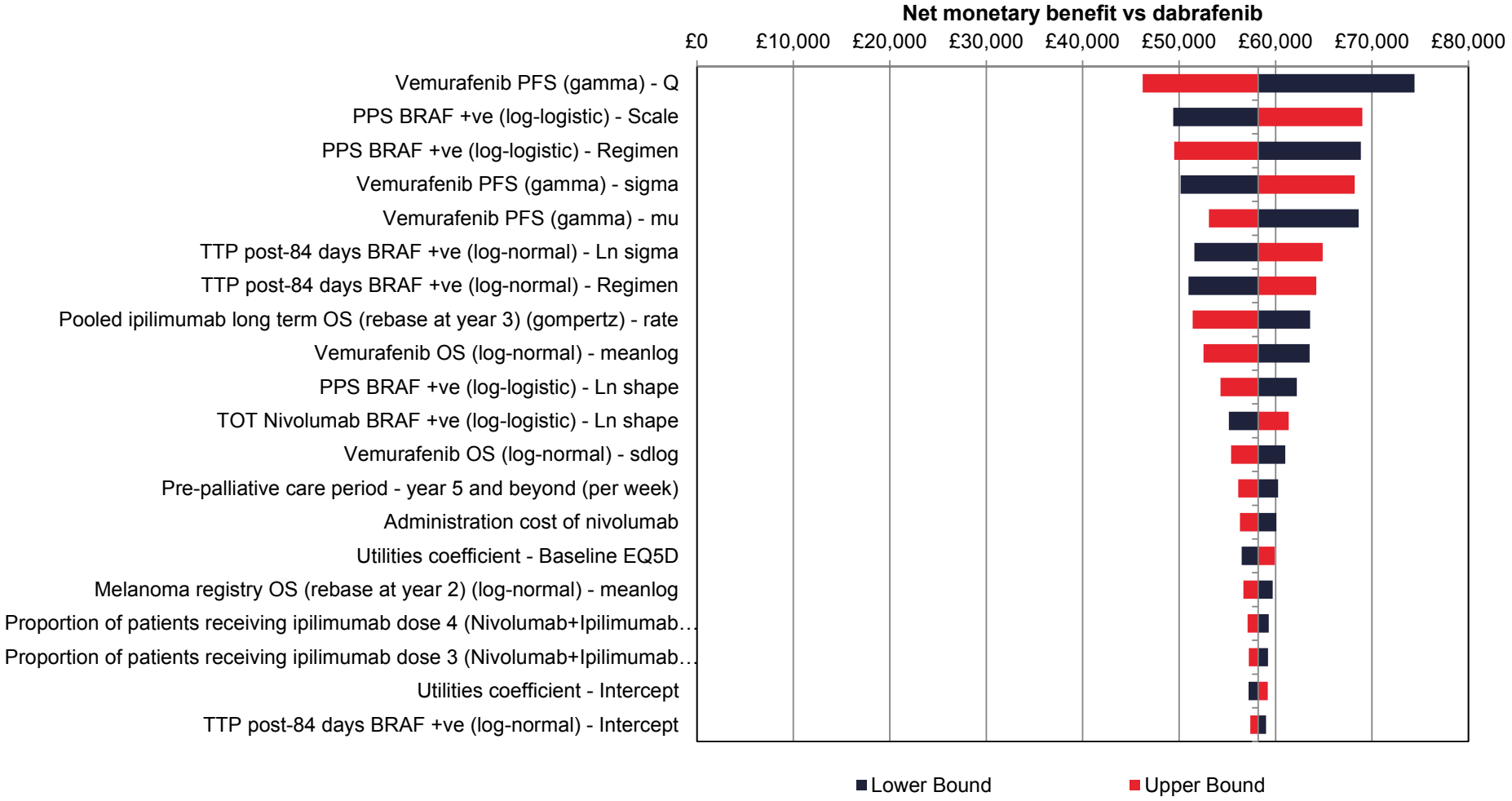


Key: OS, overall survival; PPS, post-progression survival; TTP, time to progression.

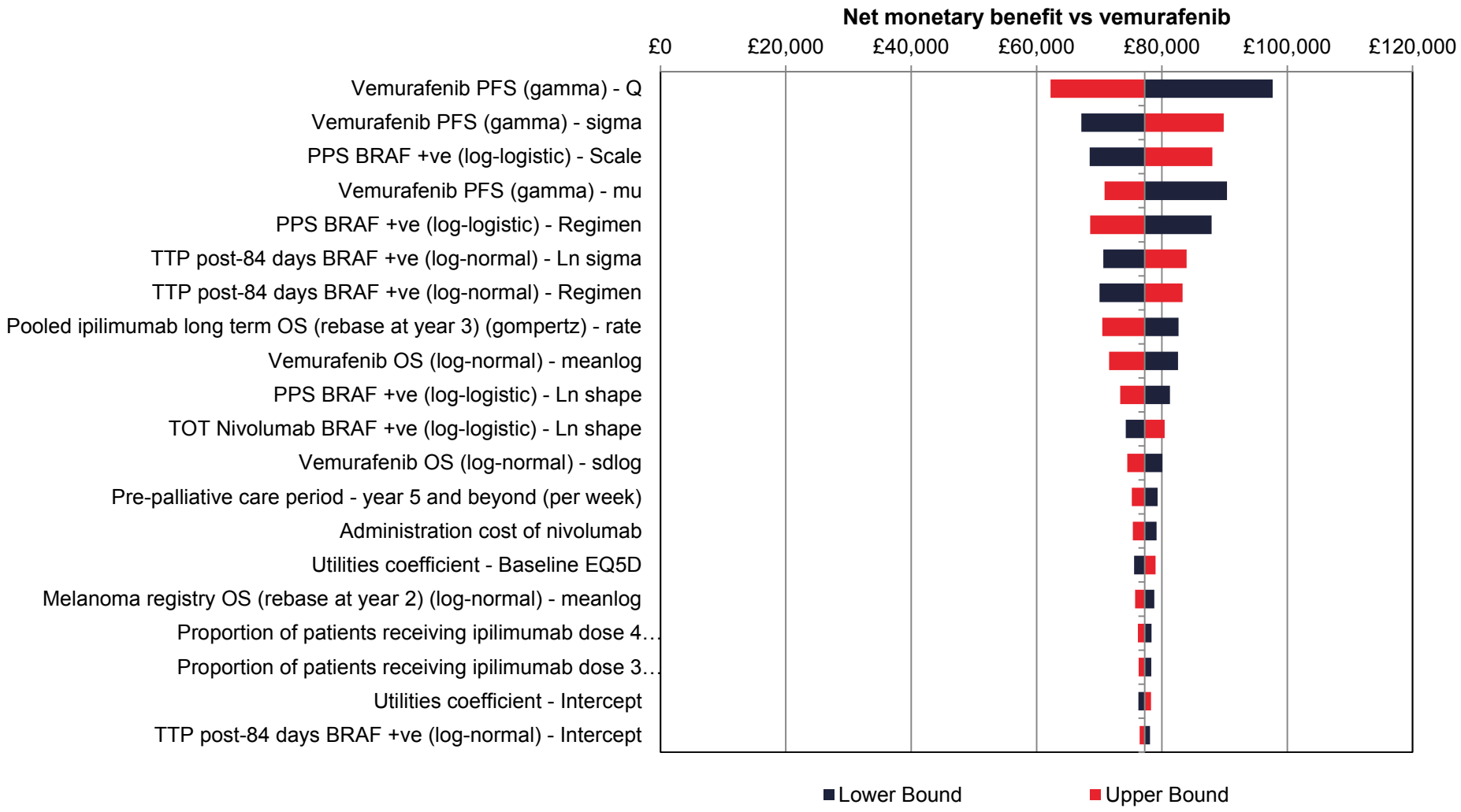
Figure 72: Tornado diagram containing 20 most influential parameters – BRAF mutation-positive (base case)



Key: OS, overall survival; PPS, post-progression survival; TOT, time on treatment; TTP, time to progression.



Key: OS, overall survival; PPS, post-progression survival; TOT, time on treatment; TTP, time to progression.



Key: OS, overall survival; PPS, post-progression survival; TOT, time on treatment; TTP, time to progression.

Table 88: Results of scenario analysis – BRAF mutation-negative

Parameter	Base case	Scenario analysis	Base case (list price)		PAS drug prices for comparator treatments	
			The Regimen vs ipilimumab		The Regimen vs ipilimumab	
			ICER	Incremental net benefit[a]	ICER	Incremental net benefit[a]
Base case	**N/A**	**N/A**	**10,433**	**42,812**	[redacted]	[redacted]
Parametric curves based on indirect comparison						
TTP	Log-Normal	Exponential	11,826	33,459	[redacted]	[redacted]
		Weibull	9,639	48,111	[redacted]	[redacted]
		Gompertz	8,961	56,589	[redacted]	[redacted]
		Log-logistic	10,332	43,505	[redacted]	[redacted]
		Generalised Gamma	9,975	45,811	[redacted]	[redacted]
PPS	Log-logistic	Exponential	10,142	44,897	[redacted]	[redacted]
		Weibull	10,174	44,657	[redacted]	[redacted]
		Gompertz	10,572	41,800	[redacted]	[redacted]
		Log-Normal	10,689	40,985	[redacted]	[redacted]
		Generalised Gamma	10,543	41,987	[redacted]	[redacted]
Long-term survival						
Pooled ipilimumab long-term survival	Gompertz	Exponential	10,862	39,877	[redacted]	[redacted]
		Weibull	10,327	43,591	[redacted]	[redacted]
		Log-Logistic	10,349	43,422	[redacted]	[redacted]
		Log-Normal	10,343	43,470	[redacted]	[redacted]
		Generalised Gamma	10,326	43,595	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Base case (list price)		PAS drug prices for comparator treatments	
			The Regimen vs ipilimumab		The Regimen vs ipilimumab	
			ICER	Incremental net benefit[a]	ICER	Incremental net benefit[a]
Time on treatment						
TOT curve for nivolumab	Log-logistic	Exponential	8,085	47,984	[redacted]	[redacted]
		Weibull	10,198	43,328	[redacted]	[redacted]
		Gompertz	11,134	41,262	[redacted]	[redacted]
		Log-Normal	11,068	41,413	[redacted]	[redacted]
		Generalised Gamma	10,578	42,492	[redacted]	[redacted]
Duration of treatment	100% discontinue at 2 years	75% discontinue at 2 years[b]	20,246	21,250	[redacted]	[redacted]
		50% discontinue at 2 years[b]	30,144	-312	[redacted]	[redacted]
		25% discontinue at 2 years[b]	40,127	-21,874	[redacted]	[redacted]
		0% discontinue at 2 years (no treatment continuation rule)[b]	50,197	-43,436	[redacted]	[redacted]
	Maximum treatment duration of 2 years	Maximum treatment duration of 3 years	15,764	31,075	[redacted]	[redacted]
		Maximum treatment duration of 4 years	19,847	22,123	[redacted]	[redacted]
		Maximum treatment duration of 5 years	23,150	14,904	[redacted]	[redacted]
		No maximum treatment duration	50,197	-43,436	[redacted]	[redacted]
Dosing and drug cost						
Method for dosing for nivolumab and ipilimumab	Method of moment (weight based dosing)	Cost per mg	10,267	43,175	[redacted]	[redacted]
		Round up to the nearest full vial	8,410	47,237	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Base case (list price)		PAS drug prices for comparator treatments	
			The Regimen vs ipilimumab		The Regimen vs ipilimumab	
			ICER	Incremental net benefit[a]	ICER	Incremental net benefit[a]
Utilitiesa						
Utility analysis	CheckMate 067 trial analysis	CheckMate 066 trial analysis	10,734	40,972	[redacted]	[redacted]
		Ipilimumab NICE TA319 utilities	9,283	50,943	[redacted]	[redacted]
General model settings						
Time horizon	40 years	10 years	17,624	14,754	[redacted]	[redacted]
		20 years	11,731	34,571	[redacted]	[redacted]
		30 years	10,548	41,939	[redacted]	[redacted]
Discount rate	0.035	0.015	8,941	57,357	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; QALYs, quality-adjusted life years; TOT, time on treatment.

Notes: a, willingness to pay threshold £50,000; b, in these scenario analyses, only a proportion of patients (75% to 0%) who are still on nivolumab treatment at Year 2 will discontinue treatment from Year 2 onwards, with the time on treatment for the remaining patients (25% to 100%) based on extrapolation of the fitted TOT (capped by OS); Ex-dominated: extended dominated.

Table 89: Results of scenario analysis – BRAF mutation-positive

Parameter	Base case	Scenario analysis	Base case (list price)						PAS drug prices for comparator treatments					
			The Regimen vs Ipilimumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib		The Regimen vs Ipilimumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib	
			ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit
Base case	N/A	N/A	**4,393**	**57,849**	**11,284**	**58,191**	**5,151**	**77,261**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric curves based on indirect comparison														
TTP	Log-Normal	Exponential	4,840	44,553	15,845	29,876	6,810	48,946	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	3,996	64,506	11,417	57,122	5,213	76,192	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz	3,991	76,598	9,591	76,925	4,532	95,995	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-logistic	4,381	58,548	11,266	58,408	5,149	77,478	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	4,171	61,315	11,292	58,179	5,160	77,249	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	Log-logistic	Exponential	4,264	60,873	11,617	55,295	5,277	74,365	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	4,273	60,638	11,563	55,758	5,257	74,827	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz	4,390	57,724	11,007	60,873	5,057	79,942	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	4,443	56,424	10,779	63,198	4,979	82,268	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	4,398	57,521	11,001	60,958	5,057	80,028	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-term survival														
Registry survival (rebased at 3 years)	Weibull	Exponential	4,393	57,849	11,306	58,175	5,185	77,221	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz	4,393	57,849	11,347	57,595	5,170	76,667	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	4,393	57,849	11,344	57,621	5,169	76,694	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	4,393	57,849	11,344	57,621	5,169	76,694	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	4,393	57,849	11,296	58,070	5,152	77,142	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled ipilimumab long-term survival	Gompertz	Exponential	4,726	50,430	13,046	44,477	5,777	63,547	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	4,417	57,252	11,405	57,089	5,194	76,158	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	4,419	57,204	11,415	57,000	5,197	76,070	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	4,408	57,484	11,358	57,519	5,177	76,588	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	4,377	58,277	11,199	58,984	5,121	78,053	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Base case (list price)						PAS drug prices for comparator treatments					
			The Regimen vs Ipilimumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib		The Regimen vs Ipilimumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib	
			ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit
Time on treatment														
TOT curve for nivolumab	Log-logistic	Exponential	2,004	63,291	9,545	63,633	3,414	82,703	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	4,054	58,621	11,037	58,963	4,904	78,033	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz	4,749	57,032	11,544	57,374	5,410	76,444	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	5,319	55,736	11,959	56,078	5,824	75,148	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	4,596	57,384	11,432	57,727	5,299	76,797	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of treatment	100% discontinue at 2 years	75% discontinue at 2 years	12,014	40,496	16,833	40,838	10,685	59,908	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		50% discontinue at 2 years	19,687	23,143	22,410	23,486	16,246	42,555	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		25% discontinue at 2 years	27,411	5,791	28,013	6,133	21,835	25,203	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		0% discontinue at 2 years (no treatment continuation rule)	35,187	-11,562	33,644	-11,220	27,451	7,850	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Maximum treatment duration of 2 years	Maximum treatment duration of 3 years	8,551	48,367	14,313	48,710	8,172	67,779	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Maximum treatment duration of 4 years	11,707	41,193	16,610	41,535	10,462	60,605	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Maximum treatment duration of 5 years	14,246	35,436	18,457	35,778	12,304	54,848	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		No maximum treatment duration	35,187	-11,562	33,644	-11,220	27,451	7,850	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratios for BRAF inhibitors (dabrafenib vs vemurafenib)														
HR for PFS	HR = 1	HR = 0.97	4,393	57,849	10,225	61,456	5,151	77,261	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Base case (list price)						PAS drug prices for comparator treatments					
			The Regimen vs Ipilimumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib		The Regimen vs Ipilimumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib	
			ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit	ICER	Inc net benefit
Dosing and drug cost														
Method for dosing for nivolumab and ipilimumab	Method of moment (weight based dosing)	Cost per mg	3,976	58,791	8,807	65,893	2,674	84,963	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Round up to the nearest full vial	2,939	61,133	9,593	63,451	3,459	82,521	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities														
Utility analysis	CheckMate 067 trial analysis	CheckMate 066 trial analysis	4,547	55,554	11,857	53,689	5,412	72,759	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Ipilimumab NICE TA319 utilities	3,891	66,582	9,876	71,488	4,508	90,558	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General model settings														
Time horizon	40 years	10 years	7,080	25,492	28,113	2,319	13,296	20,532	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20 years	4,990	45,153	14,733	35,479	6,633	54,303	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		30 years	4,487	55,154	11,880	53,207	5,409	72,208	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	0.035	0.015	3,966	75,669	8,322	89,926	3,514	109,872	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; inc, incremental; NICE, National Institute for Health and Care excellence; PAS, patient access scheme; PPS, post-progression survival.

5.8.4 Summary of sensitivity analyses results

The probabilistic sensitivity analyses demonstrate that the conclusion that the Regimen is cost effective versus all relevant comparators is robust. The CEACs based on 1000 PSA runs on the PAS-based base case estimated that the probabilities of the Regimen being cost effective compared to its comparators, at WTP thresholds of £30,000 and £50,000, are 100% and 100%, respectively, for BRAF mutation-negative patients; and 100% and 100%, respectively, for BRAF mutation-positive patients.

The OWSA identified the parameters that have the biggest impact on the cost-effectiveness results and quantified the impacts of taking extreme values of these parameters on the results. The analyses showed that the cost-effectiveness results in the base case are not sensitive to the identified most impactful parameters.

A wide range of scenario analyses were performed on key model assumptions and alternative choices, including structural assumptions, to test robustness of the base case results. The results of the scenario analyses shows that the Regimen remains cost effective compared to its comparators for the majority of scenarios tested. Specifically, the Regimen remains cost effective in scenarios for alternative parametric curves for TTP, PPS, TOT and long-term OS, for alternative assumptions on method and assumptions for dosing, for alternative source for utility, and for alternative maximum treatment durations of 3, 4 or 5 years. The scenarios which show the Regimen becoming not cost effective are: (1) those that relate to treatment discontinuation rules when a low proportion of patients on nivolumab treatment at Year 2 are assumed to discontinue treatment and: (2) when no maximum treatment duration is set. However, these scenarios are not deemed clinically plausible based on the feedback from the UK clinicians.

5.9 Validation

Validation of de novo cost-effectiveness analysis

The following key aspects of the model methods and inputs were validated by health economics and clinical experts[2, 3]:

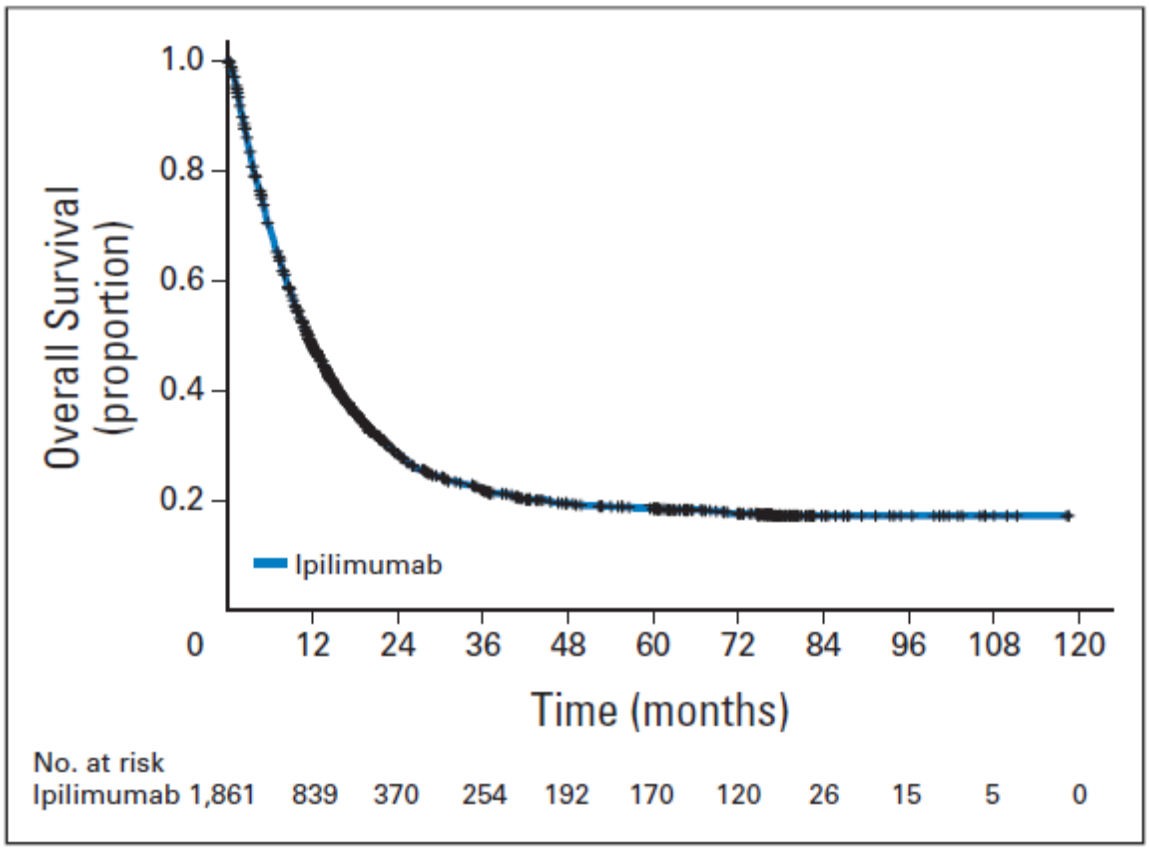
- The Markov state-transition method to estimate OS and PFS using TTP, PPS and PrePS;
- Extrapolation beyond trial period and the use of external data for long-term survival;
- The modelling of time on treatment for nivolumab within the Regimen arm and the treatment continuation rule;
- The use of utilities derived from the pivotal clinical trial based on progression status;
- Modelling costs and resource use (excluding drug costs) for advanced melanoma patients; and
- Modelling impacts of safety and AEs on resource use and utilities.

The experts were in agreement with the modelling methods, and the key feedback for other aspects has been incorporated into the analysis, including:

- The use of external long-term survival evidence so that modelled long-term survival for immunotherapy is in line with published long-term clinical data[11];
- The use of a clinically plausible and practical treatment continuation rule for nivolumab within the Regimen arm;
- Modelling resource use to reflect longer survival of advanced melanoma patients and the potential decreased resource use over time for long-term survivors;
- The use of resource use data collected within trials for modelling AEs and the importance of capturing all serious AEs.

Table 75 compares a range of model results with available corresponding clinical data for validation. Figure 73 presents the OS for ipilimumab based on a pooled analysis of 1,861 patients from 12 trials over a 10-year period.[11] The OS estimated by the model for ipilimumab (as shown in Figure 50 and Figure 54 for BRAF mutation-negative and BRAF mutation-positive patients, respectively) has a similar shape and is broadly comparable with the observed OS in clinical trials.

Figure 73: Pooled OS for ipilimumab[11]



As no OS data is available from CheckMate 067, for comparison and validation purpose, the OS KM curves for the Regimen from CheckMate 069 and the 95% CIs are presented in Figure 74 to be compared with the modelled OS. Patient characteristics differ between CheckMate 067 and CheckMate 069 (see Table 90), therefore for consistency, the modelled OS is re-estimated using patient characteristics of CheckMate 069 (through covariate adjusted PrePS, TTP and PPS) and the comparison is shown in Figure 74. The comparison for the OS in the ipilimumab arm was not deemed appropriate because of the crossover of patients in the ipilimumab arm in CheckMate 069 trial to nivolumab. The comparison shows that model estimated OS underestimates observed OS after approximately 1 year for the Regimen. Model estimated OS is, however, generally within the 95% CIs of the observed OS.

These comparisons show that the modelled OS, both regarding absolute predictions and comparable benefit, appear plausible and in line with observed data. Key limitations of the comparison are that no OS from the pivotal phase III CheckMate 067 trial is available, immature OS from the much smaller phase II CheckMate 069 (N=142, longest follow up for OS is around 20 months) and the crossover of patients in the ipilimumab arm in CheckMate 069. The smaller sample size of CheckMate 069 and the immaturity of OS data are reflected by the wide CIs of observed OS.

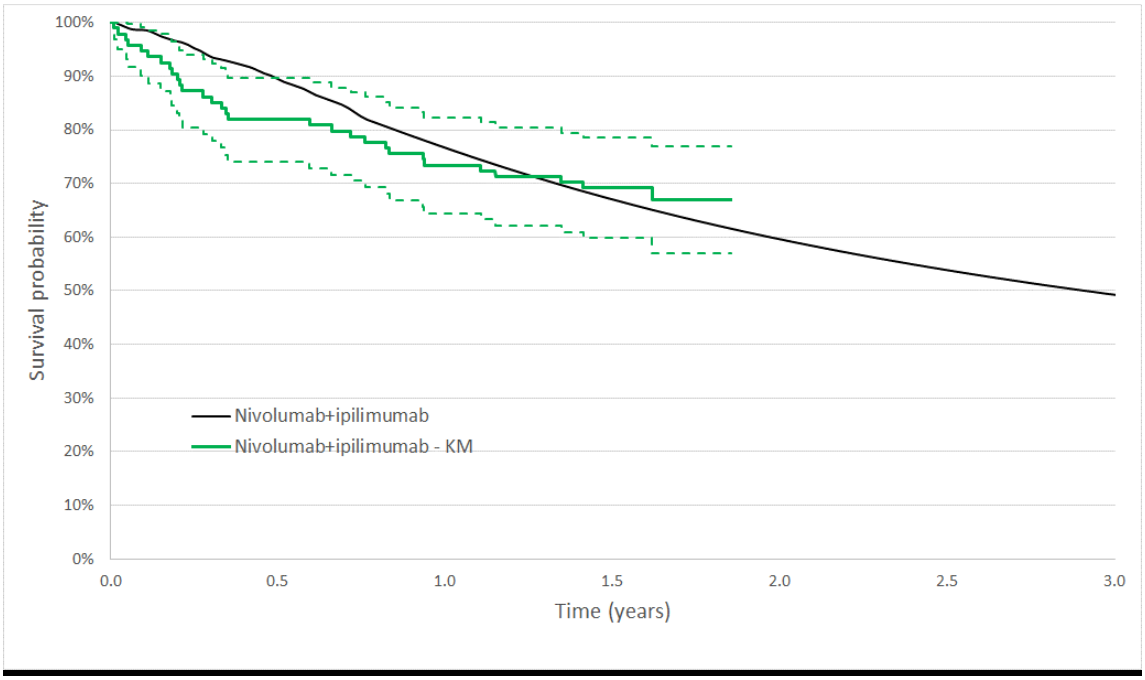
In absolute terms, as expected by the covariate adjusted models, the model estimated better OS using CheckMate 069 patient characteristics compared to using CheckMate 067 patient characteristics (estimated OS are 77%, 60% and 49% at Year 1, 2 and 3 using CheckMate 069 and 74%, 56% and 46% using CheckMate 067 patient characteristics) because patients in CheckMate 067 generally have worse prognostic factors than patients in CheckMate 069 regarding melanoma staging, ECOG status, LDH level and brain metastases (see Table 90). This also supports the general validity of the model and the use of the model for estimating TTP, PPS and PrePS and resulting PFS and OS based on alternative patient characteristics.

Table 90: Comparison of patient characteristics between CheckMate 067 and CheckMate 069

	BRAF mutation-negative (CheckMate 067) [10]	**CheckMate 069[85] – The Regimen arm**
Mean age	62	63
% male	66.2%	66.3%
% under 65	53.3%	50.5%
% stage M1c	59.2%	46.3%
ECOG status = 0	70.4%	83.2%
% elevated LDH (>ULN)	38.4%	25.3%
% with brain metastases	3.9%	4.2%

Key: ECOG, Eastern Cooperative Oncology Group; kg, kilogram; LDH, lactate dehydrogenase; m, metre; PPS, post-progression survival; PrePS, pre-progression survival; TOT, time on treatment; TTP, time to progression; ULN, upper limit of the normal range.

Figure 74: Overall survival using CheckMate 069 patient characteristics for the first 3 years



No. at risk					
Time (year)	0	0.5	1	1.5	2
Nivolumab+ipi	95	77	69	64	0

Note: Dotted lines represent the 95% CIs

5.10 Interpretation and conclusions of economic evidence

The economic analysis performed is based on a de novo economic decision model with a structure that is designed to be consistent with previously accepted melanoma modelling and to best use the available data and optimally capture the unique characteristics of emerging immunotherapy treatments, including the Regimen, for the treatment of advanced melanoma. The model brought together the most recent and relevant efficacy and safety clinical data and established the comparative efficacy of the Regimen and relevant comparators through the use of a bespoke patient-level covariate-adjusted analysis. The model also utilised the results from trial-based utility and safety analyses and used the most relevant resource use inputs from the literature and a face-to-face clinical validation meeting.

The structure and key assumption of the decision model were validated by health economics experts[2, 3], and the model estimations of OS and PFS were comparable to clinical data. No previous economic analysis was identified through the systematic literature review evaluating the cost effectiveness of the Regimen compared to existing treatments in advanced melanoma patients. Therefore, the cost-effectiveness results of nivolumab cannot be externally validated with previous studies. However, the cost-effectiveness results for ipilimumab compared to BRAF inhibitors are in line with previous published cost-effectiveness literature.[55]

In conclusion, the de novo economic analysis brings together the best available clinical, HRQL and resource use data to establish the comparable efficacy and safety of the Regimen and its comparators and to estimate the health utilities and relevant resource use for advanced melanoma patients in the UK. The base case incremental cost-effectiveness results show that the Regimen is cost effective compared to ipilimumab for BRAF mutation-negative patients and cost effective compared to ipilimumab, dabrafenib and vemurafenib for BRAF mutation-positive patients below a WTP threshold of £30,000 per QALY. The base case results are robust to uncertainties of key model parameters and assumptions.

6 Assessment of factors relevant to the NHS and other parties

6.1 Number of people eligible for treatment in England.

Eligible population numbers have been estimated as per the methodologies set out in the NICE costing template for vemurafenib[58] and these are presented in Table 91. The most recently published male and female incidence rates for malignant melanoma in 2012 in England and Wales were averaged to produce estimates for the period 2016-2020.[35]

Table 91: Estimates of incident population

Parameters		Estimate	Source
Total population of England		53,865,800	England mid-2013 population (ONS)[69]
Annual newly diagnosed of melanoma	Males	0.0210%	Cancer registrations 2012[35]
	Females	0.0212%	
	Overall	0.0211%	Average of male and female incidences
Proportion of patient with stage IIIC or IV disease		10%	Vemurafenib NICE TA269[58]
Percentage increase in incidence per year		3.5%	Decision Resources Malignant Melanoma June 2006[208]
Annual newly diagnosed of advanced melanoma (in 2013)		1,176	Calculated
% of BRAF mutation-positive		48%	Long et al. (2011)[23]
BRAF mutation-negative		612	Calculated
BRAF mutation-positive		565	Calculated
Proportion of patient requiring subsequent line treatments		21%	Ipilimumab NICE TA268[56]

The number of patients eligible for treatment with the Regimen was calculated as the proportion of malignant melanoma patients with stage IIIc or IV malignant melanoma from the overall incidence.[35]

The estimated patient numbers for the BRAF mutation-positive and mutation-negative subgroups have been estimated based on the proportion that are expected to be BRAF mutation-positive.[23] The increase in incidence per year was assumed to be 3.5%.[208]

The total numbers of eligible patients from Year 1 to Year 5 (2016 to 2020) are shown in Table 92.

Table 92: Population eligible for treatment with the Regimen in England

	2016	2017	2018	2019	2020
Expected number of newly diagnosed advanced melanoma patients	1,304	1,350	1,397	1,446	1,497
Expected number of BRAF mutation-negative patients (first line)	678	702	727	752	778
Expected number of BRAF mutation-positive patients (first line)	626	648	671	694	718
Expected number of BRAF mutation-negative patients (subsequent lines)	142	147	153	158	163
Expected number of BRAF mutation-positive patients (subsequent lines)	131	136	141	146	151

6.2 Assumptions made about current treatment options and uptake of technologies

The following assumptions were made in estimating the number of patients eligible to receive the Regimen.

- It was assumed that all patients are tested for BRAF mutation-status.[58]
- 0% are treated through clinical trials.[58]
- Only new incident patients from the year 2016 onwards were considered, and prevalent patients before 2016 are assumed to have already received treatments.
- The proportion of patients requiring subsequent line treatment is assumed to be constant over time.
- Anti-PD1 monotherapy such as pembrolizumab is included in the estimation of expected market share and budget impact because the treatment has been approved by NICE and some patients will be treated with anti-PD1 monotherapy over the 5 year time horizon of the budget impact analysis.

6.3 Assumptions made about market share in England

The estimated market share of the Regimen and each modelled comparator drug is shown in Table 93. For BRAF mutation-negative patients, the market share of the Regimen is expected to be [redacted] (first line) and [redacted] (subsequent lines) in 2016, changing to [redacted], 37%, 42% and 47% for 2017 to 2020 for the first line treatment and remaining [redacted] for 2017 to 2020 for subsequent lines treatment. For BRAF mutation-positive patients, the market share is expected to be [redacted] (first line) and [redacted] (second line) in 2016, changing to [redacted] for 2017 to 2020 for the first line treatment and remaining [redacted] for 2017 to 2020 for subsequent lines treatment.

The assumed market share in the absence of the Regimen is estimated by increasing the market share of the remaining treatments by the same percentage to reach the overall [redacted] limit. The estimated total number of new patients treated with the Regimen is [redacted] for first line and subsequent lines, respectively) in 2016 and [redacted] for first line and subsequent lines) in 2020.

Table 93: Eligible population in England: breakdown by treatment

	2016	2017	2018	2019	2020
BRAF mutation-negative (first line)					
Expected number of BRAF mutation-negative patients (first line)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regimen (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1 monotherapy (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regimen (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1 monotherapy (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRAF mutation-positive (first line)					
Expected number of BRAF mutation-positive patients (first line)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regimen (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1 monotherapy (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regimen (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1 monotherapy (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRAF mutation-negative (subsequent lines)					
Expected number of BRAF mutation-negative patients (subsequent lines)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regimen (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1 monotherapy (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regimen (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1 monotherapy (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRAF mutation-positive (subsequent lines)					
Expected number of BRAF mutation-positive patients (subsequent lines)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regimen (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1 monotherapy (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regimen (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1 monotherapy (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 Unit costs and estimates of resource savings

The costs included in the budget impact estimation are those included in the economic model, as presented in Section 5.5. For pembrolizumab which is not included as a comparator in the economic model, the estimated drug costs, administration costs and AE costs over the period 2016 to 2020 were based on the budge impact data presented in the recent pembrolizumab NICE appraisal (TA366). Other estimated per patient costs for pembrolizumab over the period 2016 to 2020 are assumed to be the same as the modelled Regimen arm in the economic model.

6.5 Estimated annual budget impact on the NHS in England

The gross budget for treating advanced melanoma (including both BRAF mutation-negative and BRAF mutation-positive patients) when the Regimen is introduced is estimated to be £128.9 million (£35.4 million for patients treated with the Regimen) and £176.6 million (£86.4 million for patients treated with the Regimen) in the years 2016 and 2020, respectively, in the base case (list price), with net budget impact of £12.1 million and £37.0 million in 2016 and 2020.

The detailed net budget impact in the base case (with list price) is shown in Table 95 for BRAF mutation-negative and mutation-positive patients respectively, as the difference in costs in the treatment arms over the first 5 years of the economic model, scaled up to account for the number of patients expected to receive each treatment each year. The net budget impact in the PAS-based base case is shown in Table 96 and Table 97.

Table 94: Estimated net budget impact over 5 years (BRAF mutation-negative patients) – base case (list price)

	2016	2017	2018	2019	2020
Drug costs	£6,635,724	£11,479,903	£13,951,992	£16,583,065	£19,381,221
Drug admin costs	£229,494	£578,727	£710,429	£850,642	£999,798
Subsequent treatment costs	-£377,823	-£16,333	£14,184	-£14,059	-£7,400
Treatment initiation	£0	£0	£0	£0	£0
Pre-palliative care	£8,105	£11,295	£7,808	£7,267	£6,630
Palliative care	-£10,914	-£2,705	£136	£1,495	£661
End of life care	-£5,602	-£1,863	-£80	£887	£403
AE costs	£248,035	£414,377	£503,168	£597,666	£698,163
Total costs	**£6,727,019**	**£12,463,402**	**£15,187,637**	**£18,026,963**	**£21,079,477**

Table 95: Estimated net budget impact over 5 years (BRAF mutation-positive patients) – base case (list price)

	2016	2017	2018	2019	2020
Drug costs	£5,368,497	£8,848,911	£10,602,741	£12,472,823	£14,444,281
Drug admin costs	£184,875	£442,611	£548,660	£664,437	£791,395
Subsequent treatment costs	-£420,865	£46,247	£139,787	£114,395	£152,914
Treatment initiation	£0	£0	£0	£0	£0
Pre-palliative care	£10,221	£20,055	£26,236	£37,978	£52,905
Palliative care	-£15,626	-£13,716	-£16,859	-£20,648	-£27,191
End of life care	-£7,637	-£7,230	-£8,751	-£10,556	-£13,962
AE costs	£204,246	£329,564	£396,700	£467,466	£541,502
Total costs	**£5,323,711**	**£9,666,441**	**£11,688,515**	**£13,725,895**	**£15,941,844**

Table 96: Estimated net budget impact over 5 years (BRAF mutation-negative patients) – assuming PAS drug prices for comparator treatments

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 97: Estimated net budget impact over 5 years (BRAF mutation-positive patients) – assuming PAS drug prices for comparator treatments

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7 References

1. Mellman I, Coukos G and Dranoff G. Cancer immunotherapy comes of age. *Nature*. 2011; 480(7378):480-9.
2. Bristol-Myers Squibb Company. Nivolumab: clinical data and model validation meeting. London. 20 March 2015. Data on File.
3. Bristol-Myers Squibb Company. Nivolumab-Ipilimumab combination in Melanoma Advisory Board. London. 23 October 2015. Data on File.
4. Clinical Care Options. Biomarkers to guide immunotherapy treatment of solid tumors: Strategies to promote best practices for quality care. 2015 (Updated: 14 October 2015). Available at: http://www.clinicaloptions.com/Oncology/Treatment%20Updates/Biomarkers%20for%20Immunotherapy.aspx Accessed: 3 November 2015.
5. Clinical Care Options. Principles and Application of Immunotherapy for Cancer (PAIC): Advanced Melanoma. 2015 (Updated: 14 October 2015). Available at: http://www.clinicaloptions.com/Oncology/Treatment%20Updates/Immunotherapy%20for%20Cancer/On%20Demand%20Webcasts/Melanoma_Webcast.aspx?lg=mobile&utm_campaign=&utm_medium=email&utm_content=&utm_source= Accessed: 12 November 2015.
6. National Institute for Health and Care Excellence (NICE). TA357: Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. 2015 (Updated: 7 October 2015). Available at: https://www.nice.org.uk/guidance/ta357 Accessed: 16 Oct 2015.
7. Postow MA, Callahan MK and Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. *J Clin Oncol*. 2015; 33(17):1974-82.
8. Bristol-Myers Squibb Company. Nivolumab treatment duration focus group. Chicago, IL, USA 31 May 2015. Data on File.
9. Bristol-Myers Squibb Pharmaceutical Limited. Summary of Product Characteristics. Ipilimumab. Available at: https://www.medicines.org.uk/emc/medicine/24779 Accessed: 10 February 2015.
10. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015; 373(1):23-34.
11. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from Phase II and Phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol*. 2015; 33(17):1889-94.
12. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline--Update 2012. *Eur J Cancer*. 2012; 48(15):2375-90.
13. American Cancer Society. Melanoma skin cancer. 2014. Available at: http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-what-is-melanoma Accessed: 9 February 2015.
14. Cancer Research UK (CRUK). Cancer Statistics Report: Skin Cancer. 2013. Available at: http://publications.cancerresearchuk.org/downloads/Product/CS_CS_SKIN.pdf Accessed: 2 February 2015.

15. American Joint Committee on Cancer. Melanoma of the Skin Staging. 2009. Available at: https://cancerstaging.org/references-tools/quickreferences/Documents/MelanomaSmall.pdf Accessed: 9 February 2015.
16. Cancer Research UK (CRUK). Melanoma skin cancer. 2015. Available at: http://www.cancerresearchuk.org/about-cancer/type/melanoma/ Accessed: 2 February 2015.
17. Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of BRAF V600 mutation in melanoma. *J Transl Med*. 2012; 10(85).
18. Bauer J, Büttner P, Murali R, et al. BRAF mutations in cutaneous melanoma are independently associated with age, anatomic site of the primary tumor and the degree of solar elastosis at the primary tumor site. *Pigment Cell Melanoma Res*. 2011; 24(2):345-51.
19. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med*. 2005; 353(20):2135-47.
20. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002; 417(6892):949-54.
21. Maldonado JL, Fridlyand J, Patel H, et al. Determinants of BRAF mutations in primary melanomas. *J Natl Cancer Inst*. 2003; 95(24):1878-90.
22. Sullivan RJ and Flaherty KT. Resistance to BRAF-targeted therapy in melanoma. *Eur J Cancer*. 2013; 49(6):1297-304.
23. Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol*. 2011; 29(10):1239-46.
24. Veierod MB, Weiderpass E, Thorn M, et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. *J Natl Cancer Inst*. 2003; 95(20):1530-8.
25. Sosman JA, Moon J, Tuthill RJ, et al. A Phase II trial of complete resection for stage IV melanoma: results of Southwest Oncology Group Clinical Trial S9430. *Cancer*. 2011; 117(20):4740-06.
26. Quinn MJ, Babb P, Brock A, et al. Cancer trends in England and Wales 1950–1999. Single Market Programme in Services No 66. London: TSO. 2004. Available at: http://www.ons.gov.uk/ons/rel/cancer-unit/cancer-trends-in-england-and-wales/smps-no--66/cancer-trends-in-england-and-wales-1950-1999--smps-no--66-and-update.pdf Accessed: 9 February 2015.
27. National Cancer Institute. SEER Stat Fact Sheets: Melanoma of the Skin. 2014. Available at: http://seer.cancer.gov/statfacts/html/melan.html Accessed: 26 Jan 2015.
28. National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Patients: Melanoma. 2013. Available at: http://www.nccn.org/patients/guidelines/melanoma/ Accessed: 9 February 2015.
29. Korn EL, Liu PY, Lee SJ, et al. Meta-analysis of Phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future Phase II trials. *J Clin Oncol*. 2008; 26(4):527-34.
30. Melanoma UK. About melanoma: Statistics. 2015. Available at: http://www.melanomauk.org.uk/about_melanoma/statistics/ Accessed: 2 February 2015.
31. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009; 27(36):6199-206.

32. Bedikian AY, Johnson MM, Warneke CL, et al. Prognostic factors that determine the long-term survival of patients with unresectable metastatic melanoma. *Cancer Invest*. 2008; 26(6):624-33.
33. Gershenwald JE, Morton DL and Thompson JF. Staging and prognostic factors for Stage IV melanoma: Initial results of an American Joint Committee on Cancer (AJCC) international evidence-based assessment of 4,895 melanoma patients. The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 30 May - 3 June 2008. Abstract 9035.
34. Erdmann F, Lortet-Tieulent J, Schuz J, et al. International trends in the incidence of malignant melanoma 1953–2008—are recent generations at higher or lower risk? *Int J Cancer*. 2013; 132:385-400.
35. Office for National Statistics (ONS). Cancer Registration Statistics, England, 2012. 2014 (Updated: 19 June 2014). Available at: www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--42--2011/rft-main-tables.xls Accessed: 27 May 2015.
36. Parkin DM, Boyd L and Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *Br J Cancer*. 2011; 105 Suppl 2:S77-81.
37. Skin Cancer Foundation. Skin Cancer Facts. 2014 (Updated: 16 October 2014). Available at: http://www.skincancer.org/skin-cancer-information/skin-cancer-facts Accessed: 9 February 2014.
38. Bleyer A, Viny A and Barr R. Cancer in 15- to 29-year-olds by primary site. *Oncologist*. 2006; 11(6):590-601.
39. Cornish D, Holterhues C, van de Poll-Franse LV, et al. A systematic review of health-related quality of life in cutaneous melanoma. *Ann Oncol*. 2009; 20 Suppl 6:vi51-8.
40. Revicki DA, van den Eertwegh AJ, Lorigan P, et al. Health related quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment. *Health Qual Life Outcomes*. 2012; 10:66.
41. Rataj D, Jankowiak B, Krajewska-Kulak E, et al. Quality-of-life evaluation in an interferon therapy after radical surgery in cutaneous melanoma patients. *Cancer Nurs*. 2005; 28(3):172-8.
42. Hatswell AJ, Pennington B, Pericleous L, et al. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. *Health Qual Life Outcomes*. 2014; 12:140.
43. Ekwueme DU, Guy GP, Jr., Li C, et al. The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity-United States, 2000 to 2006. *J Am Acad Dermatol*. 2011; 65(5 Suppl 1):S133-43.
44. Hanly P, Soerjomataram I and Sharp L. Measuring the societal burden of cancer: the cost of lost productivity due to premature cancer-related mortality in Europe. *Int J Cancer*. 2015; 136(4):E136-45.
45. Seidler AM, Pennie ML, Veledar E, et al. Economic burden of melanoma in the elderly population: population-based analysis of the Surveillance, Epidemiology, and End Results (SEER)--Medicare data. *Arch Dermatol*. 2010; 146(3):249-56.
46. Guy GP, Jr., Ekwueme DU, Tangka FK and Richardson LC. Melanoma treatment costs: a systematic review of the literature, 1990-2011. *Am J Prev Med*. 2012; 43(5):537-45.

47. Oster G, Taneja C, Penrod JR, et al. PSS28 Economic burden of advanced melanoma: Findings from a large US health insurance database. *Value Health*. 2011; 14(7):A507.
48. Reyes C, DaCosta Byfield S, Linke R, et al. The burden of metastatic melanoma: treatment patterns, healthcare use (utilization), and costs. *Melanoma Res*. 2013; 23(2):159-66.
49. Chevalier J, Bonastre J and Avril MF. The economic burden of melanoma in France: assessing healthcare use in a hospital setting. *Melanoma Res*. 2008; 18(1):40-6.
50. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006; 55(3):490-500.
51. Lorigan P, Marples M, Harries M, et al. Treatment patterns, outcomes, and resource utilization of patients with metastatic melanoma in the U.K.: the MELODY study. *Br J Dermatol*. 2014; 170(1):87-95.
52. Morris S, Cox B and Bosanquet N. Cost of skin cancer in England. *Eur J Health Econ*. 2009; 10(3):267-73.
53. Garbe C, Eigentler TK, Keilholz U, et al. Systematic review of medical treatment in melanoma: current status and future prospects. *Oncologist*. 2011; 16(1):5-24.
54. Agarwala SS. Current systemic therapy for metastatic melanoma. *Expert Rev Anticancer Ther*. 2009; 9(5):587-95.
55. National Institute for Health and Care Excellence (NICE). TA319: Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. 2014. Available at: https://www.nice.org.uk/guidance/ta319/resources/guidance-ipilimumab-for-previously-untreated-advanced-unresectable-or-metastatic-melanoma-pdf Accessed: 2 February 2015.
56. National Institute for Health and Care Excellence (NICE). TA268: Melanoma (stage III or IV) - ipilimumab: guidance. 2012 (Updated: 14 December 2012). Available at: http://guidance.nice.org.uk/TA268/Guidance/pdf/English Accessed: 2 February 2015.
57. Roche Products Limited. Summary of Product Characteristics. Vemurafenib. Available at: https://www.medicines.org.uk/emc/medicine/26056 Accessed: 10 February 2015.
58. National Institute for Health and Care Excellence (NICE). TA269: Melanoma (BRAF V600 mutation positive, unresectable metastatic) - vemurafenib: guidance. 2012 (Updated: 10 December 2012). Available at: http://guidance.nice.org.uk/TA269/Guidance/pdf/English Accessed: 2 February 2015.
59. GlaxoSmithKline UK. Summary of Product Characteristics. Dabrafenib. Available at: https://www.medicines.org.uk/emc/medicine/28432 Accessed: 10 February 2015.
60. National Institute for Health and Care Excellence (NICE). TA321: Dabrafenib for treating unresectable or metastatic BRAF V600 mutation‑positive melanoma. 2014 (Updated: October 2014). Available at: https://www.nice.org.uk/guidance/ta321 Accessed: 26 Jan 2015.
61. Merck Sharp & Dohme Limited. Summary of Product Characteristics. Pembrolizumab. 27 July 2015. Available at: https://www.medicines.org.uk/emc/medicine/30602 Accessed: 10 November 2015.

62. National Institute for Health and Care Excellence (NICE). TA366: Pembrolizumab for advanced melanoma not previously treated with ipilimumab. 2015 (Updated: 9 October 2015). Available at: https://www.nice.org.uk/guidance/ta366 Accessed: 5 January 2016.
63. Bristol-Myers Squibb Pharmaceutical Limited. Summary of Product Characteristics. Nivolumab. 3 November 2015. Available at: https://www.medicines.org.uk/emc/medicine/30476 Accessed: 10 November 2015.
64. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma version 3.2015. 2015. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf Accessed: 26 June 2015.
65. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010; 363(8):711-23.
66. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011; 364(26):2517-26.
67. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011; 364(26):2507-16.
68. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, Phase III randomised controlled trial. *Lancet*. 2012; 380(9839):358-65.
69. Office for National Statistics (ONS). Annual Mid-year Population Estimates, 2013. 2014 (Updated: 26 June 2014). Available at: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/stb---mid-2013-uk-population-estimates.html Accessed: 27 May 2015.
70. Cancer Research UK (CRUK). Skin cancer incidence statistics. 2013 (Updated: 22 July 2013). Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/skin/incidence/uk-skin-cancer-incidence-statistics Accessed: 26 Jan 2015.
71. Arnold M, Holterhues C, Hollestein LM, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. *J Eur Acad Dermatol Venereol*. 2014; 28(9):1170-8.
72. Chang AE, Karnell LH and Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer*. 1998; 83(8):1664-78.
73. National Institute for Health and Care Excellence (NICE). Melanoma: assessment and management. 2015 (Updated: July 2015). Available at: http://www.nice.org.uk/guidance/ng14 Accessed: 30 July 2015.
74. National Institute for Health and Care Excellence (NICE). Improving outcomes for people with skin tumours including melanoma (update): the management of low-risk basal cell carcinomas in the community (2010 partial guidance update). 2010 (Updated: 15 November 2010). Available at: http://guidance.nice.org.uk/CSGSTIM/Guidance/pdf/English Accessed: 2 February 2015.
75. National Institute for Health and Care Excellence (NICE). Improving outcomes for people with skin tumours including melanoma: the manual (2006 guidance). 2006 (Updated: 26 May 2010). Available at:

http://guidance.nice.org.uk/CSGSTIM/Guidance/Standard2006/pdf/English Accessed: 2 February 2015.
76. National Institute for Health and Care Excellence (NICE). Improving supportive and palliative care for adults with cancer. 2004 (Updated: 29 December 2011). Available at: http://guidance.nice.org.uk/CSGSP/Guidance/pdf/English Accessed: 2 February 2015.
77. National Institute for Health and Care Excellence (NICE). PH32: Skin cancer prevention: information, resources and environmental changes: guidance. 2011 (Updated: 23 December 2013). Available at: http://guidance.nice.org.uk/PH32/Guidance/pdf/English Accessed: 2 February 2015.
78. National Institute for Health and Care Excellence (NICE). CG27: Referral for suspected cancer: NICE guideline. 2005 (Updated: 05 December 2013). Available at: http://guidance.nice.org.uk/CG27/NICEGuidance/pdf/English Accessed: 2 February 2015.
79. National Institute for Health and Care Excellence (NICE). CG104: Metastatic malignant disease of unknown primary origin: NICE guideline. 2010 (Updated: 11 July 2013). Available at: http://guidance.nice.org.uk/CG104/NICEGuidance/pdf/English Accessed: 2 February 2015.
80. National Institute for Health and Care Excellence (NICE). ID845: Melanoma (advanced, unresectable, metastatic) - nivolumab 2015 (Updated: 3 August 2015). Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag515 Accessed: 5 January 2016.
81. Dummer R, Hauschild A, Guggenheim M, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012; 23 Suppl 7:vii86-91.
82. Hauschild A, McArthur G, Robert C, et al. Vemurafenib improves overall survival compared with dacarbazine in advanced BRAF V600-mutated melanoma: updated results from a Phase III randomized, multicenter trial. 10th International Meeting of the Society for Melanoma Research. Philadelphia, PA, USA. 17-20 November 2013. Poster.
83. Johnson DB and Sosman JA. Update on the targeted therapy of melanoma. *Curr Treat Options Oncol*. 2013; 14(2):280-92.
84. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med*. 2012; 366(8):707-14.
85. Postow MA, Chesney J, Pavlick A, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015; 372:2006-17.
86. Hamid O, Schmidt H, Nissan A, et al. A prospective Phase II trial exploring the association between tumor microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. *J Transl Med*. 2011; 9:204.
87. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, Phase II, dose-ranging study. *Lancet Oncol*. 2010; 11:155-64.
88. Ascierto PA, Simeone E, Sileni VC, et al. Sequential treatment with ipilimumab and BRAF inhibitors in patients with metastatic melanoma: data from the Italian cohort of the ipilimumab expanded access program. *Cancer Invest*. 2014; 32(4):144-9.
89. European Medicines Agency. European public assessment report: Yervoy. 2013 (Updated: 11 March 2014). Available at:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002213/human_med_001465.jsp&mid=WC0b01ac058001d124 Accessed: 2 February 2015.
90. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Efficacy and safety in key patient subgroups of nivolumab alone or combined with ipilimumab versus ipilimumab alone in treatment-naïve patients with advanced melanoma (Checkmate 067). European Cancer Congress. Vienna, Austria. 25-29 September 2015. Oral Presentation 3303.
91. Schadendorf D, Long GV, Larkin J, et al. Patient reported outcomes from a Phase 3 study of nivolumab alone or combined with ipilimumab vs ipilimumab in patients with advanced melanoma: CheckMate 067. Society for Melanoma Research 2015 International Congress. San Francisco, CA, USA. 18-21 November 2015. Oral Presentation.
92. Wolchok J, Chiarion S, V, Gonzalez R, et al. Efficacy and safety results from a Phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment naive patients (pts) with advanced melanoma (MEL) (CheckMate 067). The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Oral Presentation LBA1.
93. Bristol-Myers Squibb Company. A Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma. (Clinical Study Report: CA209067 v1.0). 19 June 2015. Data on File.
94. Abernethy AP, Postow MA, Chesney J, et al. Effect of nivolumab (NIVO) in combination with ipilimumab (IPI) versus IPI alone on quality of life (QoL) in patients (pts) with treatment-naive advanced melanoma (MEL): Results of a Phase II study (CheckMate 069). The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Poster 272.
95. Hodi FS, Postow MA, Chesney JA, et al. Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study. The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Oral Presentation 9004.
96. Bristol-Myers Squibb Company. A Phase 2, randomized, double blinded study of nivolumab (BMS-936558) in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma. (Clinical Study Report: CA209069 v1.0). 5 December 2015. Data on File.
97. Shahabi V, Whitney G, Hamid O, et al. Assessment of association between BRAF-V600E mutation status in melanomas and clinical response to ipilimumab. *Cancer Immunol Immunother*. 2012; 61(5):733-7.
98. Ji RR, Hamid O, Chasalow SD, et al. An immune-active tumor microenvironment favors clinical response to ipilimumab. *Cancer research*. 2011; 71(8 suppl. 1).
99. Hamid O. Dose effect of ipilimumab in patients with advanced melanoma: Results from a phase II, randomized, dose-ranging study [abstract no. 9025]. *J Clin Oncol*. 2008; 26(15S part I):489.
100. Lebbe C, Hoos A, Chin K, et al. Effect of dose on efficacy and safety in ipilimumab-treated patients with advanced melanoma - results from a Phase II, randomized, dose-ranging study [Abstract No. 769O]. *Ann Oncol*. 2008; 19(Supplement 8):239-40.

101. Hersh EM, O'Day SJ, Powderly J, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naïve patients with advanced melanoma. *Investigational New Drugs*. 2011; 29(3):489-98.
102. Hersh EM, Weber JS, Powderly JD, et al. Disease control and long-term survival in chemotherapy-naive patients with advanced melanoma treated with ipilimumab (MDX- 010) with or without dacarbazine [abstract no. 9022]. *J Clin Oncol*. 2008; 26(15S part I):488.
103. Hersh EM, Weber J, Powderly J, et al. A phase II, randomized multi-center study of MDX-010 alone or in combination with dacarbazine (DTIC) in stage IV metastatic malignant melanoma [abstract]. *J Clin Oncol*. 2004; 22(14s):709.
104. Koguchi Y, Hoen H, Bambina S, et al. Serum immunoregulatory proteins as predictors of overall survival of metastatic melanoma patients treated with ipilimumab. 30th Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer (SITC 2015). National Harbor, MD, USA. 4-8 November 2015. Poster P96.
105. Kaufman H, Lutzky J, Clark J, et al. Safety and efficacy of ipilimumab in melanoma patients who received prior immunotherapy on phase III study MDX010-020. *J Clin Oncol*. 2013; 31(15 suppl. 1).
106. McDermott D, Haanen J, Chen TT, et al. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). *Ann Oncol*. 2013; 24(10):2694-8.
107. Robert C, Schadendorf D, Messina M, et al. Efficacy and safety of retreatment with ipilimumab in patients with pretreated advanced melanoma who progressed after initially achieving disease control. *Clin Cancer Res*. 2013; 19(8):2232-9.
108. Weber JS, Dummer R, De Pril V, et al. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: Detailed safety analysis from a phase 3 trial in patients with advanced melanoma. *Cancer*. 2013; 119(9):1675-82.
109. O'Day S, Hodi FS, McDermott DF, et al. A phase III, randomized, double-blind, multicenter study comparing monotherapy with ipilimumab of gp100 peptide vaccine and the combination in parients with previosly treated, unresectable stage III or IV melanoma [abstract no. 4]. *J Clin Oncol*. 2010; 28(18 Suppl):6.
110. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015; 372(26):2521-32.
111. Petrella T, Robert C, Richtig W, et al. Patient-reported outcomes (PROs) in KEYNOTE-006, a randomized study of pembrolizumab (pembro) versus ipilimumab (ipi) in advanced melanoma patients (pts). Society for Melanoma Research 2015 International Congress. San Francisco, CA, USA. 18-21 November 2015. Abstract.
112. Robert C, Schachter J, Long GV, et al. Pembrolizumab (pembro) vs Ipilimumab (ipi) in Patients With Ipilimumab-Naive Advanced Melanoma: Updated Efficacy and Safety of the Phase 3 KEYNOTE-006 Study. Society for Melanoma Research 2015 International Congress. San Francisco, CA, USA. 18-21 November 2015. Abstract.
113. Grob JJ, Amonkar MM, Martin-Algarra S, et al. Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: Quality-of-life analyses of the BREAK-3 study comparing dabrafenib with dacarbazine. *Ann Oncol*. 2014; 25(7):1428-36.
114. Hauschild A, Grob JJ, Demidov LV, et al. An update on overall survival (OS) and follow-on therapies in BREAK-3, a Phase III, randomized trial: Dabrafenib (D)

vs. dacarbazine (DTIC) in patients (pts) with BRAF V600E mutation-positive metastatic melanoma (MM). The European Society for Medical Oncology (ESMO) Congress. Madrid, Spain. 26-30 September 2014. Poster 1092PD.
115. Hauschild A, Grob JJ, Demidov LV, et al. An update on BREAK-3, a Phase III, randomized trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM). The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 31 May - 4 June 2013. Abstract 9013.
116. Latimer N, Abrams KR, Amonkar M, et al. Adjusting for treatment crossover in the BREAK-3 metastatic melanoma trial for dabrafenib: Preliminary analysis. *J Clin Oncol*. 2013; 31(15 suppl. 1).
117. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*. 2014; 371(20):1877-88.
118. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. 2015; 386(9992):444-51.
119. Long GV, Stroyakovskiy D, Gogas H, et al. Overall survival in COMBI-d, a randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib with dabrafenib and placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Abstract 102.
120. Schadendorf D, Amonkar MM, Stroyakovskiy D, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. *Eur J Cancer*. 2015; 51(7):833-40.
121. Latimer N, Amonkar M, Stapelkamp C and Sun P. Adjusting for confounding effects of treatment crossover in a randomized Phase II study of dabrafenib plus trametinib in BRAF V600+ metastatic melanoma. The American Association for Cancer Research Annual Meeting. San Diego, CA, USA. 5-9 April 2014. Abstract CT330.
122. Long GV, Stroyakovsky DL, Gogas H, et al. COMBI-d: A randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAFV600E/Kmutation-positive cutaneous melanoma. *J Clin Oncol*. 2014; 32(15 suppl. 1).
123. Schadendorf D, Amonkar MM, Stroyakovskiy D, et al. COMBI-d: Quality of Life (QOL) Impact of the Combination of Dabrafenib and Trametinib (D+T) Versus Dabrafenib Monotherapy (D) in Patients with BRAF V600E/K Unresectable or Metastatic Melanoma in a Phase III Trial. The European Society for Medical Oncology (ESMO) Congress. Madrid, Spain. 26-30 September 2014. Poster 1091PD.
124. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012; 367(18):1694-703.
125. Daud A, Weber JS, Sosman JA, et al. Updated overall survival (OS) results for BRF113220, a Phase I–II study of dabrafenib alone versus combined dabrafenib and trametinib in patients with BRAF V600 metastatic melanoma (MM). The

American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Abstract 9036.
126. Menzies AM, Ashworth MT, Swann S, et al. Characteristics of pyrexia in BRAFV600E/K metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial. *Ann Oncol*. 2015; 26(2):415-21.
127. Flaherty K, Daud A, Weber JS, et al. Updated overall survival (OS) for BRF113220, a phase 1-2 study of dabrafenib (D) alone versus combined dabrafenib and trametinib (D+T) in pts with BRAF V600 mutation-positive (+) metastatic melanoma (MM). *J Clin Oncol*. 2014; 32(15 suppl. 1).
128. Johnson DB, Flaherty KT, Weber JS, et al. Combined BRAF (Dabrafenib) and MEK inhibition (Trametinib) in patients with BRAFV600-mutant melanoma experiencing progression with single-agent BRAF inhibitor. *J Clin Oncol*. 2014; 32(33):3697-704.
129. Cebon JS, Flaherty K, Weber JS, et al. Comparison of BRAF inhibitor (BRAFi)-induced cutaneous squamous cell carcinoma (cuSCC) and secondary malignancies in BRAF mutation-positive metastatic melanoma (MM) patients (pts) treated with dabrafenib (D) as monotherapy or in combination with MEK1/2 inhibitor (MEKi) trametinib (T). *J Clin Oncol*. 2013; 31(15 suppl. 1).
130. Schuchter LM, Kudchadkar RR, Gonzalez R, et al. Efficacy, safety, and pharmacokinetics (PK) of the BRAF inhibitor dabrafenib (D) hydroxypropyl methylcellulose (HPMC) capsule formulation in combination with the MEK1/2 inhibitor trametinib (T) in patients (pts) with BRAF mutation-positive metastatic melanoma (MM). *J Clin Oncol*. 2013; 31(15 suppl. 1).
131. Chapman P, Robert C, Larkin J, et al. Vemurafenib (VEM) in Patients (Pts) With BRAFV600 Mutation-Positive Metastatic Melanoma (MM): Final Overall Survival (OS) Results of the BRIM-3 Study. Society for Melanoma Research 2015 International Congress. San Francisco, CA, USA. 18-21 November 2015. Abstract.
132. Zabor EC, Heller G, Schwartz LH and Chapman PB. Correlating surrogate endpoints with overall survival at the individual patient level in BRAF-mutated metastatic melanoma patients treated with vemurafenib. The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Abstract e20020.
133. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAFV600E and BRAFV600K mutation-positive melanoma (BRIM-3): Extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol*. 2014; 15(3):323-32.
134. Chapman PB, Hauschild A, Robert C, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAFV600E-mutated melanoma. *J Clin Oncol*. 2012; 30(15 suppl. 1).
135. Chapman PB, Hauschild A, Robert C, et al. Phase III randomized, open-label, multicenter trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine (DTIC) in patients with V600EBRAF-mutated melanoma. *J Clin Oncol*. 2011; 29(18 suppl. 1).
136. Hauschild A, McArthur GA, Robert C, et al. Vemurafenib improves overall survival compared to dacarbazine in advanced BRAFV600E-mutated melanoma: An update from the phase III randomized, open-label, multicenter BRIM3 trial. *Pigment Cell Melanoma Res*. 2011; 24(5):1021.

137. McArthur G, Hauschild A, Robert C, et al. Vemurafenib improves overall survival compared to dacarbazine in advanced BRAFV600E-mutated melanoma: Updated survival results from a phase III randomised, open-label, multicentre trial. *Eur J Cancer*. 2011; 47:14.
138. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015; 372(1):30-9.
139. Ascierto PA, McArthur GA, Dréno B, et al. coBRIM: A phase 3, double-blind, placebo-controlled study of vemurafenib versus vemurafenib + cobimetinib in previously untreated BRAF ^{V600} mutation-positive patients with unresectable locally advanced or metastatic melanoma (NCT01689519). *J Transl Med*. 2015:1-2.
140. Grob JJ, Amonkar MM, Karaszewska B, et al. COMBI-v: health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with BRAF V600 metastatic melanoma (MM). European Cancer Congress. Vienna, Austria. 25-29 September 2015. Abstract 3345.
141. Robert C, Karaszewska B, Schachter J, et al. Two year estimate of overall survival in COMBI-v, a randomized, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) with vemurafenib (Vem) as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. European Cancer Congress. Vienna, Austria. 25-29 September 2015. Abstract 3301.
142. Robert C, Karaszewska B, Schachter J, et al. COMBI-v: A randomised, open-label, Phase III study comparing the combination of dabrafenib and trametinib with vemurafenib as first-line therapy in patients with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. The European Society for Medical Oncology (ESMO) Congress. Madrid, Spain. 26-30 September 2014. Abstract LBA4_PR.
143. Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014; 371(20):1867-76.
144. de La Cruz-Merino L, Di Guardo L, Grob JJ, et al. Clinical features of cobimetinib (COBI)–associated serous retinopathy (SR) in BRAF-mutated melanoma patients (pts) treated in the coBRIM study. The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Abstract 9033.
145. Dreno B, Bartley K, Ascierto PA, et al. Quality-of-life (QOL) assessment in patients (pts) with metastatic melanoma receiving vemurafenib (V) and cobimetinib (C). The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Abstract 9021.
146. Larkin JMG, Yan Y, McArthur GA, et al. Update of progression-free survival (PFS) and correlative biomarker analysis from coBRIM: Phase III study of cobimetinib (cobi) plus vemurafenib (vem) in advanced BRAF-mutated melanoma. The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Abstract 9006.
147. McArthur G, Larkin J, dreno B, et al. Impact of baseline genetic heterogeneities on progression-free survival (PFS) in patients (pts) with advanced BRAFV600-mutated melanoma treated with cobimetinib (COBI) + vemurafenib (VEM) in the phase 3 coBRIM study. European Cancer Congress. Vienna, Austria. 25-29 September 2015. Abstract 25LBA.

148. McArthur GA, Ascierto PA, Larkin J, et al. Phase 3, double-blind, placebo-controlled study of vemurafenib versus vemurafenib + cometinib in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma (NCT01689519). The European Society for Medical Oncology (ESMO) Congress. Madrid, Spain. 26-30 September 2014. Abstract LBA5_PR.
149. Grippo JF, Zhang W, Heinzmann D, et al. A phase I, randomized, open-label study of the multiple-dose pharmacokinetics of vemurafenib in patients with BRAF V600E mutation-positive metastatic melanoma. *Cancer Chemother Pharmacol*. 2014; 73(1):103-11.
150. Bristol-Myers Squibb Company. CheckMate 067: HRQL output tables. . 2015. Data on File.
151. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998; 16(1):139-44.
152. Pickard AS, Neary MP and Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007; 5:70-.
153. Larkin J, D'Angelo SP, Sosman JA, et al. Efficacy and safety of nivolumab alone or in combination with ipilimumab in the treatment of advanced mucosal melanoma. Society for Melanoma Research 2015 International Congress. San Francisco, CA, USA. 18-21 November 2015. Oral Presentation.
154. Bristol-Myers Squibb Pharmaceuticals Limited. Single technology appraisal: Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID845] - Company evidence submission. Data on File.
155. Atkinson V, Ascierto PA, Long GV, et al. Two-Year Survival and Safety Update in Patients With Treatment-Naïve Advanced Melanoma (MEL) Receiving Nivolumab or Dacarbazine in CheckMate 066. Society for Melanoma Research 2015 International Congress. San Francisco, CA, USA. 18-21 November 2015. Poster.
156. Feng Y, Berman D, Chen T-T, et al. Ipilimumab exposure-response and meta-analysis of overall survival of advanced melanoma patients. The European Society for Medical Oncology (ESMO) Congress. Madrid, Spain. 26-30 September 2014. Poster 1100P.
157. Won Kim D, Chakravarti N, Trinh VA, et al. Predictive markers for programmed death1 (PD1)/programmed deathligand 1(PD-L1) axis blockade therapy in patients with metastatic melanoma (MM). The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 29 May - 2 June 2015. Abstract e20029.
158. R Development Core Team. R: A language and environment for statistical computing. 2008. Available at: http://www.R-project.org. Accessed: May 2015.
159. Guyot P, Ades AE, Ouwens MJ and Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012; 12:9.
160. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013; 369(2):122-33.
161. Bristol-Myers Squibb Company. A Phase Ib, open-label, multicenter, multidose, dose-escalation study of MDX-1106 (BMS-936558) in combination with ipilimumab (BMS-734016) in subjects with unresectable Stage III or Stage IV malignant melanoma. (Clinical Study Report: CA209004 v1.0). 5 December 2014. Data on File.

162. Sznol M, Kluger H, Callahan MK, et al. Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL) The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 30 May - 3 June 2014. Oral Presentation LBA9003.
163. Sznol M, Callahan MK, Kluger H, et al. Updated survival, response and safety data in a Phase 1 dose-finding study (CA209-004) of concurrent nivolumab (NIVO) and ipilimumab (IPI) in advanced melanoma. Society for Melanoma Research 2015 International Congress. San Francisco, CA, USA. 18-21 November 2015. Poster.
164. Feng Y, Agrawal S, Gupta M, et al. Association between immune checkpoint inhibitor-induced tumour shrinkage (TS) and overall survival (OS) in advanced melanoma and non-small cell lung cancer (NSCLC). The American Society of Clinical Oncology Annual Meeting. Chicago, IL, USA. 30 May - 3 June 2014. Poster 120.
165. Flaherty KT, Hennig M, Lee SJ, et al. Surrogate endpoints for overall survival in metastatic melanoma: A meta-analysis of randomised controlled trials. *Lancet Oncol*. 2014; 15(3):297-304.
166. Bristol-Myers Squibb Company. Summary of Product Characteristics. OPDIVO 10 mg/ml concentrate for solution for infusion. 2015. Available at: https://www.medicines.org.uk/emc/medicine/30476 Accessed: 30 July 2015.
167. National Institute for Health and Care Excellence (NICE). TA257: Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. 2012. Available at: https://www.nice.org.uk/guidance/ta257 Accessed: 2 February 2015.
168. National Institute for Health and Care Excellence (NICE). TA258: Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer. 2012. Available at: https://www.nice.org.uk/guidance/ta258 Accessed: 2 February 2015.
169. National Institute for Health and Care Excellence (NICE). TA311: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. 2014. Available at: https://www.nice.org.uk/guidance/ta311 Accessed: 2 February 2015.
170. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*. 2001; 19(16):3635-48.
171. Oxford Outcomes. Advanced melanoma resource use and costs in Europe: Final report. 16 May 2011. Data on File.
172. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013. Available at: http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf Accessed: 2 February 2015.
173. Latimer N. National Institute for Health an Clinical Excellence (NICE) DSU technical support document 14: Survival analysis for economic evaluations alongside clinical trials - Extrapolation with patient-level data 2011 (Updated: March 2013). Available at: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf Accessed: 2 February 2015.

174. Office for National Statistics (ONS). National Life Tables, England 2011-2013. 2014. Available at: http://www.ons.gov.uk/ons/rel/lifetables/national-life-tables/2011-2013/stb-uk-2011-2013.html Accessed: 4 December 2015.
175. Long GV, Atkinson V, Ascierto PA, et al. Effect of nivolumab (NIVO) on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): Results of a phase III study (CheckMate 066). *J Clin Oncol*. 2015; 33(15).
176. Delea TE, Amdahl J, Wang A, et al. Cost Effectiveness of Dabrafenib as a First-Line Treatment in Patients with BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma in Canada. *PharmacoEconomics*. 2015; 33(4):367-80.
177. Li Y, Bare LA, Bender RA, et al. Cost Effectiveness of Sequencing 34 Cancer-Associated Genes as an Aid for Treatment Selection in Patients with Metastatic Melanoma. *Molecular Diagnosis and Therapy*. 2015; 19(3):169-77.
178. Matter-Walstra K, Braun R, Kolb C, et al. A cost-effectiveness analysis of trametinib plus dabrafenib as first-line therapy for metastatic BRAF V600-positive melanoma in the Swiss setting. *Br J Dermatol*. 2015.
179. Shih V, Ten Ham RM, Bui CT, et al. Targeted therapies compared to dacarbazine for treatment of braf^{v600e} metastatic melanoma: A cost-effectiveness analysis. *J Skin Cancer*. 2015; 2015:Article ID 595302.
180. Porter J, Lee D, Hertel N and Hatswell AJ. Patient reported utilities in first-line advanced or metastatic melanoma: Analysis of trial CA 184-024. ISPOR 17th Annual European Congress. Amsterdam, The Netherlands. 8-12 November 2014. Poster PRM148.
181. Beusterien KM, Szabo SM, Kotapati S, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. *Br J Cancer*. 2009; 101(3):387-9.
182. Dixon S, Walters SJ, Turner L and Hancock BW. Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial. *Br J Cancer*. 2006; 94(4):492-8.
183. King SM, Bonaccorsi P, Bendeck S, et al. Melanoma quality of life: pilot study using utility measurements. *Arch Dermatol*. 2011; 147(3):353-4.
184. Askew RL, Swartz RJ, Xing Y, et al. Mapping FACT-melanoma quality-of-life scores to EQ-5D health utility weights. *Value Health*. 2011; 14(6):900-6.
185. Batty A, Lee D, Winn B, et al. Estimating quality of life in advanced melanoma; a comparison of standard gamble, SF-36 mapped, and EORTC QLQ-C30 mapped utilities. ISPOR 14th Annual European Congress. Madrid, Spain. 5-8 November 2011. Poster PCN148.
186. Batty AJ, Winn B, Pericleous L, et al. A comparison of general population and patient utility values for advanced melanoma. The European Society for Medical Oncology (ESMO) Congress. Vienna, Austria. 28 September - 2 October 2012. Poster 1143P.
187. Amdahl J, Wang A, Thabane M, et al. Cost Effectiveness of Trametinib as First-Line (1l) Treatment for Braf V600 Positive Advanced or Metastatic Melanoma — A Canadian Societal Perspective. *Value Health*. 17(3):A83.
188. Rowen D, Brazier J, Young T, et al. Deriving a preference-based measure for cancer using the EORTC QLQ-C30. *Value Health*. 2011; 14(5):721-31.
189. Barzey V, Atkins MB, Garrison LP, et al. Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis. *J Med Econ*. 2013; 16(2):202-12.

190. Cormier JN, Xing Y, Ding M, et al. Cost effectiveness of adjuvant interferon in node-positive melanoma. *J Clin Oncol*. 2007; 25(17):2442-8.
191. Kilbridge KL, Weeks JC, Sober AJ, et al. Patient preferences for adjuvant interferon alfa-2b treatment. *J Clin Oncol*. 2001; 19(3):812-23.
192. Hirst NG, Gordon LG, Scuffham PA and Green AC. Lifetime cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use. *Value Health*. 2012; 15(2):261-8.
193. Stratton KR, Durch JS and Lawrence RS. *Vaccines for the 21st Century: A Tool for Decisionmaking*. Washington, DC: The National Academies Press, 2000.
194. Morton RL, Howard K and Thompson JF. The cost-effectiveness of sentinel node biopsy in patients with intermediate thickness primary cutaneous melanoma. *Ann Surg Oncol*. 2009; 16(4):929-40.
195. Chen SC, Bendeck S, Hadley JC, et al. Can melanoma patients predict the quality of life of an alternate melanoma stage? . 26th Annual Meeting of the Society for Medical Decision Making. Atlanta, GA, USA. 17-20 October 2004. Abstract P332.
196. Lee D, Pennington B, Lebmeier M and Batty AJ. Modelling the cost effectiveness of ipilimumab for previously-treated, metastatic melanoma. ISPOR 15th Annual European Congress. Berlin, Germany. 3-7 November 2012. Poster PCN80.
197. Losina E, Walensky RP, Geller A, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. *Arch Dermatol*. 2007; 143(1):21-8.
198. Mooney MM, Mettlin C, Michalek AM, et al. Life-long screening of patients with intermediate-thickness cutaneous melanoma for asymptomatic pulmonary recurrences: a cost-effectiveness analysis. *Cancer*. 1997; 80(6):1052-64.
199. Hillner BE, Smith TJ and Desch CE. Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. Estimates using decision analysis while awaiting clinical trial results. *JAMA*. 1992; 267(15):2055-61.
200. Wong JB, Koff RS, Tine F and Pauker SG. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. *Ann Intern Med*. 1995; 122(9):664-75.
201. National Institute for Health Research (NIHR) Horizon Scanning Centre (HSC). MEK162 for NRAS mutation positive advanced malignant melanoma - first and second line. 2013 (Updated: 2013). Available at: http://www.hsc.nihr.ac.uk/topics/mek162-for-nras-mutation-positive-advanced-maligna/ Accessed: 2 February 2015.
202. National Institute for Health Research (NIHR) Horizon Scanning Centre (HSC). MK-3475 for advanced melanoma - first or second line, in patients naïve to ipilimumab. 2013 (Updated: 2013). Available at: http://www.hsc.nihr.ac.uk/topics/mek162-for-nras-mutation-positive-advanced-maligna/ Accessed: 2 February 2015.
203. Johnston K, Levy AR, Lorigan P, et al. Economic impact of healthcare resource utilisation patterns among patients diagnosed with advanced melanoma in the United Kingdom, Italy, and France: results from a retrospective, longitudinal survey (MELODY study). *Eur J Cancer*. 2012; 48(14):2175-82.
204. Lorigan P, Maio M, Middleton M, et al. PCN111 Health-care resource utilization in advanced melanoma: An analysis from the melody observational study. *Value Health*. 2010; 13(7):A272.

205. Oxford Outcomes. MELODY study resource use data analysis: UK results – final draft. December 2010. Data on File.
206. Department of Health. NHS Reference Costs 2014-15. 2015. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015 Accessed: 6/1/2016.
207. Personal Social Services Research Unit (PSSRU). Unit costs for health and social care 2015. 2015. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php Accessed: 6/1/2016.
208. Gricks C, Graham J and Vora P. Malignant melanoma. 2006. Available at: http://decisionresources.com/Products-and-Services/Report?r=pcoron0406 Accessed: 2 February 2015.

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Single technology appraisal

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

Dear [redacted] ,

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received on 12th January 2016 from BMS. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on 19th February 2016.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals **https://appraisals.nice.org.uk/request/11044** .

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted] Technical Lead. Any procedural questions should be addressed to [redacted] , Project Manager [redacted]
Yours sincerely

[redacted]
Technical Advisor – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on clinical effectiveness data

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Literature searching

A1. Please clarify why a search for non-RCT evidence was not carried out.

Methods and results

A2. **Priority question:** As required in the NICE scope, please carry out a comparison of combination immunotherapy (i.e. nivolumab in combination with ipilimumab) and pembrolizumab using ipilimumab as a common comparator by including the trials: CheckMate 067, CheckMate 069 and Keynote 006.Please also adjust for relevant covariates and report the residual deviance when comparing the outcomes of the ipilimumab treatment groups in CheckMate 067, CheckMate 069 and Keynote 006.

A3. Please provide the clinical study reports for CheckMate 066 and CheckMate 004.

A4. As a validation exercise please carry out an indirect comparison of nivolumab and ipilimumab using dacarbazine (DTIC/gp100) as a common comparator. Please also adjusti for relevant covariates and report residual deviance when comparing the outcomes of the two DTIC/gp100 treatment groups from their respective studies (CheckMate 066 and MDX010-20).

A5. Please provide results (summary tables of model parameter estimate, goodness of fit statistics and curves) for the indirect comparison of combination therapy versus ipilimumab for:

a. Time to treatment progression , Post-progression survival , and Pre-progression survival , unadjusted for any covariates;

b. Time to treatment progression, Post-progression survival , and Pre-progression survival adjusted for statistically significantly different covariates;

c. Post-progression survival unadjusted for subsequent therapy.

A6. Please complete the following table for CheckMate 067, CheckMate 069 CheckMate 066, MDX010-20, BRIM-3 and BREAK-3 for the numbers and percentage ofpatients on crossover/subsequent therapies:

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Trial	Treatment	No subsequent therapy post progression	Crossover pre-progression	Crossover post-progression	Crossover total	Subsequent ipilimumab therapy
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
CheckMate 067	Nivolumab plus ipilimumab					
	Nivolumab					
	Ipilimumab					
CheckMate 069	Nivolumab plus ipilimumab					
	Ipilimumab					
CheckMate 066	Nivolumab					
	Dacarbazine					
MDX010-20	Ipilimumab 3mg/kg					
	gp-100					
	Ipilimumab 3mg/kg + gp-100					
BRIM-3	Vemurafenib					
	Dacarbazine					
BREAK-3	Dabrafenib					
	Dacarbazine					

A7. Please complete the following table of overall survival and progression free survival for CheckMate067 and CheckMate069 based on length of treatment (4 doses or fewer, more than 4 doses):

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Trial	Treatment	OS		PFS	
		≤ 4 doses	> 4 doses	≤ 4 doses	> 4 doses
		n/N (%)	n/N (%)	n/N (%)	n/N (%)
CheckMate 067	Nivolumab plus Ipilimumab	N/A	N/A		
	Nivolumab	N/A	N/A		
	Ipilimumab	N/A	N/A		
CheckMate 069	Nivolumab plus Ipilimumab				
	Ipilimumab				

A8. Please complete the following table of baseline characteristics of CheckMate 066 and MDX010-20:

	CheckMate 066		MDX010-20	
Characteristic	DTIC (n=) n/N (%)	Nivolumab (n=) n/N (%)	gp100 (n=) n/N (%)	Ipilimumab (n=) n/N (%)
ECOG = 0				
LDH (>ULN)				
M stage = M1c				
History of brain metastases				
Age (under 65)				
Gender (males)				

A9. Please complete the following table summarising the trial design of CheckMate 066, MDX010-20, BRIM and BREAK-3 (as per Table 11 on page 47 of the company's submission):

	CheckMate 066	MDX010-20	BRIM-3	BREAK-3
Location				

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	CheckMate 066	MDX010-20	BRIM-3	BREAK-3
Trial design				
Eligibility criteria for participants				
Settings and locations where the data were collected				
Trial drugs				
Permitted concomitant medication				
Disallowed concomitant medication				

A10. Please complete the following table of patient characteristics for the UK population subgroup in CheckMate 067:

CheckMate 067	Nivolumab plus ipilimumab (ITT population, n=30)	Ipilimumab (ITT population, n=36)
Age, median years (range)		

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Age, mean years (SD)		
Aged under 65 years old (n/N)		
Gender, male n (%)		
Race, caucasian n (%)		
Region, n (%)		
ECOG PS, n (%)	0: 1: 2: Not available:	0: 1: 2: Not available:
Metastasis stage, n (%)	M0-M1B: M1C:	M0-M1B: M1C:
Common metastasis site, n (%)	Lymph node: Lung: Liver:	Lymph node: Lung: Liver:
Elevated LDH, n (%)		
History of brain metastases, yes n (%)		
Disease duration, median years (range)		
PD-L1-positive, n (%)		
BRAF mutation-negative (wild-type), n (%)		
Subsequent ipilimumab, n (%)		

A11. Please complete the following table of outcome data for the UK population subgroup in CheckMate 067:

Trial	**Treatment**	**PFS**	**ORR**		
			Responders	**CR**	**PR**

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		n/N (%)	n/N (%)	n/N (%)	n/N (%)
CheckMate 067	Nivolumab plus ipilimumab				
	Nivolumab				
	Ipilimumab				

A12. Please carry out a meta-analysis of CheckMate 067 and 069 for progression free survival and complete the table below. Please also describe the model used for the meta-analysis.

Outcome	**Trial**	**Nivolumab plus Ipilimumab**		**Ipilimumab**		**HR (95% CI)**	**p value**	**I^2**
		n	**N**	**n**	**N**			
PFS	CheckMate 067							
	CheckMate 069							
ORR						**OR (95% CI)**	**p value**	**I^2**
Responders	CheckMate 067							
	CheckMate 069							
CR	CheckMate 067							
	CheckMate 069							
PR	CheckMate 067							
	CheckMate 069							

A13. Please provide a description of the methods used for data extraction of all the RCTs.

A14. Table 11 on page 47 of the company's submission: Please include a description of the assessments of disease progression, including at what time points these were carried out.

A15. Please provide individual Kaplan Meier curves for each parametric curve s for Figures 28, 30, 34 and 35 (pages 91, 94, 100 and 101) compared to the trial data.

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Section B: Clarification of cost-effectiveness data

B1. **Priority question:** Please provide an updated cost-effectiveness analysis using CheckMate 067 Overall Survival Efficacy Update Report. If possible adopt a partitioned survival approach for this analysis. .

B2. **Priority question:** Please provide the number of patients at risk and the observed number of events, separately by treatment arm, at each available time point for:

PUpdated OS Kaplan Meier curves (i.e. shown in Figure 5.1-1 of the Study CA209067 Overall Survival Efficacy Update Report);

- Pre-progression survival (PrePS) Kaplan Meier curves from CheckMate 067 (i.e. shown in Figure 31 on page 96 of the company's submission);
- Time-to-progression (TTP) Kaplan Meier curves from CheckMate 067 (i.e. shown in Figure 25 on page 88 of the company's submission);
- Progression-free survival (PFS) Kaplan Meier curves from CheckMate 067 (i.e. shown in Figure 1, Panel A of the article by Larkin *et al*., 2015).

B3. **Priority question:** Please clarify how the model results compare to the results of the CheckMate 066, CheckMate 067 and CheckMate 069 trials in terms of extrapolated outcomes for progression free survival , time to progression, overall survival and if possible for pre-progression survival and post-progression survival . Please provide graphical comparisons between the Kaplan Meier curves and the curves estimated in the economic model for the outcomes mentioned.

.

B4. **Priority question:** Table 68 on page 176 in the company's submission,: please explain and justify the reasons that :

:

- Not all patients received subsequent treatments;
- The proportions of untreated patients vary across treatments;
- Patients who had received dabrafenib or vemurafenib were assumed not to receive pembrolizumab, nivolumab or nivolumab plus ipilimumab, considering that these treatments were not available at the time of the BRIM-3 trial but they are now included in the treatment pathway.

B5. **Priority question:** Please explain how the proportional hazards assumption was tested in the model for the outcomes pre-progression survival and time to progression (post 84 days). Also please provide the results of any statistical tests

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undertaken.

B6. **Priority question:** Please explain why the first 84 days were not utilized when implementing the time to progression parametric models in the economic model.

.

B7. Please explain why a partitioned survival model approach was not considered.. Please provide further justification and explanation of why the particular model structure was considered reasonable, apart from that it had been used in a previous submission to NICE..

.

Section C: Textual clarifications and additional points

C1. Figure 30 on page 94 of the company's submission: Please clarify the captions and the axis labels for each panel of Figure 30 in the CS.

C2. Figure 39 on page 110 of the company's submission: Please clarify which patient cohorts from CheckMate 004 were used to produce this figure.

C3. Please provide the PRISMA diagrams and search strategies for the original searches carried out in November 2014 for cost-effectiveness, costs and utility studies and in May 2013 for costs and utility studies. Please provide full references for papers reviewed at the full text phase in the original searches, together with justifications for inclusion or exclusion.

C4. Please clarify why the number of patients at risk reported in the electronic model (KM Data sheet, cells AL12 and AO12 onwards t) do not match the number of patients at risk reported in Figure 1, Panel A of the trial publication by Larkin *et al*., 2015

24th February 2016

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Single technology appraisal

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

Updated Company response to clarification question A6 – 24th February 2016

Dear Bijal,

As a follow up to the response to the clarification questions submitted on the 19th of February, please find below an update to the response for question A6. This response has been updated with an earlier data cut as the company submission was based, in part, on an earlier (12-month) data cut and we are providing these data for completeness.

The response to question A11 has not been updated as there is no difference in the results using the earlier 12 month data cut.

Yours sincerely,

[redacted]
Bristol-Myers Squibb Pharmaceuticals Limited

A6. Please complete the following table for CheckMate 067, CheckMate 069 CheckMate 066, MDX010-20, BRIM-3 and BREAK-3 for the numbers and percentage of patients on crossover/subsequent therapies:

Data from the most recent data cut for CheckMate 067 & 069 studies are presented, and also for CheckMate 066 (as data presented in the original submission from this study, used the most recent data cut). Additionally, data from the 12 month data cut for CheckMate 067 & 069 are also presented.

For column 3, the number of patients that had no subsequent systemic anti-cancer therapy post progression are presented as a proportion of all treated patients that had disease progression.

For columns 4-6, crossover was not permitted in the CheckMate 066 & 067 studies. For CheckMate 069, upon discontinuation of study treatment for progressive disease, subjects could remain blinded and receive treatment beyond progression or be unblinded and receive standard of care treatment; subjects in the ipilimumab arm had the option to cross over to nivolumab 3mg/kg Q2W upon unblinding. The total number of subjects that crossover to nivolumab is presented as a proportion of all treated subjects.

For column 7, the number of subjects that received subsequent ipilimumab therapy are presented as a proportion of all treated patients.

An additional column was included to present data for the number of subjects that received subsequent systemic anti-cancer therapy as a proportion of all treated subjects.

Trial	Treatment	No subsequent therapy post progression	Crossover pre-progression	Crossover post-progression	Crossover total	Subsequent ipilimumab therapy	Subsequent systemic anti-cancer therapy (including crossover)
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 067 (17 February 2015 datacut)	The Regimen	86/150 (71.7)	N/A	N/A	N/A	7/313 (2.2)	69/313 (22.0)
	Nivolumab	74/184 (40.2)	N/A	N/A	N/A	61/313 (19.5)	112/313 (35.8)
	Ipilimumab	92/249 (36.9)	N/A	N/A	N/A	4/311 (1.29)	162/311 (52.1)

Trial	Treatment	No subsequent therapy post progression	Crossover pre-progression	Crossover post-progression	Crossover total	Subsequent ipilimumab therapy	Subsequent systemic anti-cancer therapy (including crossover)
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 069 (30 January 2015 datacut)	The Regimen	26/31 (83.9)	N/A	N/A	N/A	0	6/94 (6.4)
	Ipilimumab	11/35 (31.4)	0	22/35 (62.9)	22/46 (47.8)	0	24/46 (52.2)
CheckMate 066 (18 month datacut)	Nivolumab	47/122 (38.5%)	N/A	N/A	N/A	57/206 (27.7)	79/206 (38.3)
	Dacarbazine	70/187 (37.4%)	N/A	N/A	N/A	89/205 (43.4)	122/205 (59.5)
MDX010-20 (19th June 2009 datacut)	Ipilimumab 3mg/kg	14/23 (60.9)	0	0	0	0	23/24 (95.8)
	gp-100	2/16 (12.5)	0	0	0	0	16/16 (100)
	Ipilimumab 3mg/kg + gp-100	15/51 (29.4)	0	0	0	0	51/54 (94.4)
BRIM-3 (20th Dec 2012 datacut)	Vemurafenib	192/337 (56.9)	0	0	0	74/337 (22.0)	145/337 (43.0)
	Dacarbazine	175/338 (51.8)	Not reported	Not reported	84/338 (24.9)	81/338 (24.0)	163/338 (48.2)
BREAK-3 (Jan 2014 datacut)	Dabrafenib	71/187 (38.0)	0	0	0	27/187 (14.4)	116/187 (62)
	Dacarbazine	12/63 (19.0)	0	37/63 (58.7)	37/63 (58.7)	3/63 (4.8)	51/63 (81)

Single technology appraisal

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

Company response to clarification questions – 19th February 2016

Appendix

Appendix 1: Detailed cost-effectiveness results for the revised base case

Disaggregated results of the base case incremental cost-effectiveness analysis

Table 1 and Table 2 present the disaggregated QALY gains by health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively. Table 3 and Table 4 present the disaggregated life year gains by health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively.

Table 5 and Table 6 present the disaggregated costs by cost category and health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively, in the base case with list drug costs. Table 7 and Table 8 present the disaggregated costs by cost category health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the PAS-based base case.

Table 1: Summary of QALY gain by health state – BRAF mutation-negative

Health state	QALY – the Regimen	QALY - ipilimumab	QALY - pembrolizumab	Absolute increment (vs ipilimumab)	Absolute increment (vs pembrolizumab)	% increment (vs ipilimumab)	% increment (vs pembrolizumab)
Progression free	3.869	0.863	2.054	3.007	1.815	78%	47%
Progressed	1.577	2.045	1.738	-0.468	-0.161	-30%	-10%
Disutility due to AE	-0.023	-0.007	0.000	-0.016	-0.023	69%	100%
Total QALYs	**5.423**	**2.901**	**3.792**	**2.523**	**1.631**	**47%**	**30%**

Key: AE, adverse event; DTIC, dacarbazine; QALY, quality-adjusted life year; Regimen, nivolumab plus ipilimumab.

Table 2: Summary of QALY gain by health state – BRAF mutation-positive

Health state	QALY – the Regimen	QALY - ipi	QALY-pembro	QALY - dab	QALY – vem	Absolute inc (vs ipi)	Absolute inc (vs pembro)	Absolute inc (vs dab)	Absolute inc (vs vem)	% inc (vs ipi)	% inc (vs pembro)	% inc (vs dab)	% inc (vs vem)
Progression free	3.378	0.637	1.655	0.807	0.807	2.741	1.723	2.571	2.571	81%	51%	76%	76%
Progressed	1.814	1.964	1.880	0.936	0.936	-0.150	-0.066	0.878	0.878	-8%	-4%	48%	48%
Disutility due to AE	-0.020	-0.007	0.000	0.000	0.000	-0.013	-0.020	-0.020	-0.020	64%	100%	100%	100%
Total QALYs	**5.172**	**2.593**	**3.535**	**1.743**	**1.743**	**2.578**	**1.637**	**3.429**	**3.429**	**50%**	**32%**	**66%**	**66%**

Key: dab, dabrafenib; inc, incremental; ipi, ipilimumab; nivo, nivolumab; pembro, pembrolizumab; QALY, quality-adjusted life year; Regimen, nivolumab plus ipilimumab; vem, vemurafenib.

Table 3: Summary of LY gain by health state – BRAF mutation-negative

Health state	LY - the Regimen	LY - ipilimumab	LY - pembrolizumab	Absolute increment (vs ipilimumab)	Absolute increment (vs pembrolizumab)	% increment (vs ipilimumab)	% increment (vs pembrolizumab)

Health state	LY - the Regimen	LY - ipilimumab	LY - pembrolizumab	Absolute increment (vs ipilimumab)	Absolute increment (vs pembrolizumab)	% increment (vs ipilimumab)	% increment (vs pembrolizumab)
Progression free	4.865	1.085	2.583	3.780	2.282	78%	47%
Progressed	2.068	2.682	2.279	-0.614	-0.212	-30%	-10%
Total LYs	**6.933**	**3.767**	**4.862**	**3.166**	**2.071**	**46%**	**30%**
Key: DTIC, dacarbazine; LY, life year; Regimen, nivolumab plus ipilimumab.							

Table 4: Summary of LY gain by health state – BRAF mutation-positive

Health state	LY - nivo	LY - ipi	LY - pembro	LY - dab	LY – vem	Absolute inc (vs ipi)	Absolute inc (vs pembro)	Absolute inc (vs dab)	Absolute inc (vs vem)	% inc (vs ipi)	% inc (vs pembro)	% inc (vs dab)	% inc (vs vem)
Progression free	4.247	0.801	2.080	1.015	1.015	3.446	2.167	3.232	3.232	81%	51%	76%	76%
Progressed	2.379	2.576	2.466	1.228	1.228	-0.197	-0.087	1.151	1.151	-8%	-4%	48%	48%
Total LYs	**6.626**	**3.376**	**4.546**	**2.243**	**2.243**	**3.250**	**2.080**	**4.383**	**4.383**	**49%**	**31%**	**66%**	**66%**
Key: dab, dabrafenib; inc, incremental; ipi, ipilimumab; LY, life year; nivo, nivolumab; Regimen, nivolumab plus ipilimumab; vem, vemurafenib.													

Table 5: Summary of costs by health state – BRAF mutation-negative (base case)

Health state	Cost – the Regimen	Costs - ipilimumab	Costs - pembrolizumab	Absolute increment (vs ipilimumab)	Absolute increment (vs pembrolizumab)	% increment (vs ipilimumab)	% increment (vs pembrolizumab)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	Cost – the Regimen	Costs - ipilimumab	Costs - pembrolizumab	Absolute increment (vs ipilimumab)	Absolute increment (vs pembrolizumab)	% increment (vs ipilimumab)	% increment (vs pembrolizumab)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AE, adverse event; DTIC, dacarbazine; Regimen, nivolumab plus ipilimumab.							

Table 6: Summary of costs by health state – BRAF mutation-positive (base case)

Health state	Cost – the Regimen	Cost – ipilimumab	Cost – pembrolizumab	Cost – dabrafenib	Cost – vemurafenib	Absolute increment (vs ipilimumab)	Absolute increment (vs pembrolizumab)	Absolute increment (vs dabrafenib)	Absolute increment (vs vemurafenib)	% increment (vs ipilimumab)	% increment (vs pembrolizumab)	% increment (vs dabrafenib)	% increment (vs vemurafenib)
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													

Key: AE, adverse event; PAS, patient access scheme; Regimen, nivolumab plus ipilimumab.

Table 7: Summary of costs by health state – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)

Health state	Cost – the Regimen	Costs - ipilimumab	Costs - pembrolizumab	Absolute increment (vs ipilimumab)	Absolute increment (vs pembrolizumab)	% increment (vs ipilimumab)	% increment (vs pembrolizumab)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment initiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; DTIC, dacarbazine; Regimen, nivolumab plus ipilimumab.

Table 8: Summary of costs by health state – BRAF mutation-positive (assuming PAS drug prices for comparator treatments)

Health state	Cost – the Regimen	Cost - ipilimumab	Cost - pembrolizumab	Cost - dabrafenib	Cost – vemurafenib	Absolute increment (vs ipilimumab)	Absolute increment (vs pembrolizumab)	Absolute increment (vs dabrafenib)	Absolute increment (vs vemurafenib)	% increment (vs ipilimumab)	% increment (vs pembrolizumab)	% increment (vs dabrafenib)	% increment (vs vemurafenib)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment initiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; PAS, patient access scheme Regimen, nivolumab plus ipilimumab.

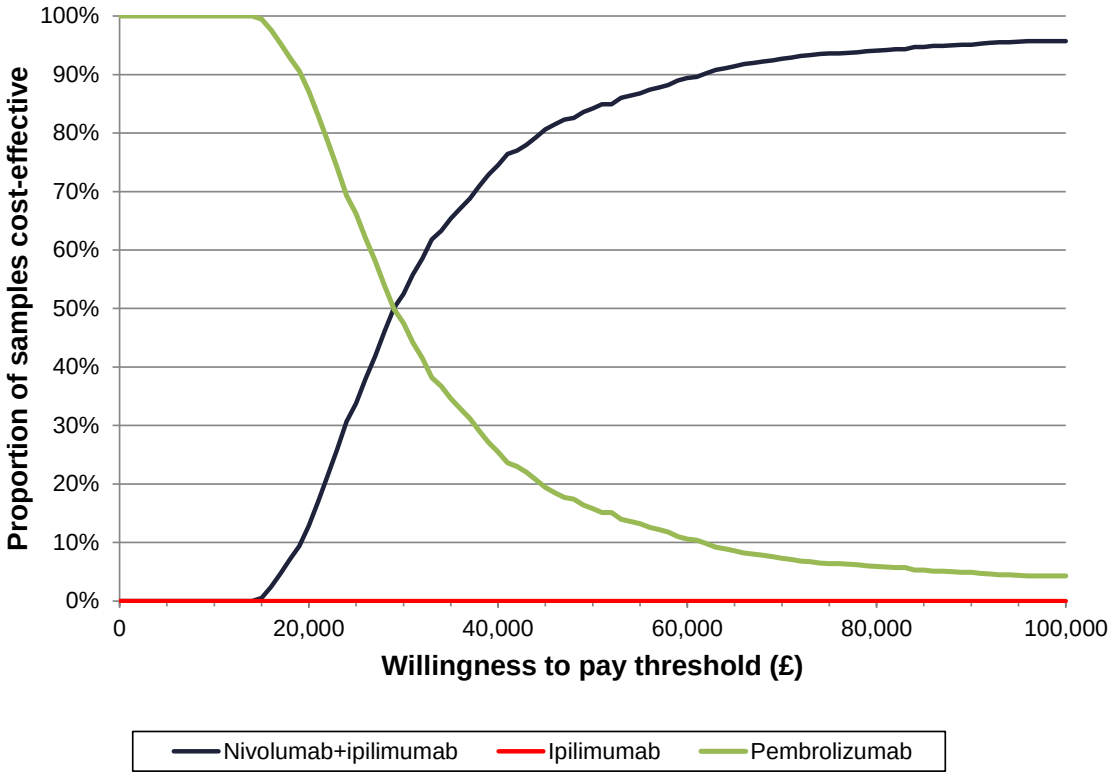
Probabilistic sensitivity analysis

Figure 1 and Figure 2 present the cost-effectiveness acceptability curves (CEACs) for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the base case. The probabilities of the Regimen being most cost effective are 52.5% and 84.2% for willingness to pay (WTP) thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-negative patients. The probabilities of the Regimen being most cost effective are 55.5% and 82.2% for WTP thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-positive patients. Figure 3 and Figure 4 present the CEACs for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the PAS-based base case. The probabilities of the Regimen being most cost effective are 65.1% and 85.5% for WTP thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-negative patients. The probabilities of the Regimen being most cost effective are 69.0% and 86.7% for WTP thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-positive patients.

Figure 5 and Figure 6 present probabilistic sensitivity analysis (PSA) scatter plots (the Regimen vs its comparators) for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the base case. Figure 7 and Figure 8 present PSA scatter plots (the Regimen vs its comparators) for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the PAS-based base case. Each PSA scatter plot is drawn based on the result of 1,000 PSA runs.

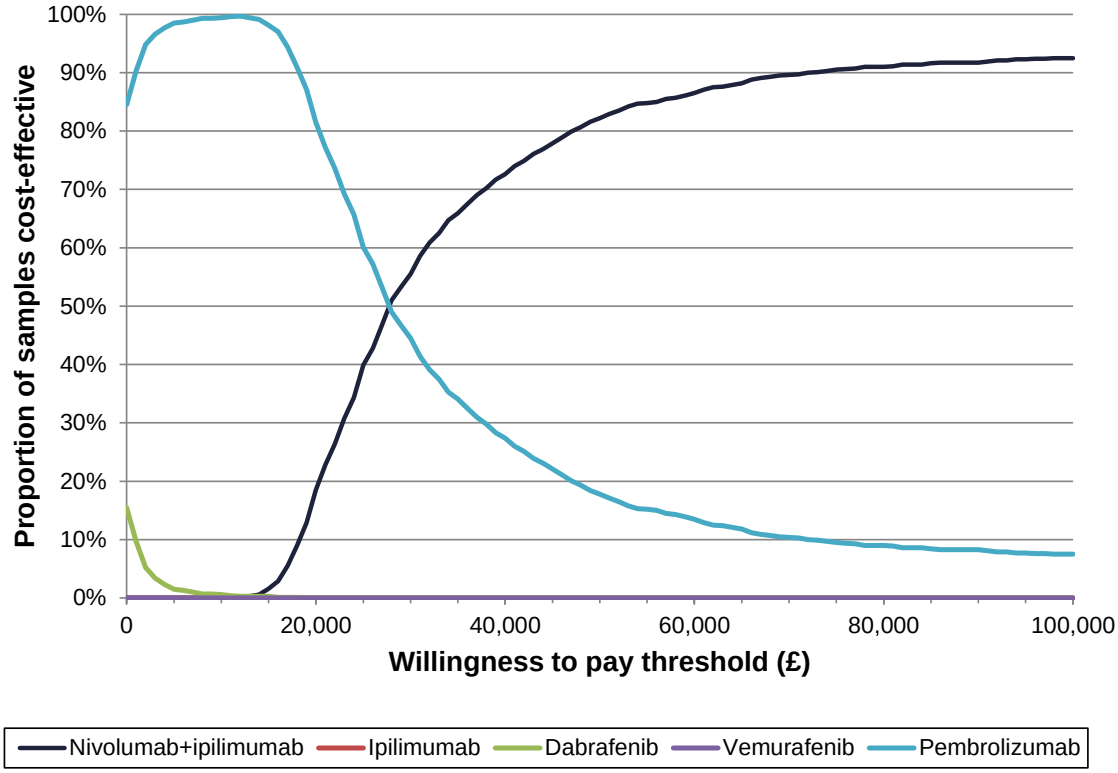
Table 9 and Table 10 present the mean model results based on PSA (1,000 runs) and compare the PSA results with the deterministic results for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the base case. Table 11 and Table 12 present the same results for the PAS-based base case. The results show that the results of the probabilistic analysis are similar to those of the deterministic analysis.

Figure 1: Cost-effectiveness acceptability curve – BRAF mutation-negative (base case)



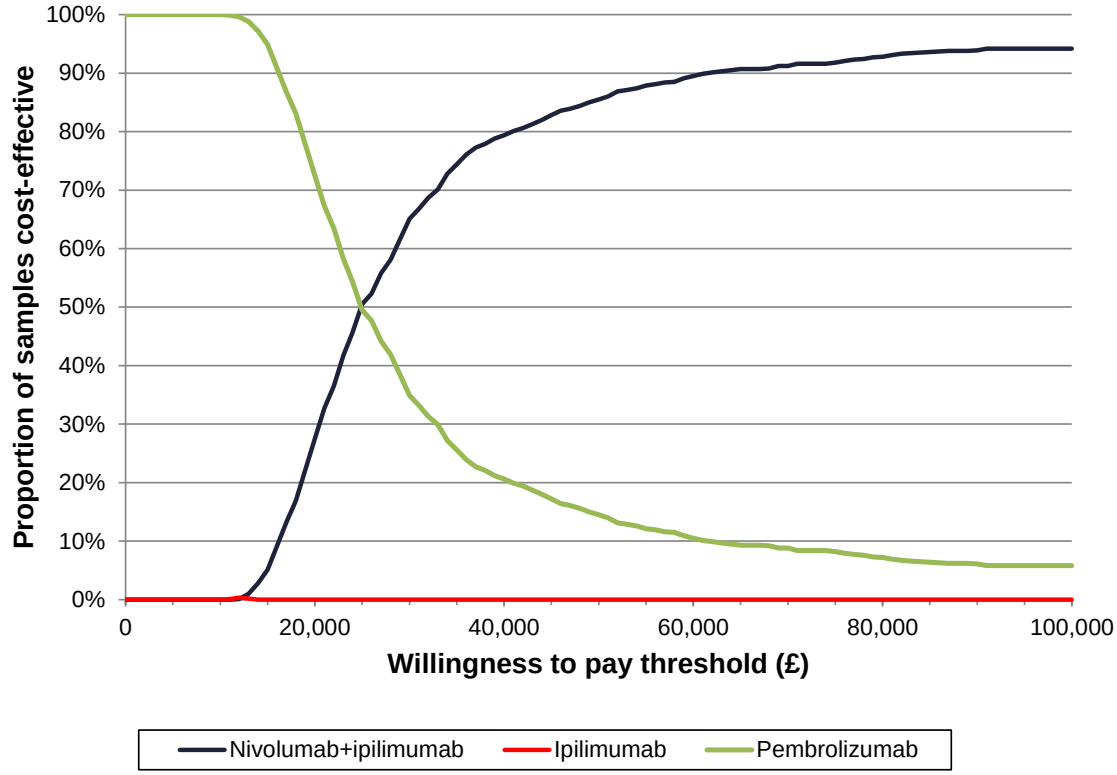
Key: WTP, willingness to pay.

Figure 2: Cost-effectiveness acceptability curve – BRAF mutation-positive (base case)



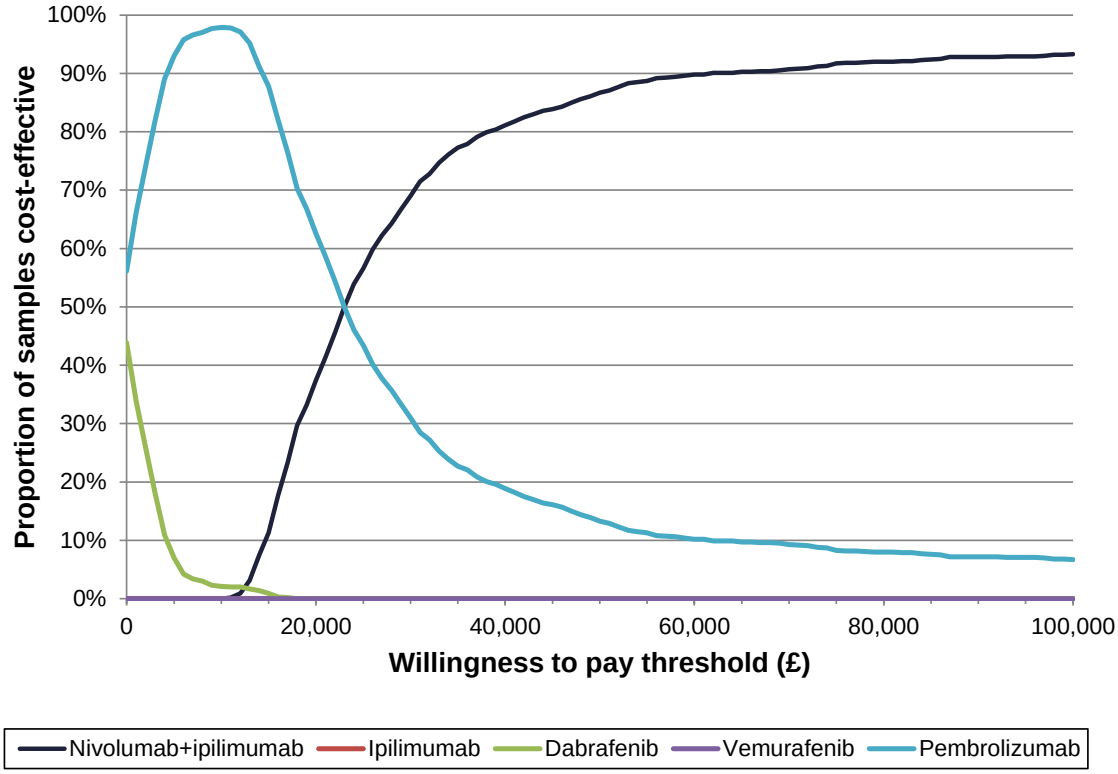
Key: WTP, willingness to pay.

Figure 3: Cost-effectiveness acceptability curve – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)



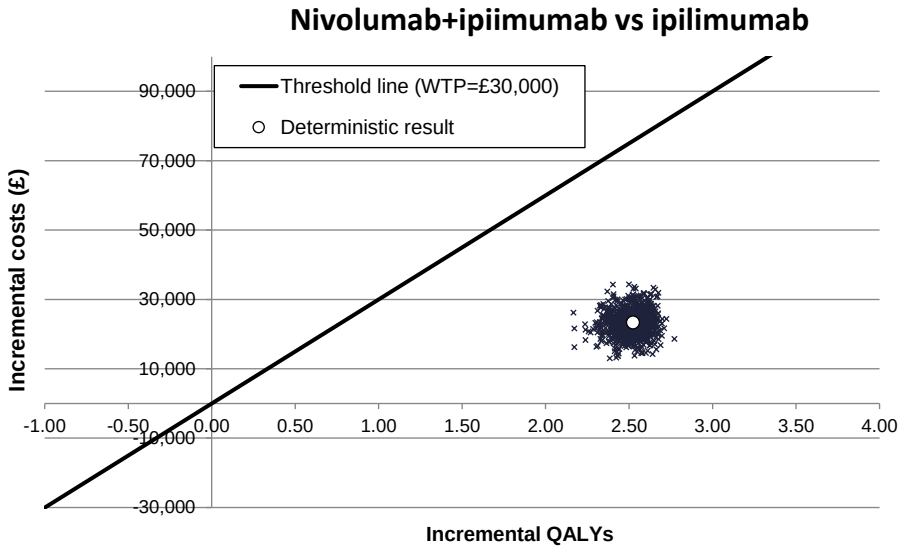
Key: PAS, patient access scheme; WTP, willingness to pay.

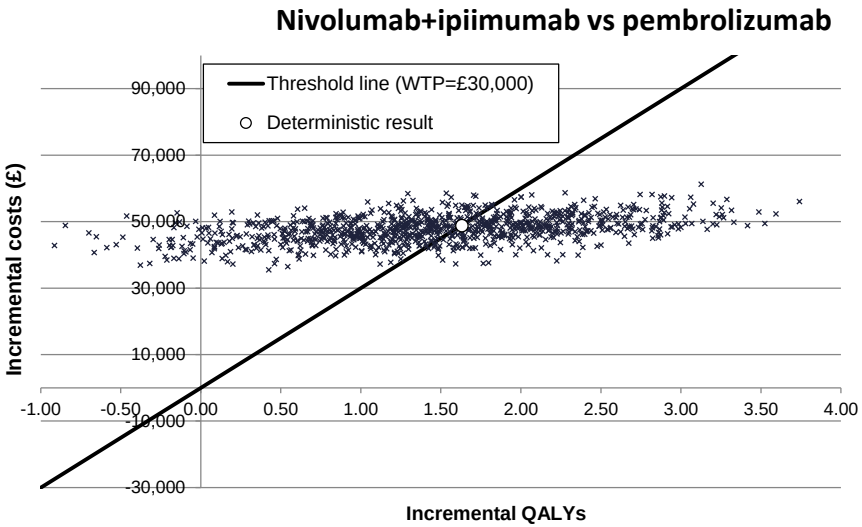
Figure 4: Cost-effectiveness acceptability curve – BRAF mutation-positive assuming PAS drug prices for comparator treatments)



Key: PAS, patient access scheme; WTP, willingness to pay.

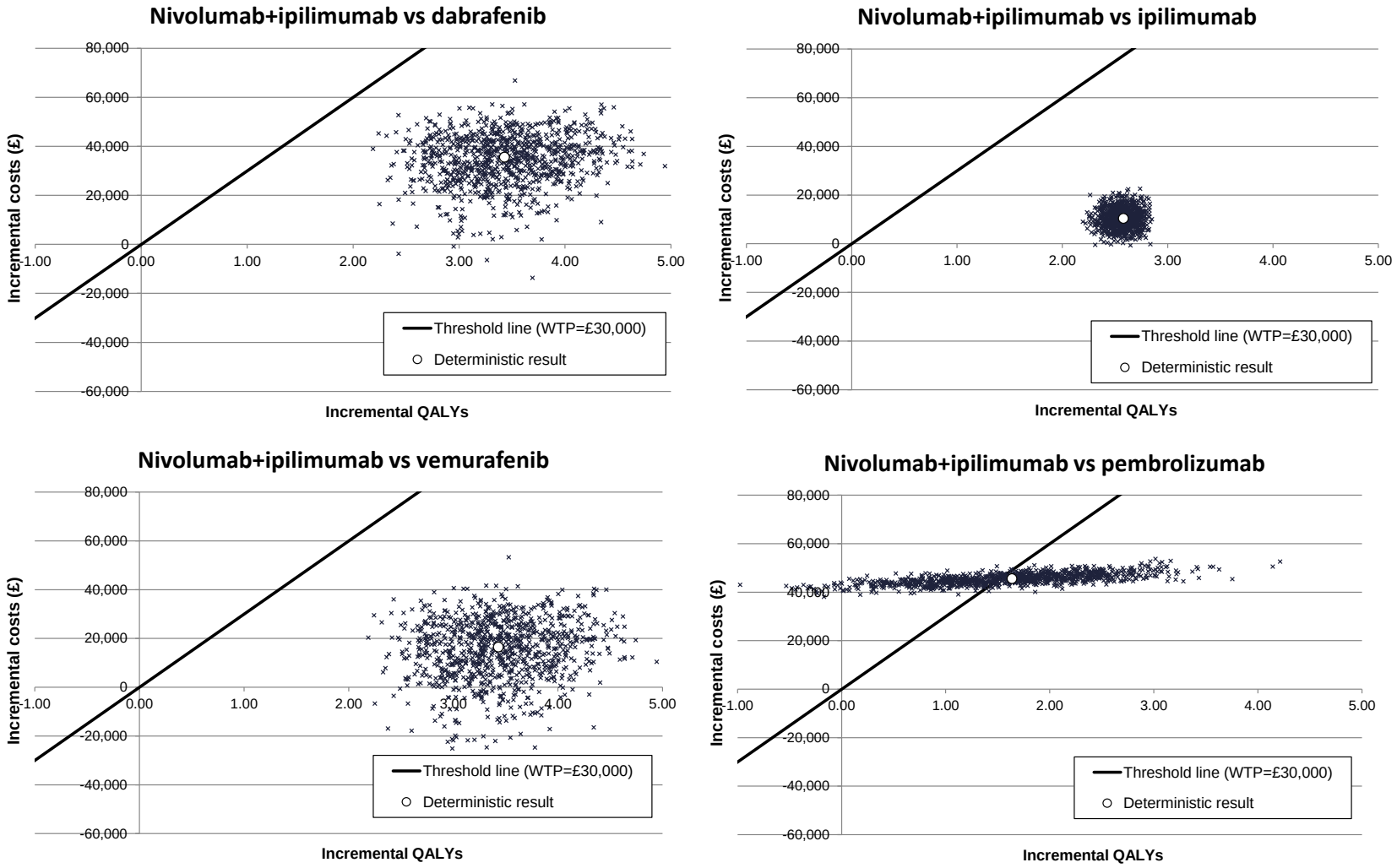
Figure 5: PSA scatter plots of the Regimen vs its comparators – BRAF mutation-negative (base case)





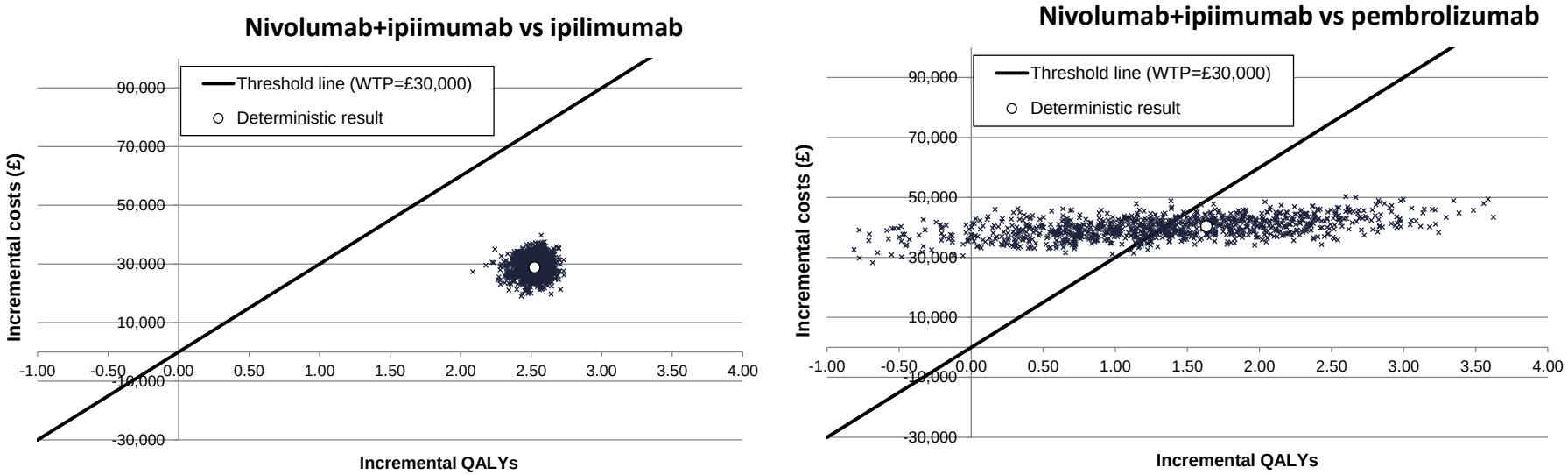
Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 6: PSA scatter plots of the Regimen vs its comparators – BRAF mutation-positive (base case)



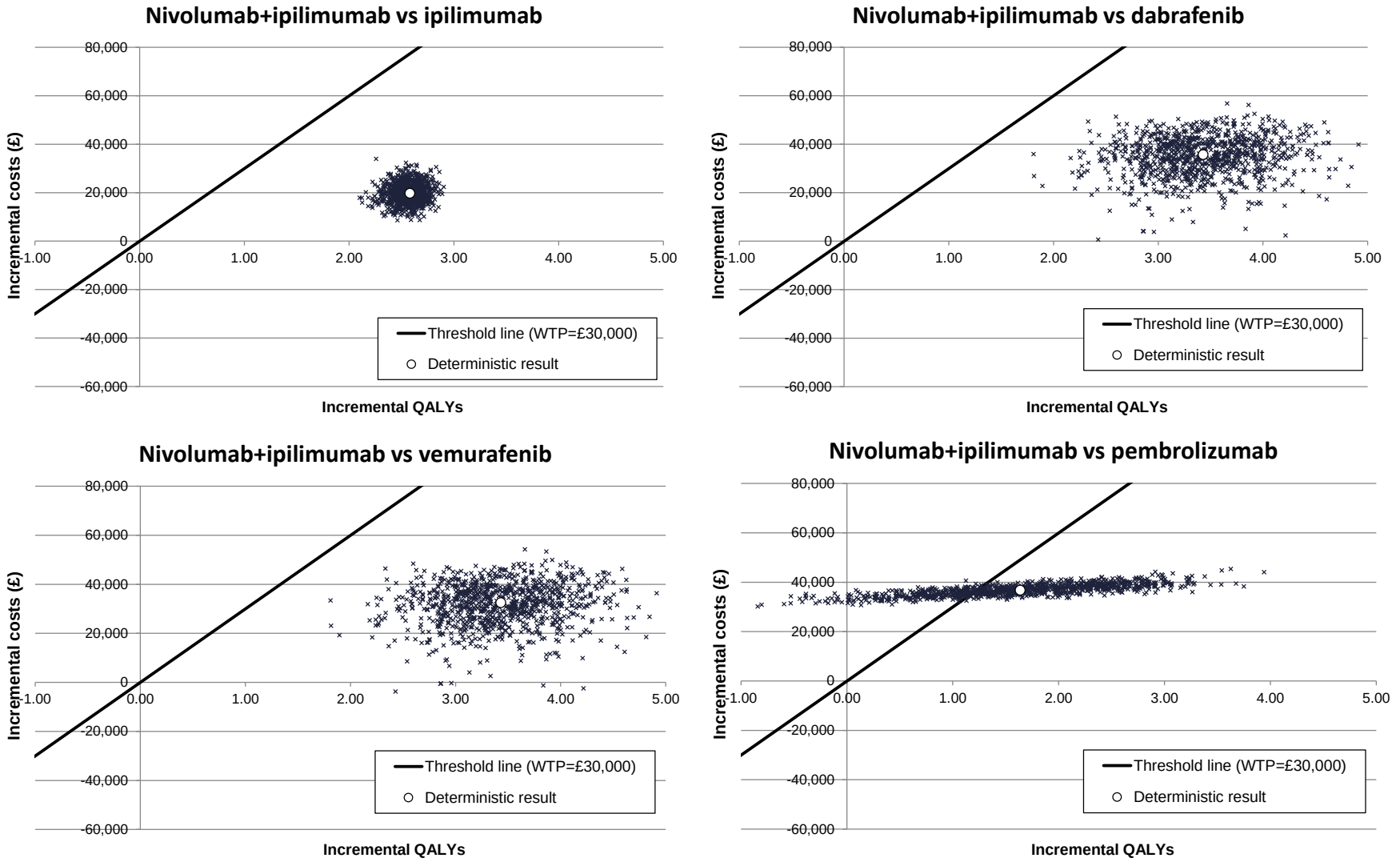
Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 7: PSA scatter plots of the Regimen vs its comparators – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)



Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 8: PSA scatter plots of the Regimen vs its comparators – BRAF mutation-positive (assuming PAS drug prices for comparator treatments)



Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Table 9: Mean results of PSA (1,000 runs) and comparison with deterministic results – BRAF mutation-negative (base case)

Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)		Dominance		ICER (£) incremental (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
Pembrolizumab	[redacted]	[redacted]	3.77	3.79						
Ipilimumab	[redacted]	[redacted]	2.94	2.90	-£31,109	-£28,555	Dominated	Dominated	Excluded due to dominance	Excluded due to dominance
Nivolumab plus Ipilimumab	[redacted]	[redacted]	5.46	5.42	£28,898	£29,923			£28,898	£29,923

Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 10: Mean results of PSA (1,000 runs) and comparison with deterministic results – BRAF mutation-positive (base case)

Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)		Dominance		ICER (£) incremental (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
Pembrolizumab	[redacted]	[redacted]	3.576	3.53						
Dabrafenib	[redacted]	[redacted]	1.745	1.74	-£6,077	-£5,607	Dominated	Dominated	Excluded due to dominance	Excluded due to dominance
Vemurafenib	[redacted]	[redacted]	1.745	1.74	-£16,657	-£16,253	Dominated	Dominated	Excluded due to dominance	Excluded due to dominance
Ipilimumab	[redacted]	[redacted]	2.612	2.593	-£36,435	-£37,403	Dominated	Dominated	Excluded due to dominance	Excluded due to dominance
Nivolumab plus Ipilimumab	[redacted]	[redacted]	5.182	5.17	£28,354	£27,859			£28,354	£27,859

Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 11: Mean results of PSA (1,000 runs) and comparison with deterministic results – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)

Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)		Dominance		ICER (£) incremental (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; Pembro, pembrolizumab; QALYs, quality-adjusted life years.

Table 12: Mean results of PSA (1,000 runs) and comparison with deterministic results – BRAF mutation-positive (assuming PAS drug prices for comparator treatments)

Technology	Total costs (£)		Total QALYs		ICER (£) versus baseline (QALYs)		Dominance		ICER (£) incremental (QALYs)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

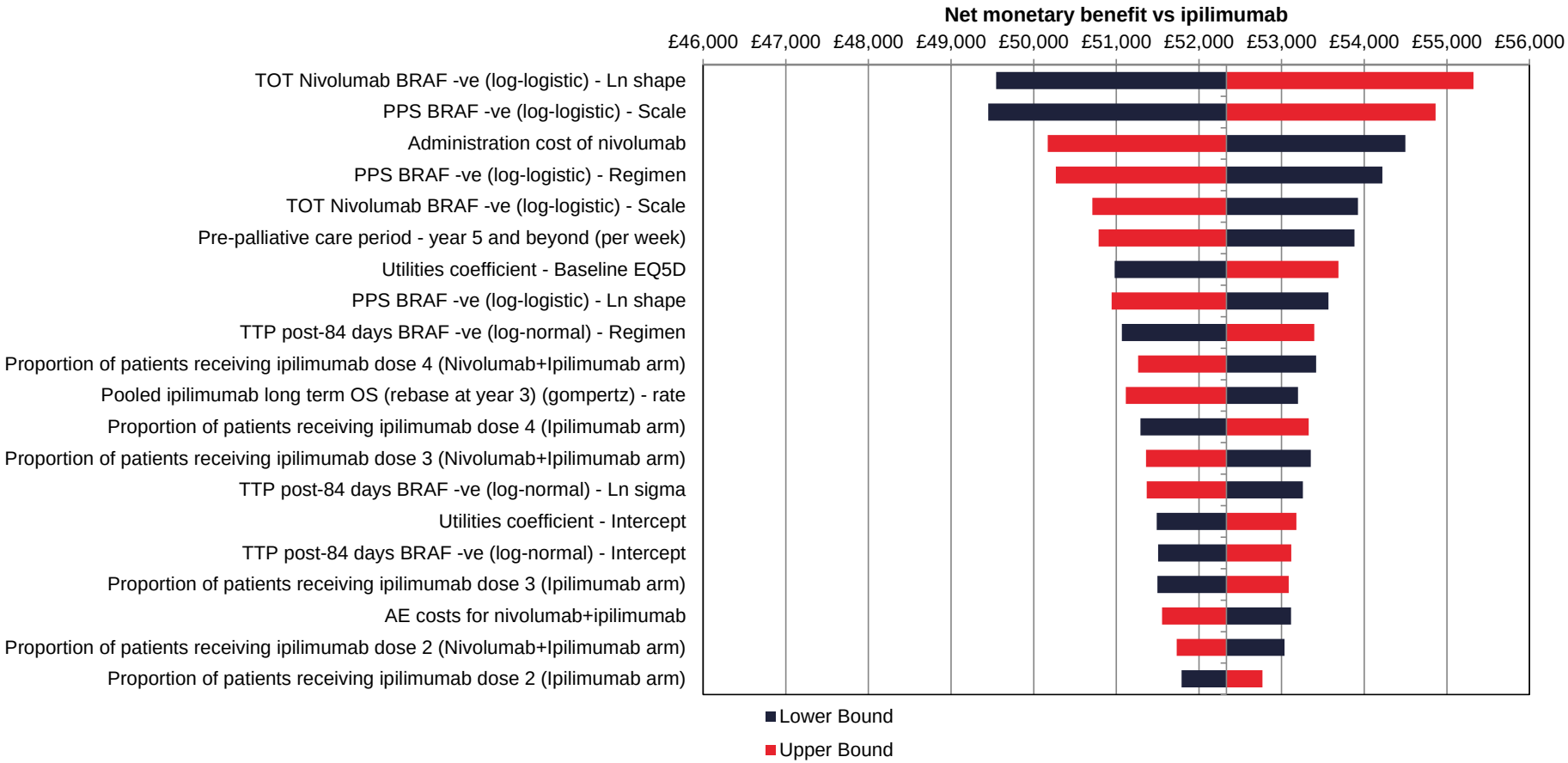
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.										

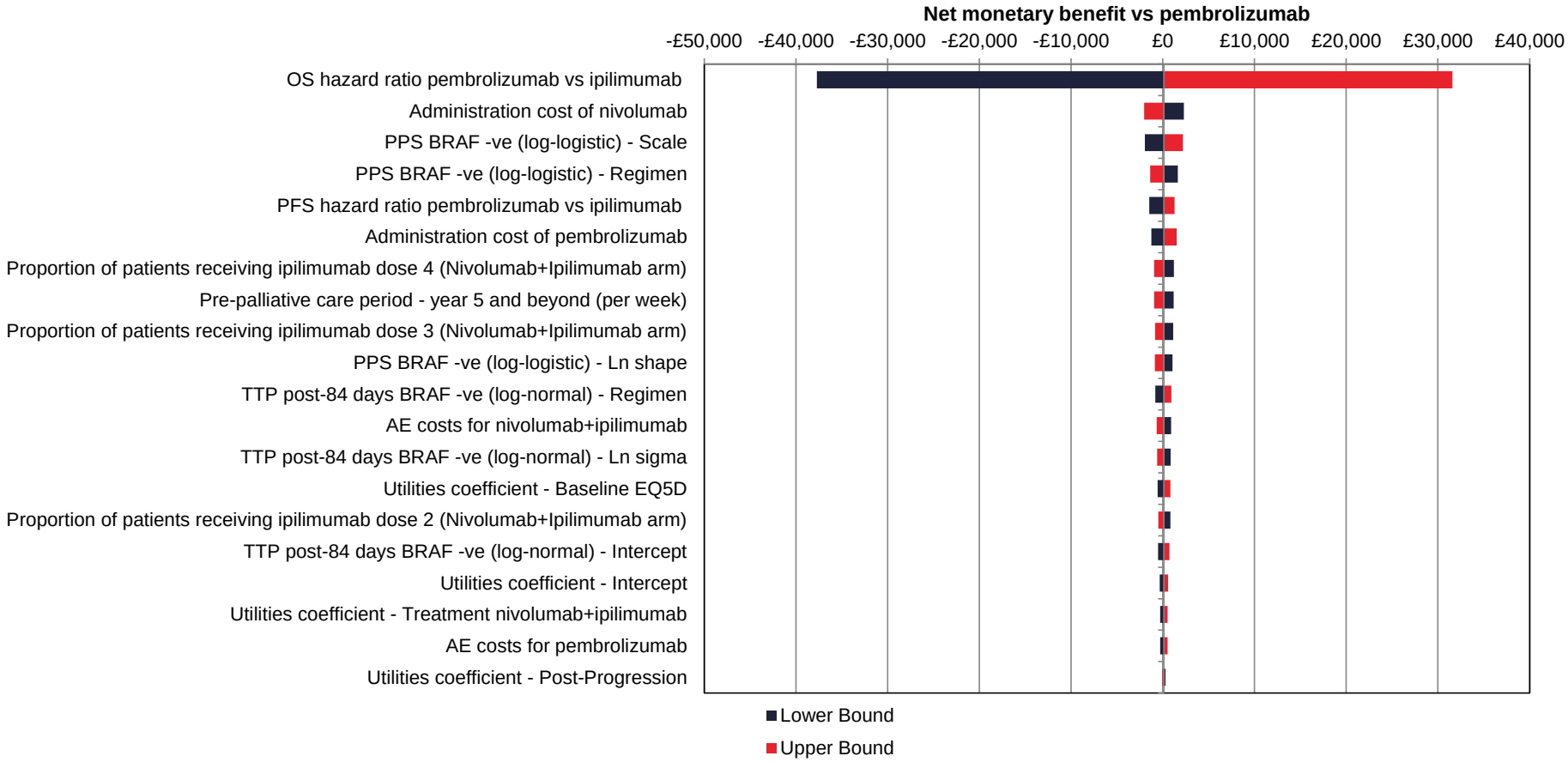
Deterministic sensitivity analysis

Figure 9 *and* ***Figure 10*** *present tornado diagrams from the deterministic one-way sensitivity analyses (OWSA), illustrating the effect on the net benefit per patient of treatment with the Regimen of varying the 20 most influential parameters between their upper and lower bounds, for BRAF mutation-negative and BRAF mutation-positive patients, respectively. Net benefit has been chosen as the results are easier to interpret in cases where one drug dominates another. The assumed WTP threshold for a QALY used in the net benefit calculation is £30,000. The same analysis was performed for the PAS-assumed base case, and the results were presented in*

[redacted] and [redacted]

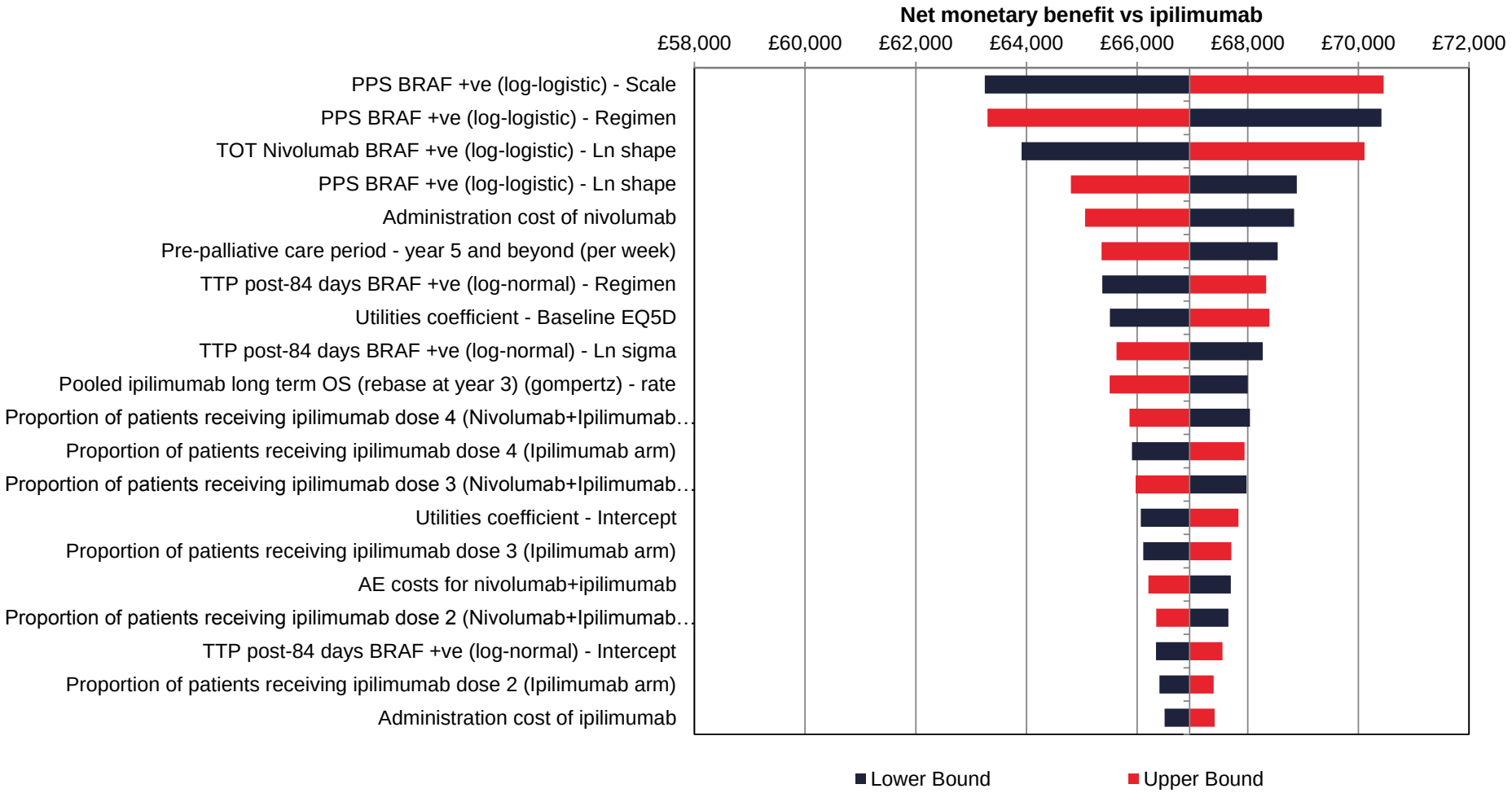
Figure 9: Tornado diagram containing 20 most influential parameters – BRAF mutation-negative (base case)



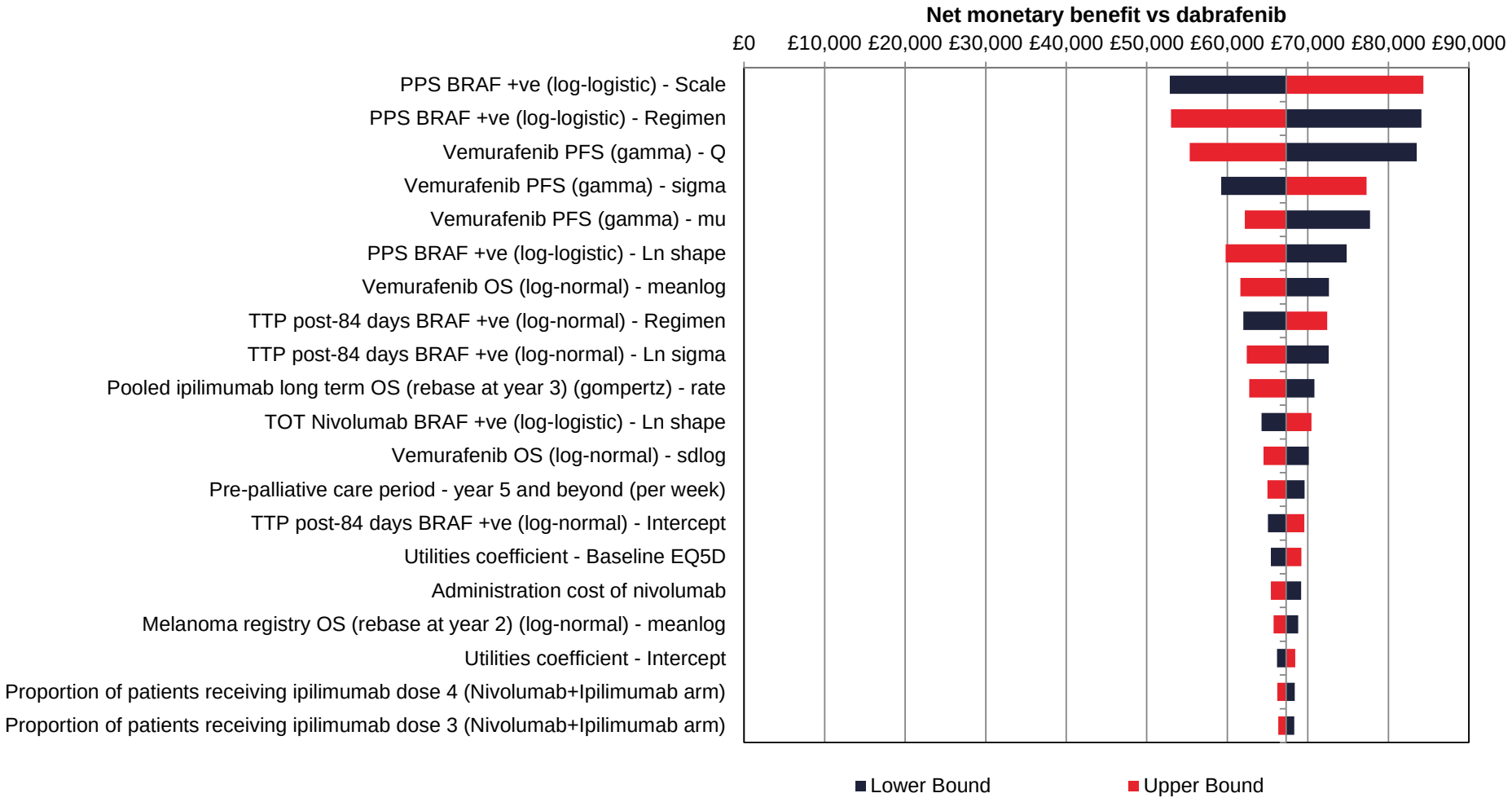


Key: OS, overall survival; PPS, post-progression survival; TTP, time to progression.

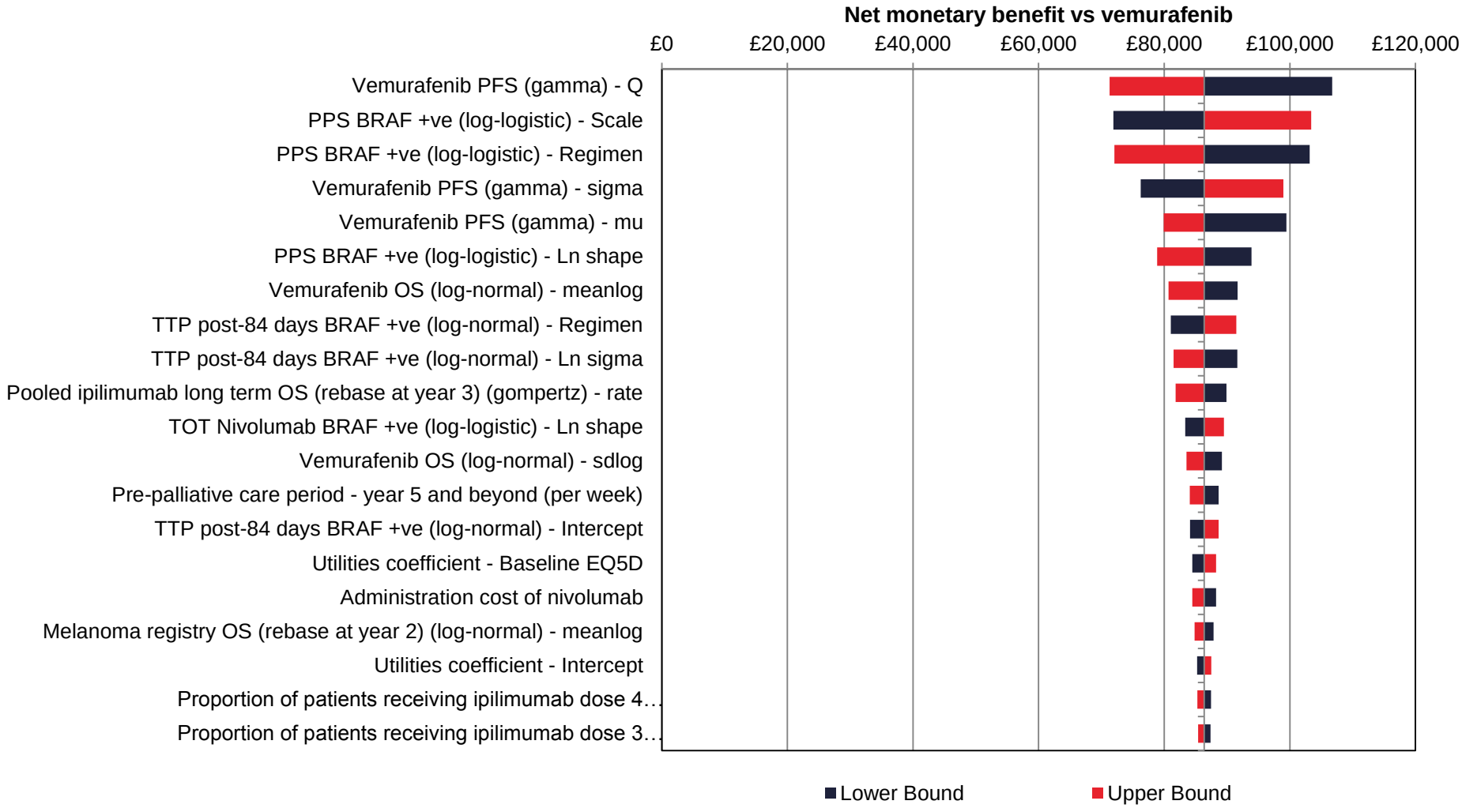
Figure 10: Tornado diagram containing 20 most influential parameters – BRAF mutation-positive (base case)



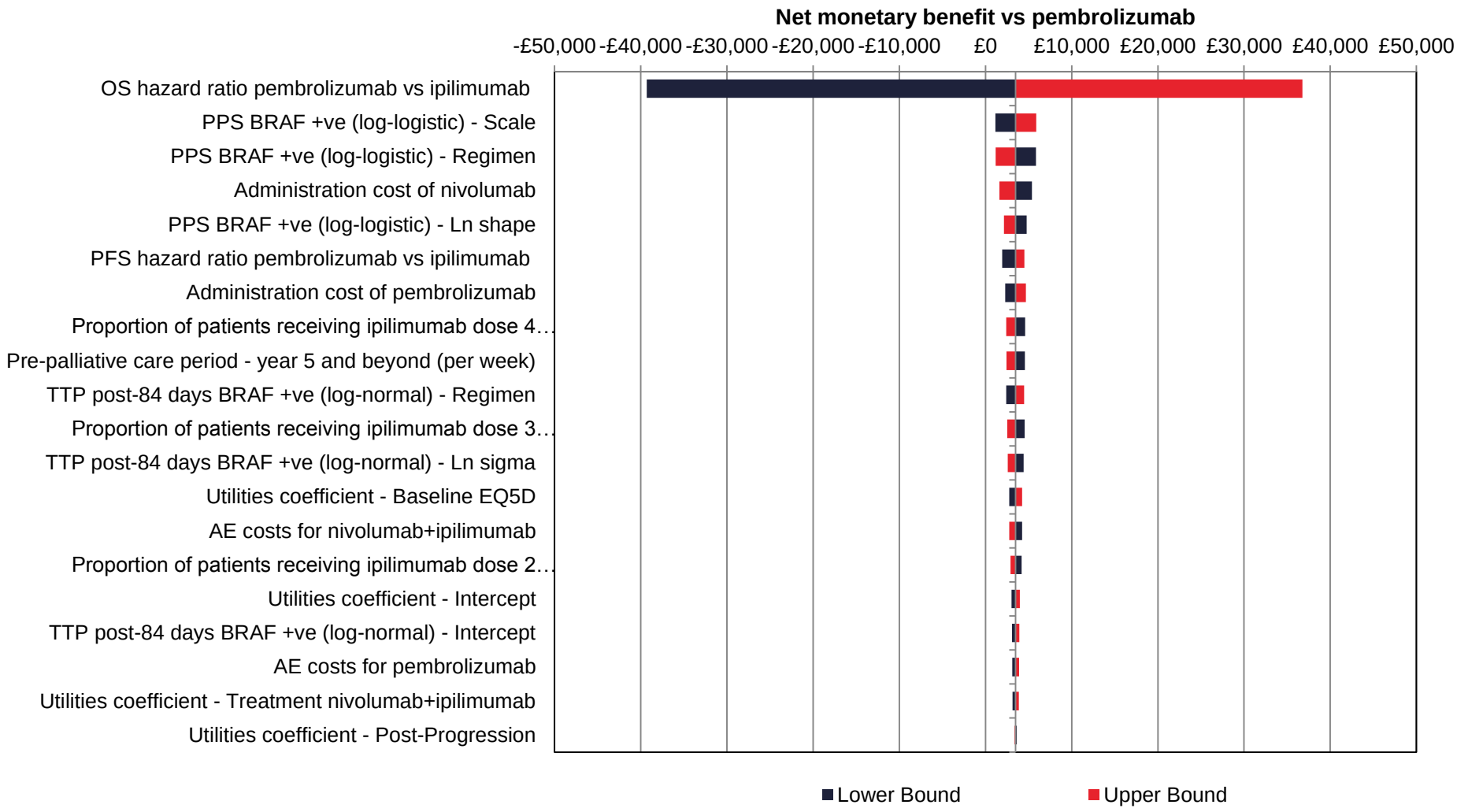
Key: OS, overall survival; PPS, post-progression survival; TOT, time on treatment; TTP, time to progression.



Key: OS, overall survival; PPS, post-progression survival; TOT, time on treatment; TTP, time to progression.

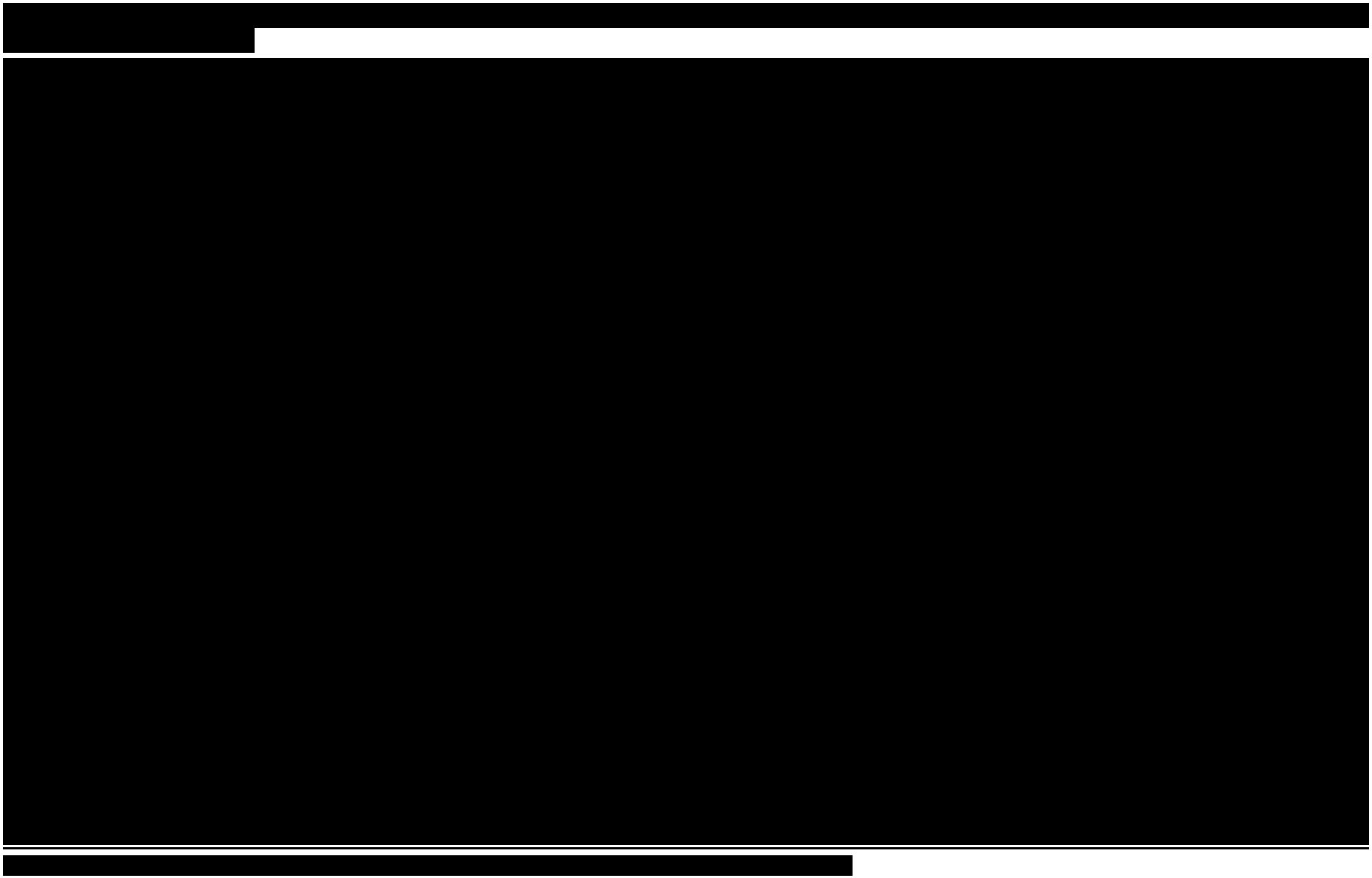


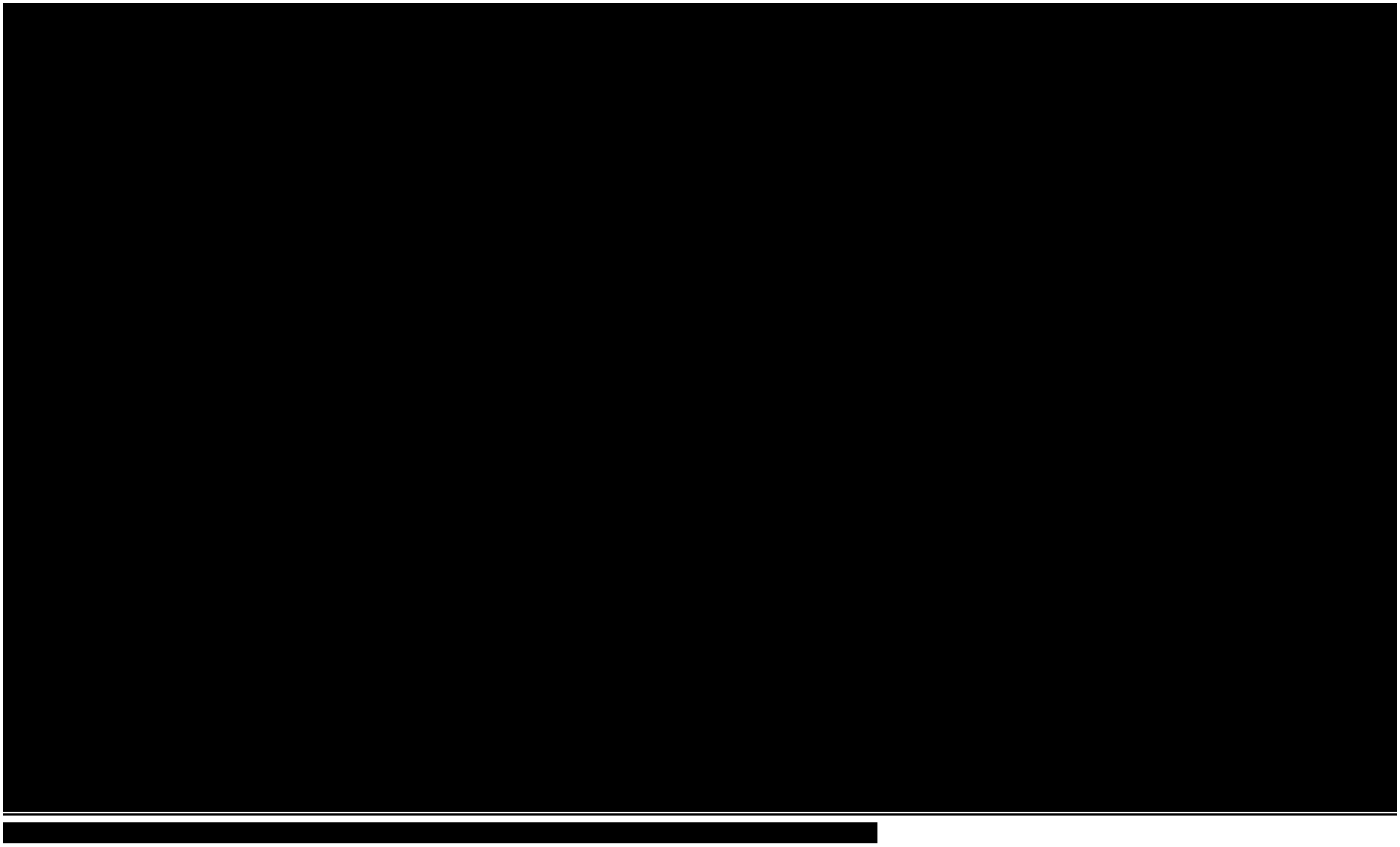
Key: OS, overall survival; PPS, post-progression survival; TOT, time on treatment; TTP, time to progression.



Key: OS, overall survival; PPS, post-progression survival; TOT, time on treatment; TTP, time to progression.

[redacted]





Scenario analysis

Table 13 and Table 14 present the scenario analysis performed for BRAF mutation-negative for the base case and PAS-assumed base case respectively. Table 15 and Table 16 present the scenario analysis performed for BRAF mutation-positive for the base case and PAS-assumed base case respectively

Table 13: Results of scenario analysis – BRAF mutation-negative (base case)

Parameter	**Base case**	**Scenario analysis**	**The Regimen vs Ipilimumab**		**The Regimen vs Pembrolizumab**	
			Incremental ICER	**Incremental net benefit**	**Incremental ICER**	**Incremental net benefit**
Base case	**N/A**	**N/A**	**9,254**	**52,334**	**29,923**	**125**
Hazard ratios PFS (regimen vs ipilimumab)	CheckMate 067	CheckMate 069	9,197	52,805	29,638	596
		Meta-analysis of CheckMate 069/067	9,235	52,486	29,831	277
Parametric curves based on indirect comparison						
TTP	Log-normal	Exponential	10,282	42,899	34,615	-6,467
		Weibull	9,661	47,928	31,978	-3,011
		Gompertz	9,374	52,310	29,904	157
		Log-logistic	9,292	51,886	30,130	-210
		Generalised Gamma	9,375	50,770	30,630	-1,003
PPS	Log-logistic	Exponential	9,402	50,911	30,557	-888
		Weibull	9,380	51,122	30,462	-740
		Gompertz	9,160	53,235	29,515	803
		Log-Normal	9,109	53,712	29,294	1,178
		Generalised Gamma	9,176	53,055	29,590	676
Long-term survival						
Pooled ipilimumab long-term survival	Gompertz	Exponential	9,461	50,407	30,413	-661

Parameter	Base case	Scenario analysis	The Regimen vs Ipilimumab		The Regimen vs Pembrolizumab	
			Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit
		Weibull	9,234	52,545	29,975	41
		Log-Logistic	9,239	52,493	29,967	54
		Log-Normal	9,236	52,521	29,961	63
		Generalised Gamma	9,227	52,609	29,938	102
Time on treatment						
TOT curve for nivolumab	Log-logistic	Exponential	7,219	57,506	29,092	1,483
		Weibull	9,051	52,850	29,870	213
		Gompertz	9,862	50,784	29,798	330
		Log-Normal	9,804	50,935	30,022	-36
		Generalised Gamma	9,380	52,014	29,957	70
Treatment continuation rule	100% discontinue at 2 years	75% discontinue at 2 years	17,854	30,525	29,925	121
		50% discontinue at 2 years	26,519	8,716	29,927	118
		25% discontinue at 2 years	35,249	-13,093	29,929	115
		0% discontinue at 2 years (no treatment continuation rule)	44,046	-34,902	29,930	111
	2 year maximum treatment periods	3 year maximum treatment periods	13,874	40,597	29,941	97
		4 year maximum treatment periods	17,411	31,645	29,639	586
		5 year maximum treatment periods	20,271	24,426	29,662	548
		No maximum treatment periods (no treatment continuation rule)	44,046	-34,902	29,930	111
Dosing and drug cost						

Parameter	Base case	Scenario analysis	The Regimen vs Ipilimumab		The Regimen vs Pembrolizumab	
			Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit
Method for dosing for nivolumab and ipilimumab	Method of moment (weight based dosing)	Cost per mg	9,110	52,697	28,858	1,862
		Round up to the nearest full vial	7,500	56,759	23,754	10,188
Adverse events Pembrolizumab						
AEs data source	Pembrolizumab 2mg - previously treated	Pembrolizumab 10mg - untreated	9,254	52,334	29,923	126
Utilities						
Utility	CA209-067 trial analysis	CA209-066 trial analysis	9,347	51,579	30,376	-604
		Ipilimumab NICE TA319 utilities	8,353	60,494	26,880	5,665
General model settings						
Time horizon	40 years	10 years	18,606	12,763	75,116	-28,070
		20 years	11,460	35,796	41,267	-13,035
		30 years	9,618	48,728	32,054	-3,106
Discount rate	0.035	0.015	7,652	74,037	22,642	16,252

Key: ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; QALYs, quality-adjusted life years; TOT, time on treatment.

Notes: a, willingness to pay threshold £50,000; b, in these scenario analyses, only a proportion of patients (75% to 0%) who are still on nivolumab treatment at Year 2 will discontinue treatment from Year 2 onwards, with the time on treatment for the remaining patients (25% to 100%) based on extrapolation of the fitted TOT (capped by OS); Ex-dominated: extended dominated.

Table 14: Results of scenario analysis – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)

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Key: ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; QALYs, quality-adjusted life years; TOT, time on treatment.

Notes: a, willingness to pay threshold £50,000; b, in these scenario analyses, only a proportion of patients (75% to 0%) who are still on nivolumab treatment at Year 2 will discontinue treatment from Year 2 onwards, with the time on treatment for the remaining patients (25% to 100%) based on extrapolation of the fitted TOT (capped by OS); Ex-dominated: extended dominated.

Table 15: Results of scenario analysis – BRAF mutation-positive (Base case)

Parameter	Base case	Scenario analysis	The Regimen vs Ipilimumab		The Regimen vs pembrolizumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib	
			Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit
Base case	**N/A**	**N/A**	**4,035**	**66,950**	**27,859**	**3,505**	**10,373**	**67,292**	**4,811**	**86,362**
Hazard ratios PFS (regimen vs ipilimumab)	CheckMate 067	CheckMate 069	4,011	67,418	27,596	3,974	10,326	67,761	4,789	86,830
		Meta-analysis of CheckMate 069/067	4,027	67,100	27,774	3,655	10,358	67,442	4,804	86,512
Parametric curves based on indirect comparison										
TTP	Log-Normal	Exponential	4,191	57,736	31,894	-2,693	13,290	43,060	5,890	62,129
		Weibull	4,059	62,310	29,802	302	11,662	54,926	5,296	73,996
		Gompertz	4,256	66,971	27,714	3,760	10,354	67,298	4,787	86,368
		Log-logistic	4,045	66,799	27,910	3,415	10,429	66,659	4,830	85,729
		Generalised Gamma	4,016	65,182	28,573	2,275	10,877	62,046	4,999	81,116
PPS	Log-logistic	Exponential	4,133	63,776	29,067	1,460	11,276	58,199	5,141	77,268
		Weibull	4,122	64,124	28,932	1,679	11,164	59,243	5,100	78,313
		Gompertz	4,012	67,648	27,610	3,950	10,080	70,797	4,715	89,867
		Log-Normal	3,971	68,931	27,144	4,807	9,695	75,705	4,580	94,775
		Generalised Gamma	4,006	67,769	27,562	4,037	10,048	71,206	4,704	90,276
Long-term survival										
Registry survival (rebased at 3 years)	Weilbull	Exponential	4,035	66,950	27,859	3,505	10,393	67,276	4,842	86,322
		Gompertz	4,035	66,950	27,859	3,505	10,425	66,696	4,827	85,768
		Log-Logistic	4,035	66,950	27,859	3,505	10,422	66,722	4,826	85,795
		Log-Normal	4,035	66,950	27,859	3,505	10,422	66,722	4,826	85,795
		Generalised Gamma	4,035	66,950	27,859	3,505	10,382	67,171	4,812	86,243
Pooled ipilimumab long-term survival	Gompertz	Exponential	4,178	62,472	28,756	1,970	11,453	56,519	5,196	75,589

Parameter	Base case	Scenario analysis	The Regimen vs Ipilimumab		The Regimen vs pembrolizumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib	
			Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit
		Weibull	4,046	66,610	27,917	3,403	10,449	66,447	4,838	85,517
		Log-Logistic	4,046	66,606	27,908	3,418	10,453	66,402	4,840	85,472
		Log-Normal	4,042	66,738	27,896	3,440	10,420	66,773	4,828	85,843
		Generalised Gamma	4,031	67,105	27,866	3,492	10,327	67,812	4,795	86,881
Time on treatment										
TOT curve for nivolumab	Log-logistic	Exponential	1,942	72,392	26,847	5,167	8,796	72,734	3,237	91,804
		Weibull	3,738	67,722	27,704	3,759	10,149	68,064	4,588	87,134
		Gompertz	4,347	66,133	27,648	3,850	10,609	66,475	5,046	85,545
		Log-Normal	4,846	64,837	27,900	3,436	10,985	65,179	5,421	84,249
		Generalised Gamma	4,213	66,485	27,840	3,536	10,507	66,828	4,945	85,898
Treatment continuation rule	100% discontinue at 2 years	75% discontinue at 2 years	10,708	49,597	27,695	3,756	15,402	49,939	9,828	69,009
		50% discontinue at 2 years	17,421	32,244	27,529	4,008	20,454	32,587	14,867	51,656
		25% discontinue at 2 years	24,173	14,892	27,362	4,260	25,527	15,234	19,928	34,304
		0% discontinue at 2 years (no treatment continuation rule)	30,966	-2,461	27,193	4,511	30,623	-2,119	25,012	16,951
	2 year maximum treatment periods	3 year maximum treatment periods	7,677	57,468	27,879	3,464	13,118	57,811	7,550	76,880
		4 year maximum treatment periods	10,440	50,294	27,641	3,844	15,200	50,636	9,626	69,706
		5 year maximum treatment periods	12,662	44,537	27,663	3,803	16,873	44,879	11,295	63,949
		No maximum treatment	30,966	-2,461	27,193	4,511	30,623	-2,119	25,012	16,951

Parameter	Base case	Scenario analysis	The Regimen vs Ipilimumab		The Regimen vs pembrolizumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib	
			Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit
		periods (no treatment continuation rule)								
BRAF inhibitor efficacy										
HR for PFS (dab bs vem)	1	0.97	4,035	66,950	27,859	3,505	9,412	70,557	4,811	86,362
Dosing and drug cost										
Method for dosing for nivolumab and ipilimumab	Method of moment (weight based dosing)	Cost per mg	3,670	67,892	26,773	5,283	8,127	74,994	2,565	94,064
		Round up to the nearest full vial	2,761	70,234	22,237	12,709	8,839	72,552	3,277	91,622
Adverse events Pembrolizumab										
AEs data source	Pembrolizumab 2mg - previously treated	Pembrolizumab 10mg - untreated	4,035	66,950	27,859	3,506	10,373	67,292	4,811	86,362
Utilities										
Utility	CA209-067 trial analysis	CA209-066 trial analysis	4,105	65,638	28,372	2,617	10,741	63,773	4,982	82,843
		Ipilimumab NICE TA319 utilities	3,622	75,776	24,957	9,217	9,178	80,682	4,257	99,752
General model settings										
Time horizon	40 years	10 years	7,183	24,808	71,556	-25,306	28,642	1,636	13,518	19,848
		20 years	4,854	46,795	40,348	-11,416	14,399	37,121	6,488	55,945
		30 years	4,219	60,618	31,172	-1,699	11,231	58,671	5,152	77,672
Discount rate	0.035	0.015	3,580	91,597	20,685	21,085	7,520	105,854	3,284	125,800

Parameter	Base case	Scenario analysis	The Regimen vs Ipilimumab		The Regimen vs pembrolizumab		The Regimen vs dabrafenib		The Regimen vs vemurafenib	
			Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit	Incremental ICER	Incremental net benefit
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; inc, incremental; NICE, National Institute for Health and Care excellence; PAS, patient access scheme; PPS, post-progression survival.										

Table 16: Results of scenario analysis – BRAF mutation-positive (assuming PAS drug prices for comparator treatments)

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Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; inc, incremental; NICE, National Institute for Health and Care excellence; PAS, patient access scheme; PPS, post-progression survival.

Appendix 2: Time, Events and Numbers at Risk for OS, PrePS, TTP, and PFS

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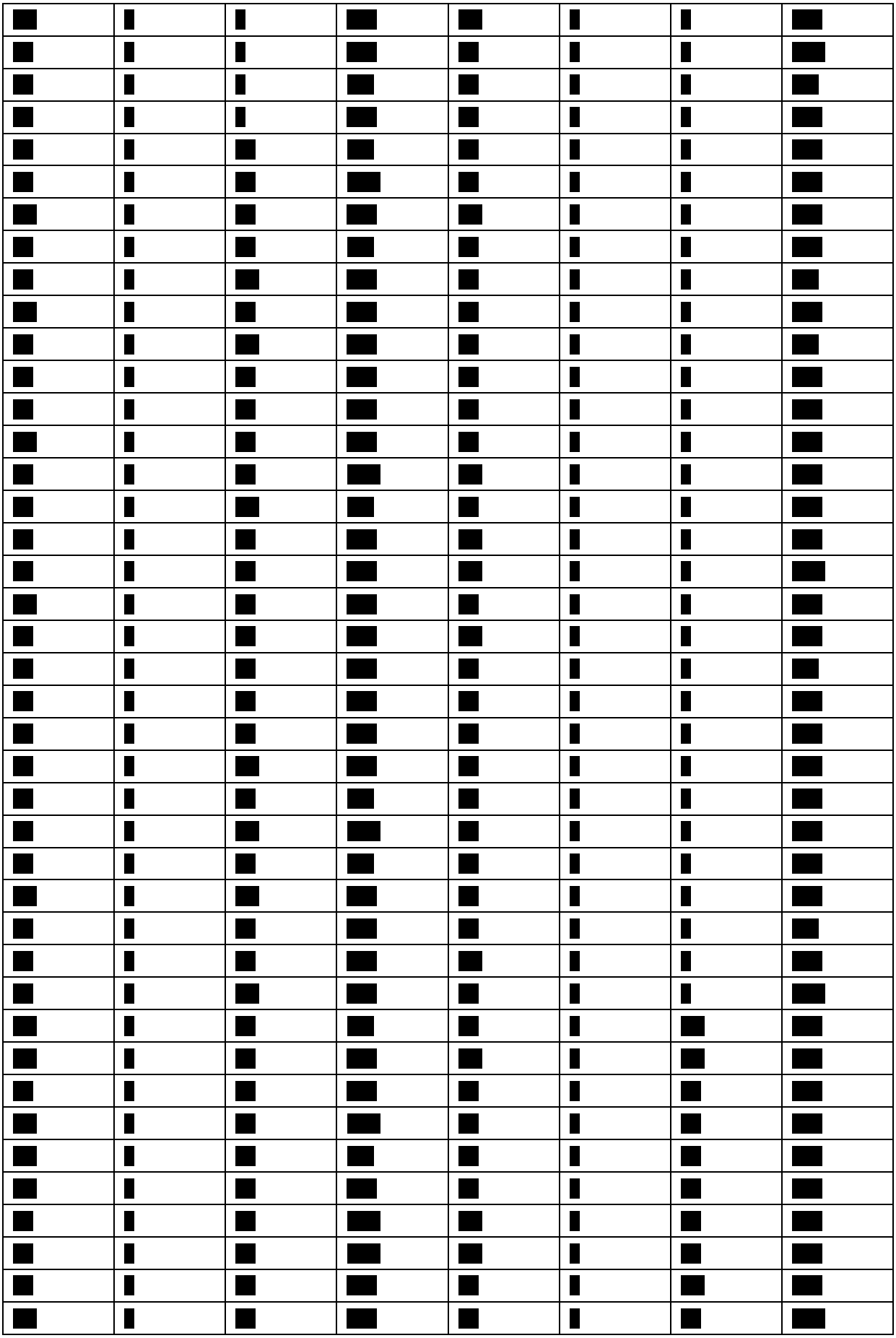

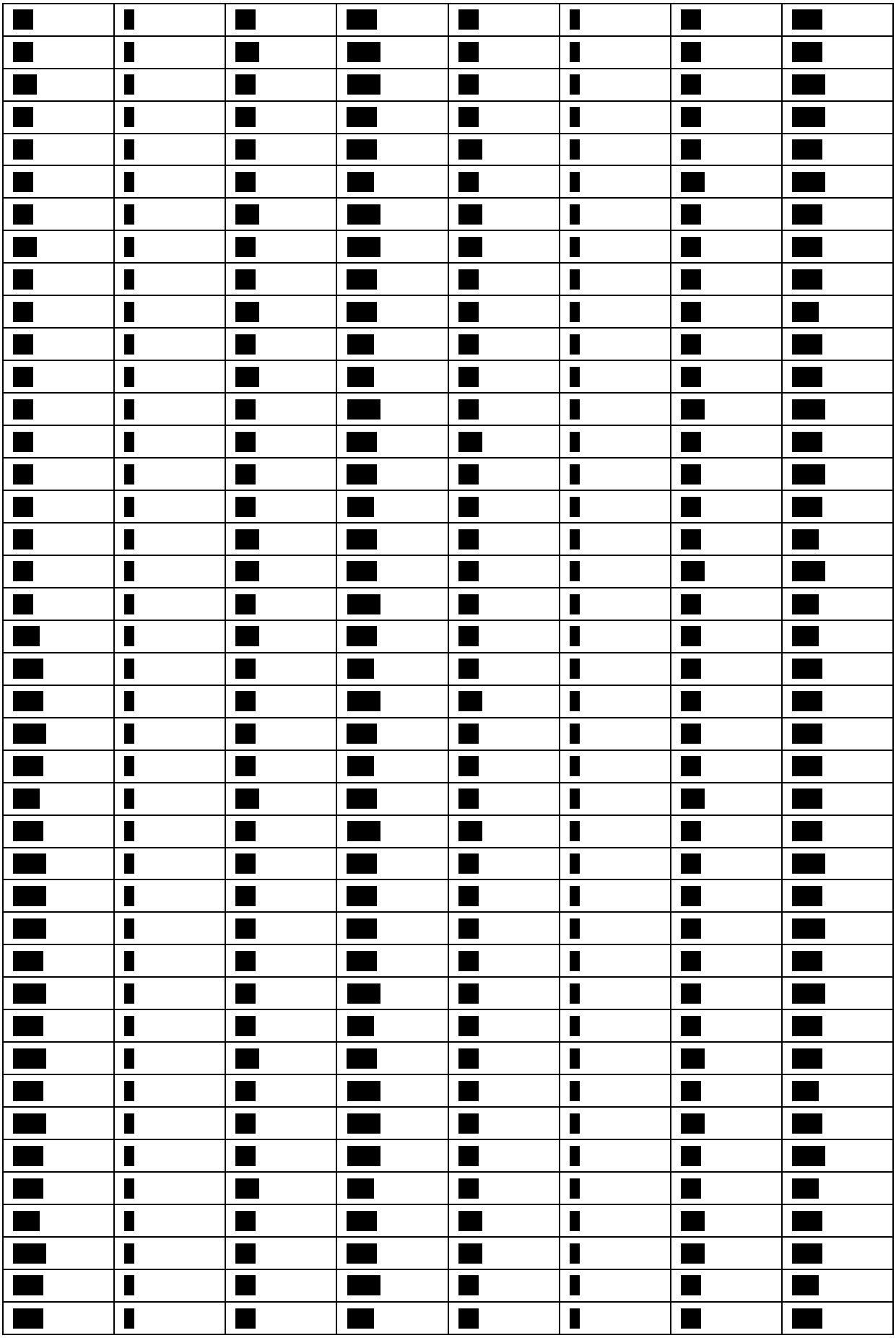

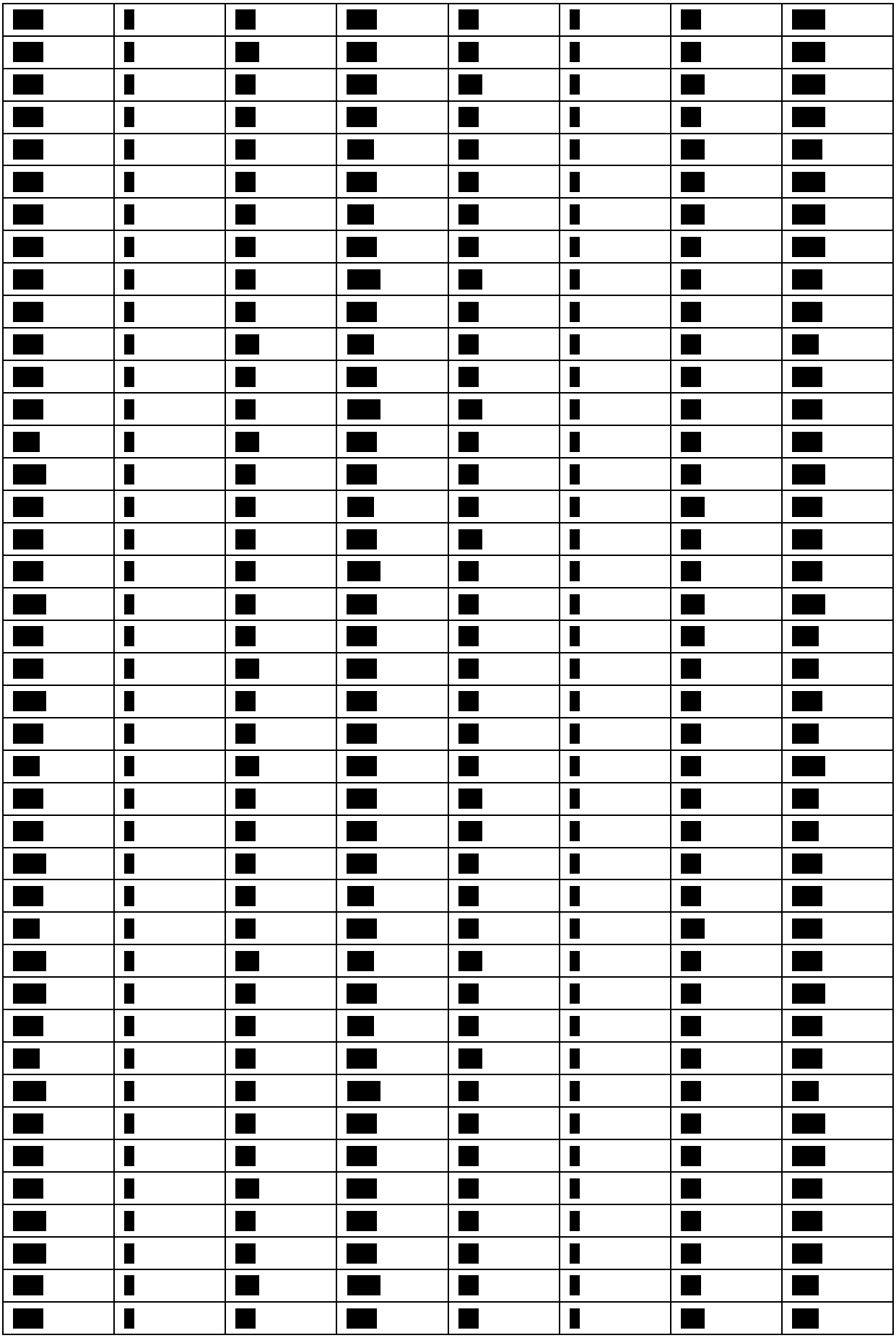

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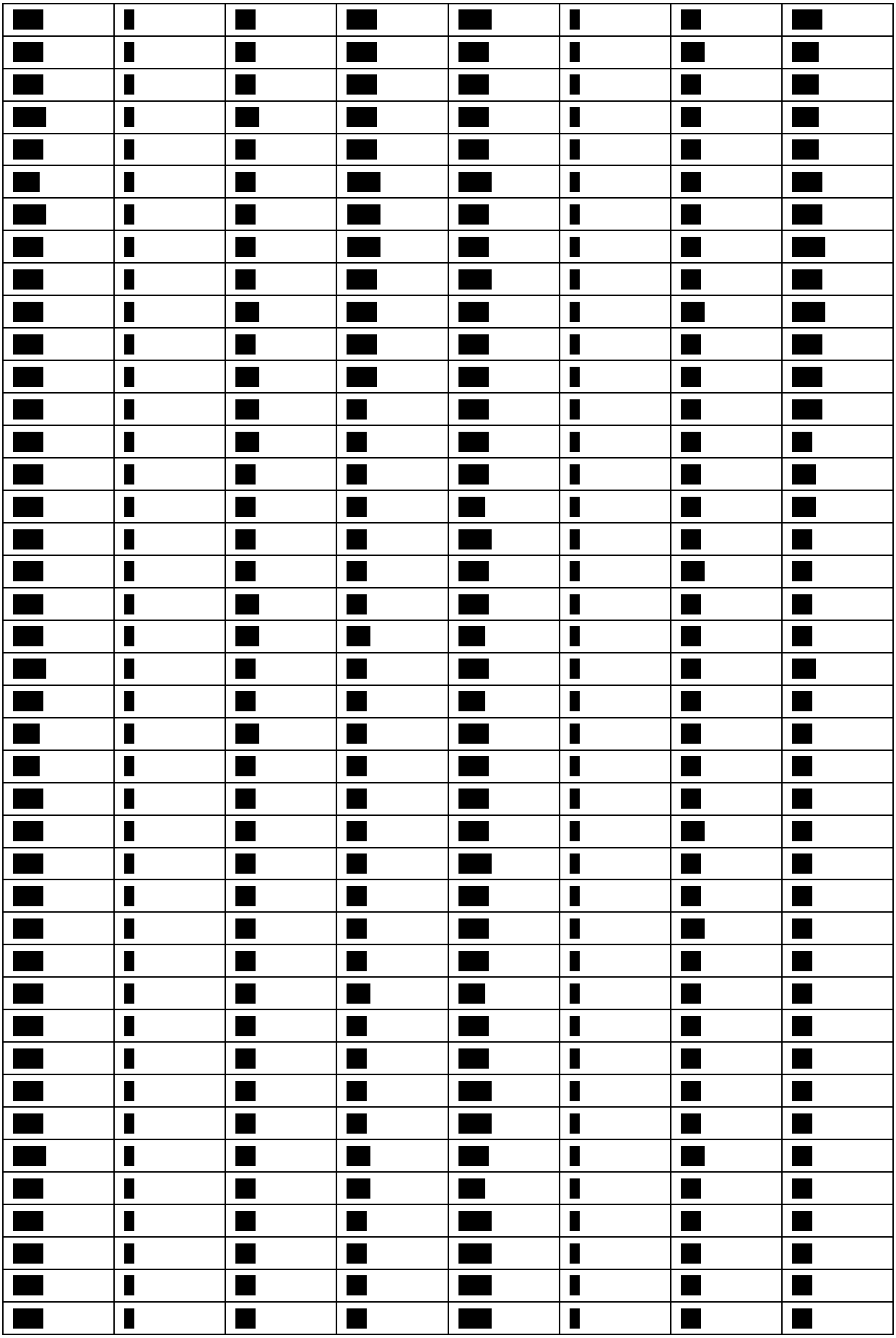

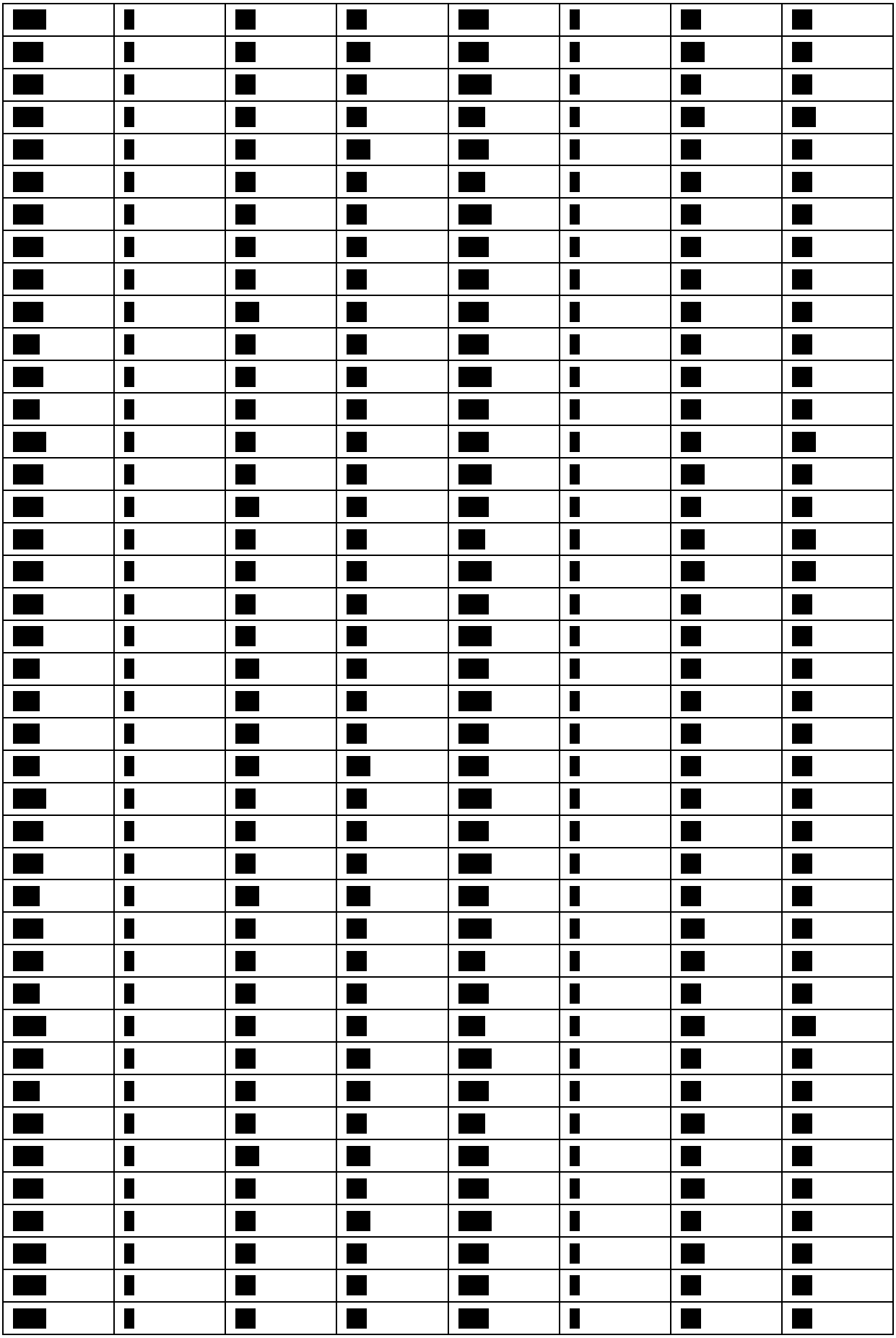

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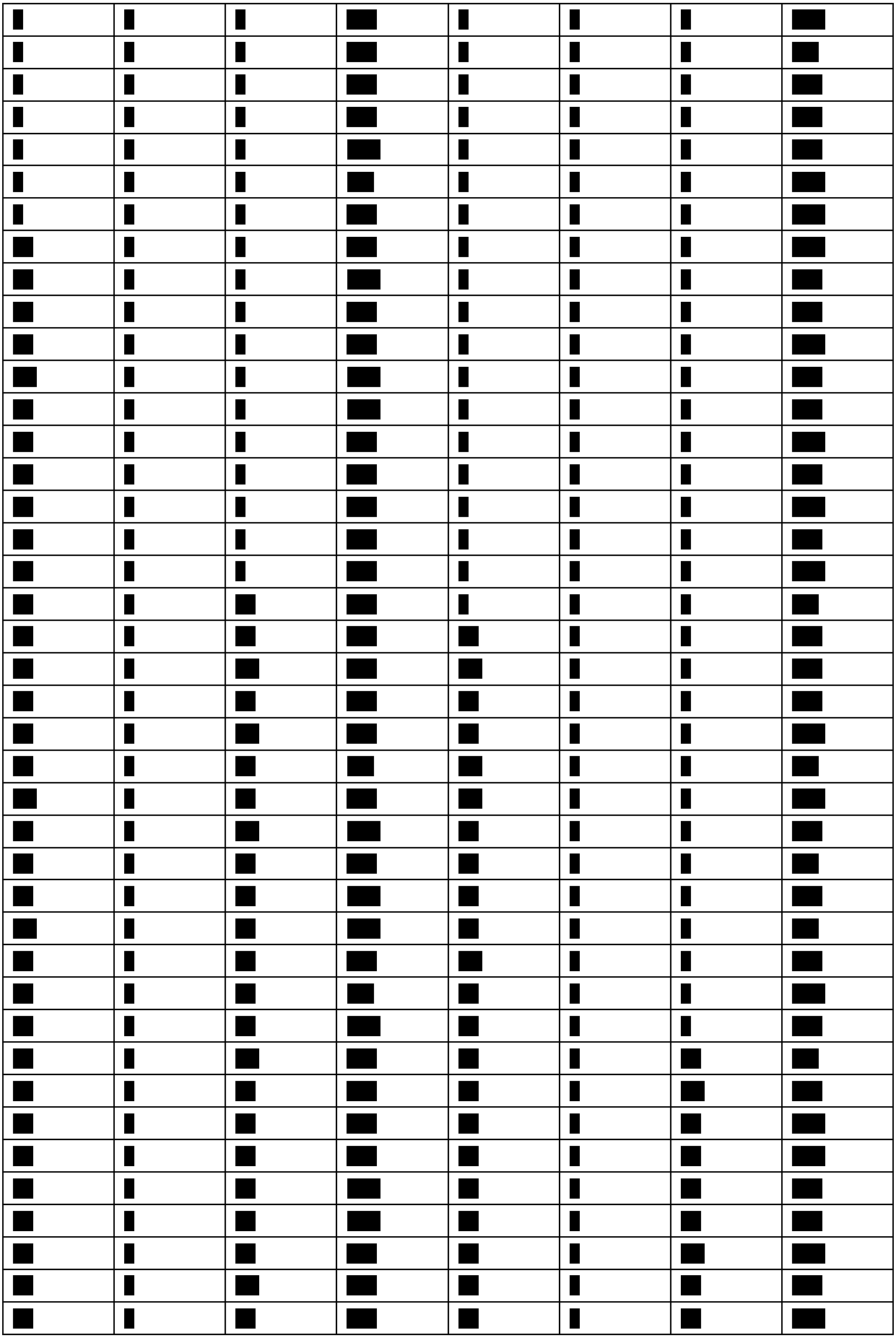

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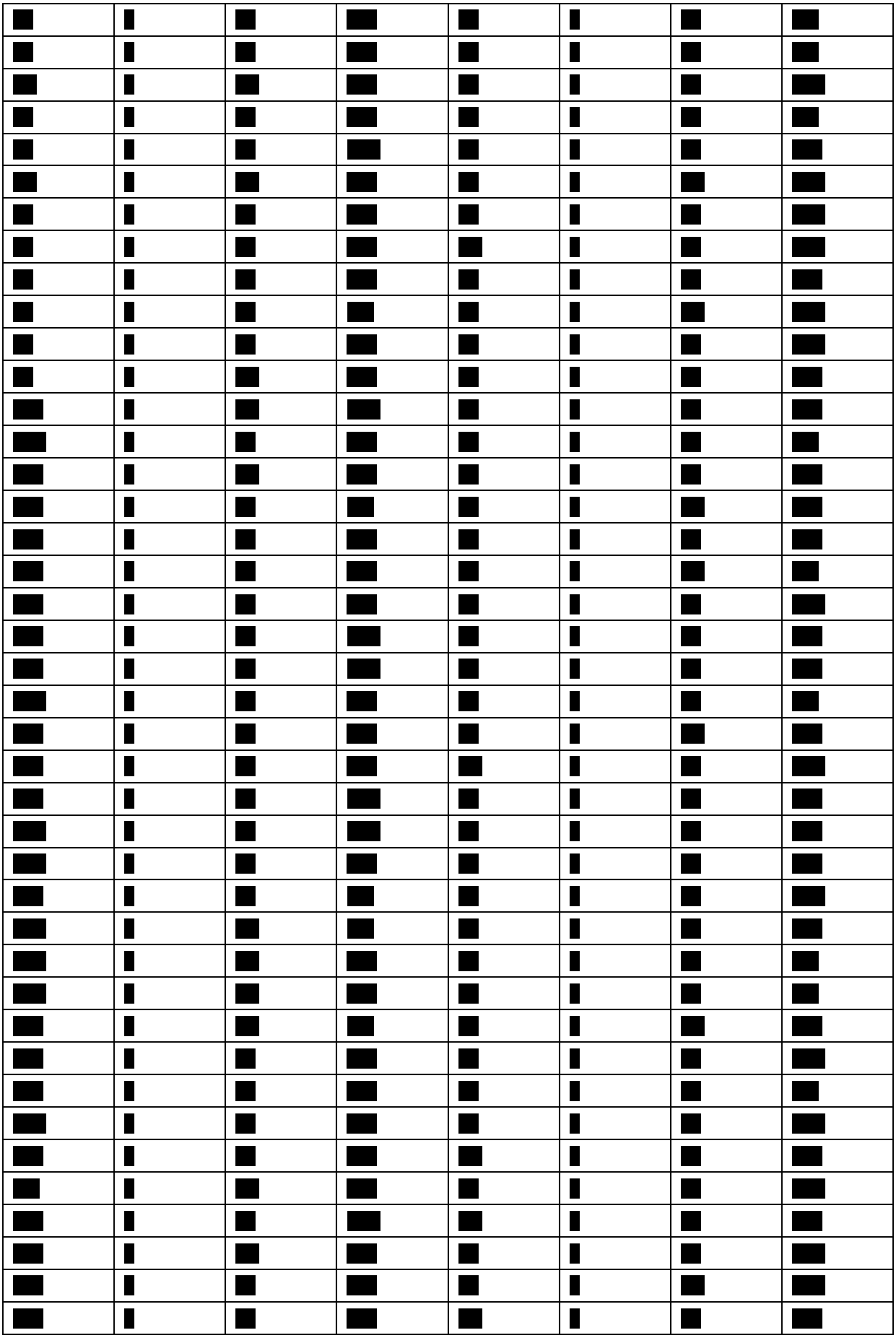

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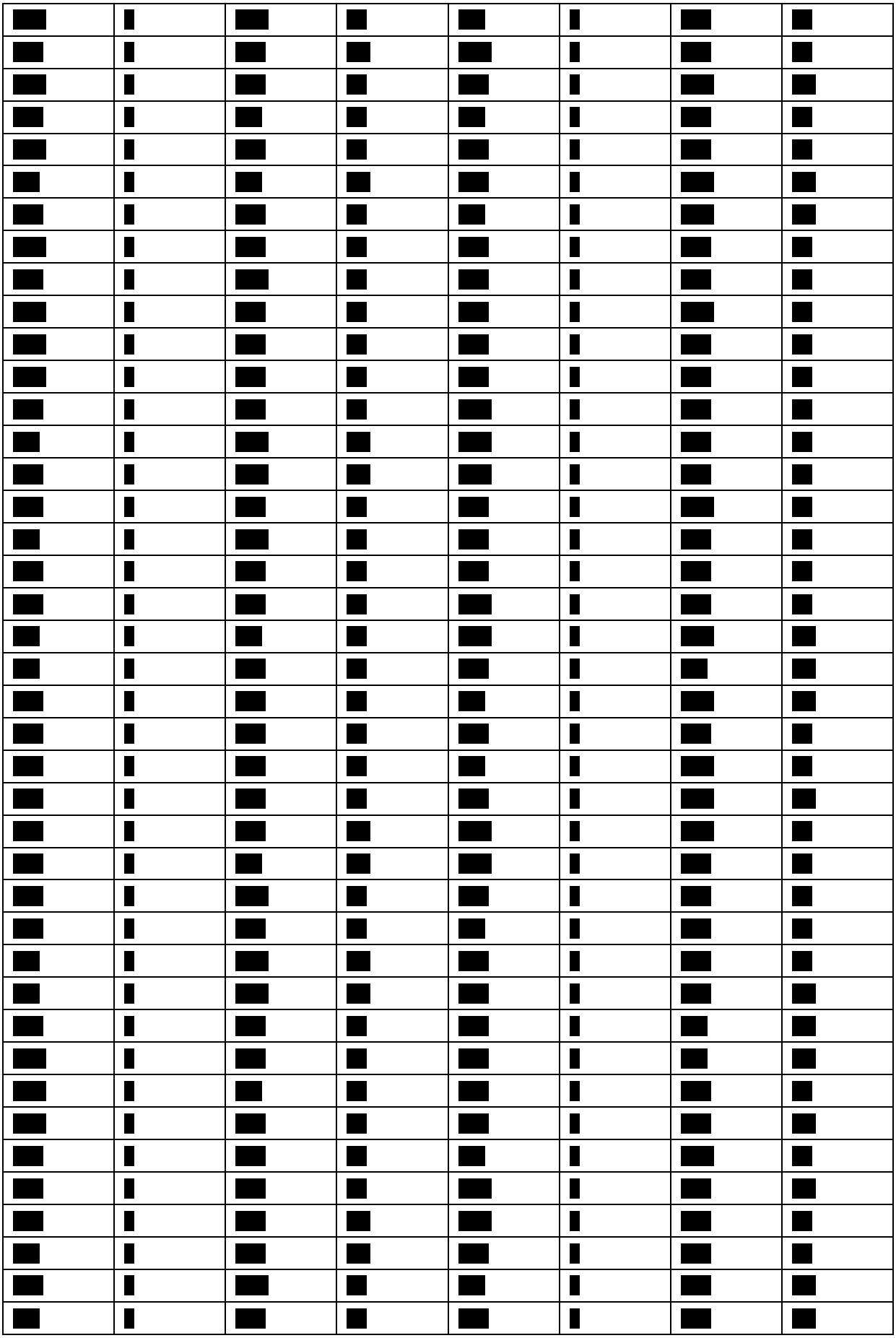

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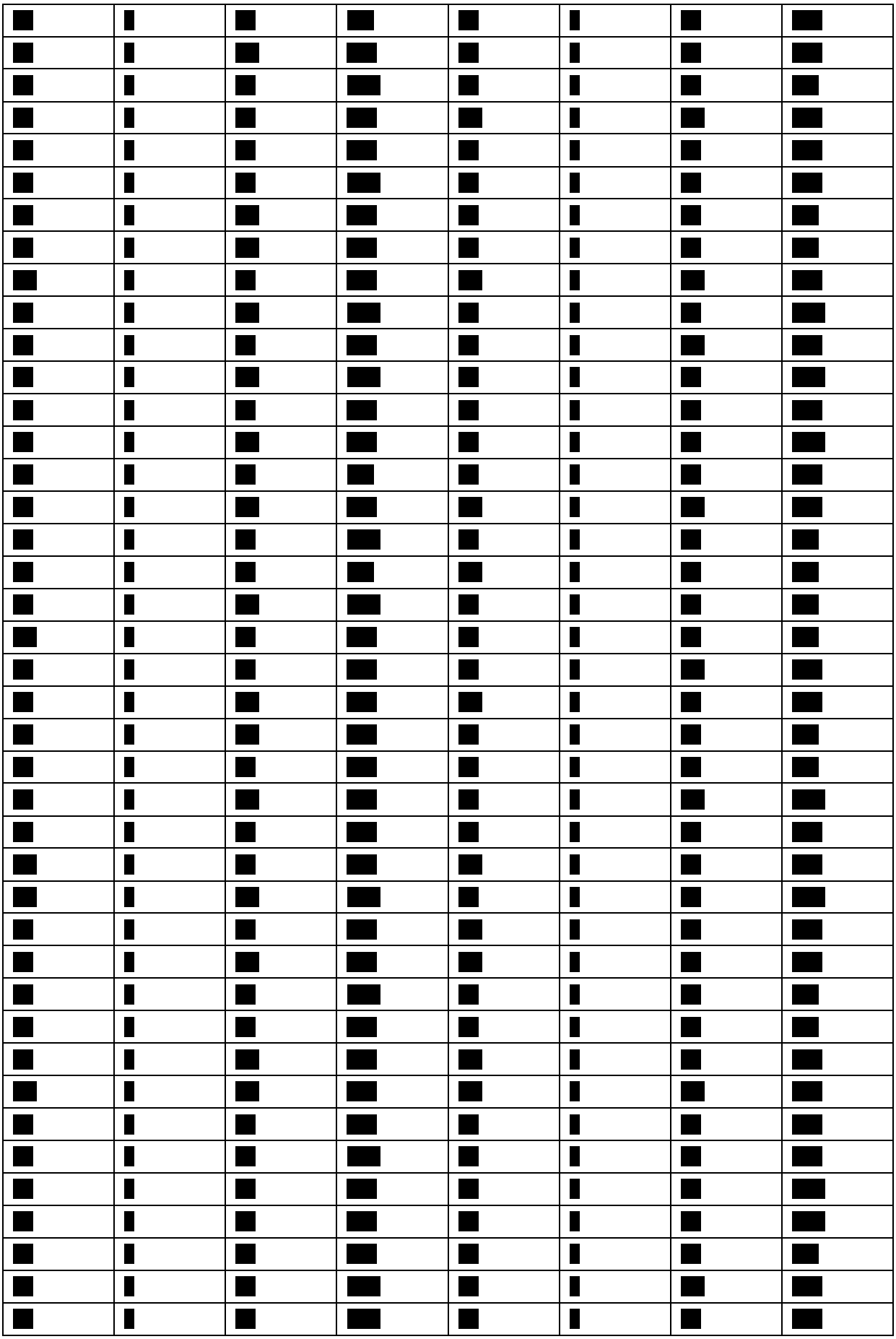

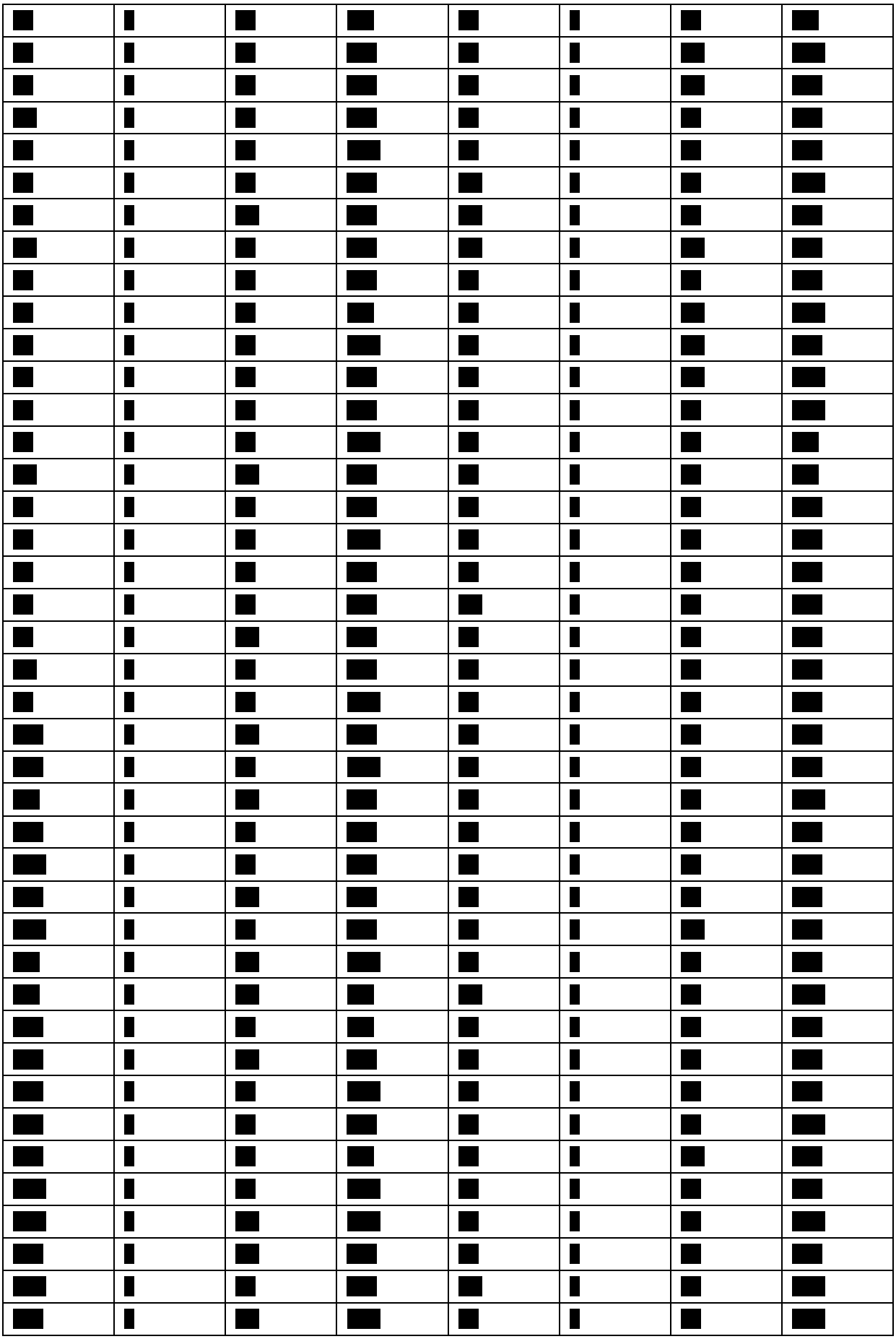

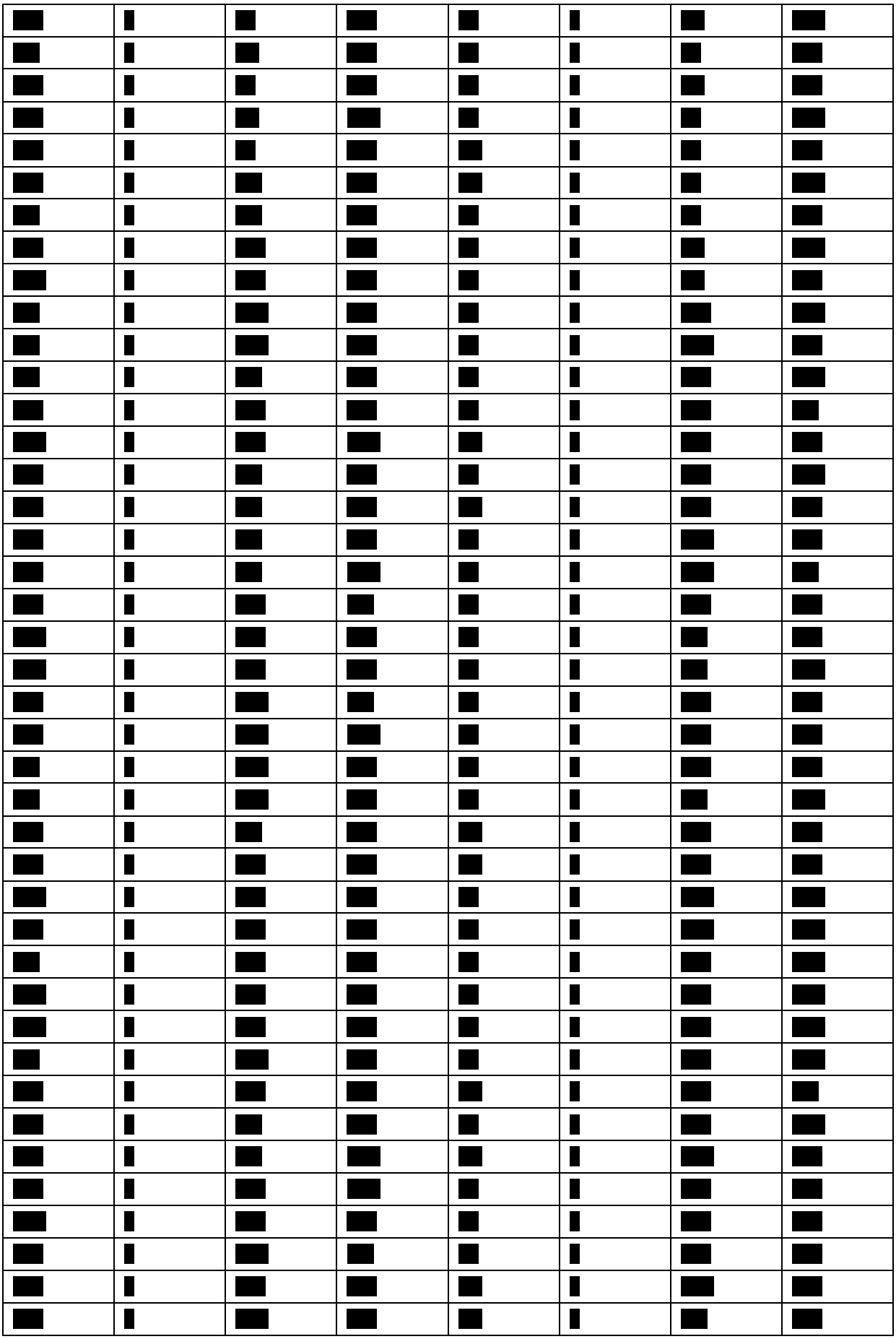

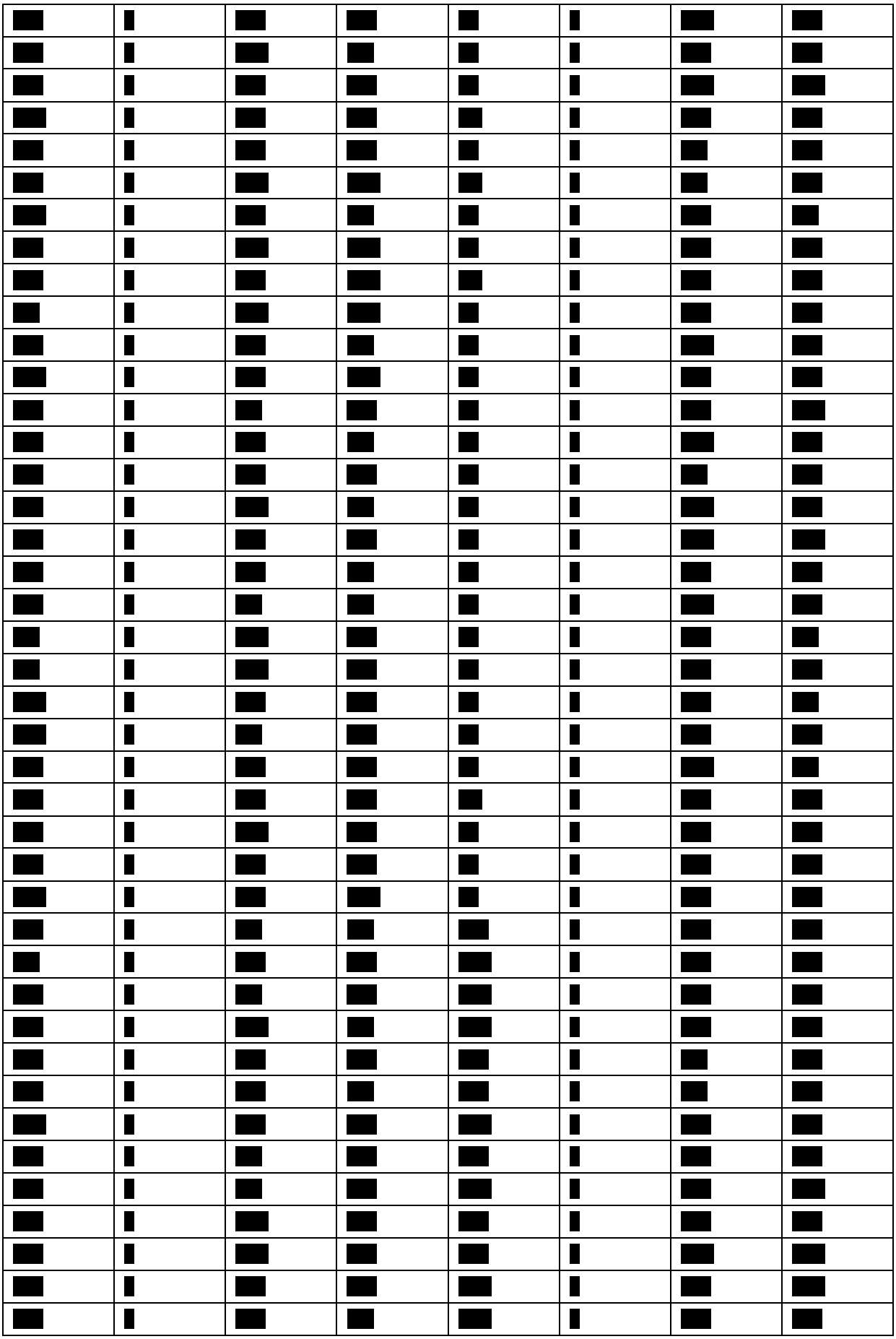

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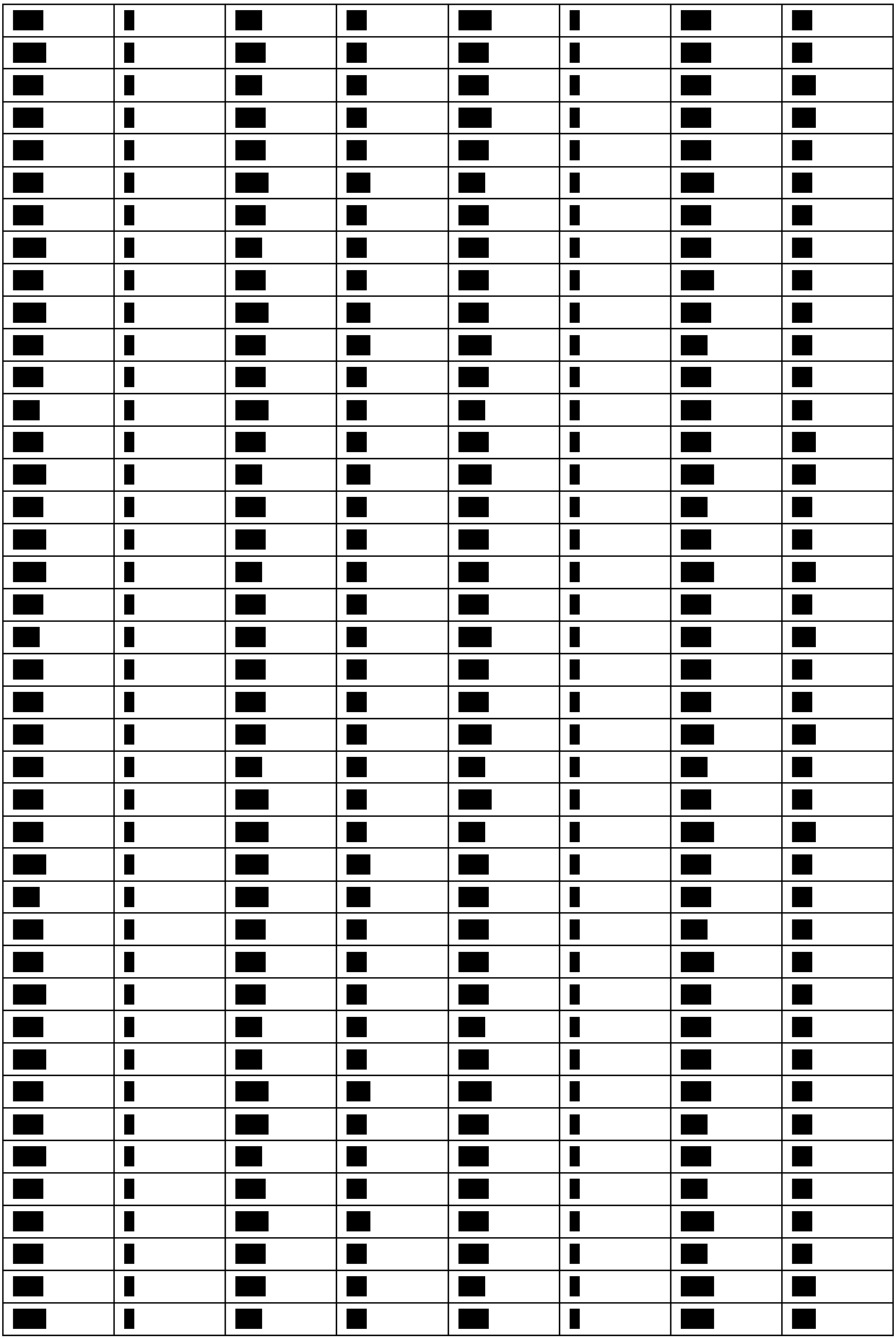

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Appendix 3: Search strategy for cost-effectiveness studies (November 2014)

Databases searched:

- Medline and Medline in Process & other non-indexed citations
- Embase
- EconLIT
- Cochrane Library
    - NHS EED
    - Cochrane database of systematic reviews (CDSR)
    - HTA database
    - Dare
- CINAHL

The dates on which the search was conducted are presented in the table below.

Database	**Date searched**
Medline and Medline in Process & other non-indexed citations	25/11/2014
Embase	25/11/2014
EconLIT	25/11/2014
NHS EED	25/11/2014
CDSR	25/11/2014
HTA database	25/11/2014
DARE	25/11/2014
CINAHL	25/11/2014

The span of the search can be found within the search strategies presented below.

A precise search strategy was utilised, incorporating terms for nivolumab and its comparators, together with terms for melanoma and an economics filter, as reported on the Centre for Reviews and Dissemination (CRD) (http://www.york.ac.uk/inst/crd/index_guidance.htm).

The complete search strategies used, including all the search terms and the relationship between the search terms are presented in the tables below.

Medline and Medline In-Process & other non-indexed citations: Ovid. 1946 to present

1. nivolumab.mp.
2. opdivo.mp.
3. ONO-4538.mp.
4. BMS-936558.mp.

5. MDX1106.mp.
6. 946414-94-4.rn.
7. ipilimumab.mp.
8. yervoy.mp.
9. MDX-010.mp.
10. MDX-101.mp.
11. 477202-00-9.rn.
12. or/1-11
13. exp Melanoma/
14. melanoma$.mp.
15. exp Skin Neoplasms/
16. (skin adj3 (cancer$ or oncolog$ or malignan$ or neoplasia or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.
17. or/13-16
18. 12 and 17
19. Economics/
20. "costs and cost analysis"/
21. Cost allocation/
22. Cost-benefit analysis/
23. Cost control/
24. Cost savings/
25. Cost of illness/
26. Cost sharing/
27. "deductibles and coinsurance"/
28. Medical savings accounts/
29. Health care costs/
30. Direct service costs/
31. Drug costs/
32. Employer health costs/
33. Hospital costs/
34. Health expenditures/
35. Capital expenditures/
36. Value of life/
37. exp economics, hospital/
38. exp economics, medical/
39. Economics, nursing/
40. Economics, pharmaceutical/
41. exp "fees and charges"/
42. exp budgets/
43. (low adj cost).mp.
44. (high adj cost).mp.
45. (health?care adj cost$).mp.
46. (fiscal or funding or financial or finance).tw.

47. (cost adj estimate$).mp.
48. (cost adj variable).mp.
49. (unit adj cost$).mp.
50. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
51. or/19-50
52. 18 and 51
53. limit 52 to yr="1970 -Current"

Embase: Ovid. 1974 to 18 November 2014

1. nivolumab/
2. nivolumab.mp.
3. opdivo.mp.
4. ONO-4538.mp.
5. BMS-936558.mp.
6. MDX1106.mp.
7. 946414-94-4.rn.
8. ipilimumab/
9. ipilimumab.mp.
10. yervoy.mp.
11. MDX-010.mp.
12. MDX-101.mp.
13. 477202-00-9.rn.
14. or/1-13
15. exp melanoma/
16. melanoma$.mp.
17. exp skin tumor/
18. (skin adj3 (cancer$ or oncolog$ or malignan$ or neoplasia or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.
19. or/15-18
20. 14 and 19
21. Socioeconomics/
22. Cost benefit analysis/
23. Cost effectiveness analysis/
24. Cost of illness/
25. Cost control/
26. Economic aspect/
27. Financial management/
28. Health care cost/
29. Health care financing/
30. Health economics/
31. Hospital cost/

32. (fiscal or financial or finance or funding).tw.	
33. Cost minimization analysis/	
34. (cost adj estimate$).mp.	
35. (cost adj variable$).mp.	
36. (unit adj cost$).mp.	
37. or/21-36	
38. 20 and 37	
39. limit 38 to yr="1970 -Current"	

Cochrane Library

Cochrane database of systematic reviews (CDSR): Wiley Intersceince, 1996-present

Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present

Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present

NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	nivolumab:ti,ab,kw
#2	opdivo:ti,ab,kw
#3	ONO-4538:ti,ab,kw
#4	BMS-936558:ti,ab,kw
#5	MDX1106:ti,ab,kw
#6	ipilimumab:ti,ab,kw
#7	yervoy:ti,ab,kw
#8	MDX-010:ti,ab,kw
#9	MDX-101:ti,ab,kw
#10	1-#9

Cinahl: EBSCO. 1981 to present

S27	S10 AND S26
S26	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25
S25	quality adjusted life year or quality adjusted life years
S24	qaly or qalys
S23	value and (money or monetary)
S22	fee or fees
S21	financial or finance or finances or financed
S20	price* or pricing*
S19	TI economic* or pharmacoeconomic* or pharmaco-economic*
S18	AB cost* and (effective* or utilit* or benefit* or minimi*)
S17	cost*
S16	budget*
S15	(MH "Budgets")
S14	(MH "Fees and Charges+")

S13	(MH "Economics, Pharmaceutical")
S12	(MH "Economics")
S11	(MH "Costs and Cost Analysis+")
S10	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9	MDX-101
S8	MDX-010
S7	yervoy
S6	ipilimumab
S5	MDX1106
S4	BMS-936558
S3	ONO-4538
S2	opdivo
S1	nivolumab

EconLit: Ovid. 1961 to October 2014

1. nivolumab.tw.
2. opdivo.tw.
3. ONO-4538.tw.
4. BMS-936558.tw.
5. MDX1106.tw.
6. ipilimumab.tw.
7. yervoy.tw.
8. MDX-010.tw.
9. MDX-101.tw.
10. or/1-9

Appendix 4: Search strategies for cost and healthcare resource identification, measurement and valuation (November 2014)

Databases searched:

- Medline and Medline in Process & other non-indexed citations
- Embase
- EconLIT
- Cochrane Library

- NHS EED
- Cochrane database of systematic reviews (CDSR)
- HTA database
- Dare

- CINAHL

The dates on which the search was conducted are presented in the table below.

Database	**Date searched**
Medline and Medline in Process & other non-indexed citations	25/11/2014
Embase	25/11/2014
EconLIT	25/11/2014
NHS EED	25/11/2014
CDSR	25/11/2014
HTA database	25/11/2014
DARE	25/11/2014
CINAHL	25/11/2014

The span of the search can be found within the search strategies presented below.

The complete search strategies used, including all the search terms and the relationship between the search terms are presented in the tables below.

Medline and Medline In-Process & other non-indexed citations: Ovid. 1946 to present

1. Melanoma/
2. melanoma$.mp.
3. Skin Neoplasms/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or neoplasia or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.
5. or/1-4

6. exp "Costs and Cost Analysis"/
7. Economics/
8. exp Economics, Hospital/
9. exp Economics, Medical/
10. Economics, Nursing/
11. exp models, economic/
12. Economics, Pharmaceutical/
13. exp "Fees and Charges"/
14. exp Budgets/
15. budget$.tw.
16. ec.fs.
17. cost$.ti.
18. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
19. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
20. (price$ or pricing$).tw.
21. (financial or finance or finances or financed).tw.
22. (fee or fees).tw.
23. (value adj2 (money or monetary)).tw.
24. quality-adjusted life years/
25. (qaly or qalys).af.
26. (quality adjusted life year or quality adjusted life years).af.
27. exp hospitalization/
28. consumer satisfaction/
29. patient acceptance of health care/
30. disease management/
31. physician's practice patterns/
32. health care rationing/
33. ((clinical or critical or patient) adj path$).tw.
34. (managed adj2 (care or clinical or network)).tw.
35. (resource$ adj2 allocat$).tw.
36. or/6-35
37. 5 and 36
38. limit 37 to yr="2013 -Current"

Embase: Ovid. 1974 to 18 November 2014

1. melanoma/
2. melanoma$.tw.
3. skin tumor/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or neoplasia or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.
5. or/1-4

6. Socioeconomics/
7. Cost benefit analysis/
8. Cost effectiveness analysis/
9. Cost of illness/
10. Cost control/
11. Economic aspect/
12. Financial management/
13. Health care cost/
14. Health care financing/
15. Health economics/
16. Hospital cost/
17. (fiscal or financial or finance or funding).tw.
18. Cost minimization analysis/
19. (cost adj estimate$).mp.
20. (cost adj variable$).mp.
21. (unit adj cost$).mp.
22. exp hospitalization/
23. disease management/
24. clinical practice/
25. health care organization/
26. ((clinical or critical or patient) adj path$).tw.
27. (managed adj2 (care or clinical or network)).tw.
28. (resource$ adj2 allocat$).tw.
29. or/6-28
30. 5 and 29
31. limit 30 to yr="2013 -Current"

Cochrane Library

Cochrane database of systematic reviews (CDSR): Wiley Intersceince, 1996-present

NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present

Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present

#1	MeSH descriptor: [Melanoma] this term only
#2	melanoma*:ti,ab,kw
#3	MeSH descriptor: [Skin Neoplasms] this term only
#4	(skin next/3 (cancer* or oncolog* or malignan* or neoplasia or neoplasm* or carcinoma* or adenocarcinoma* or tumor* or tumour*)):ti,ab
#5	#1 or #2 or #3 or #4 from 2013 to 2014

Cinahl: EBSCO. 1981 to present

S30	S5 AND S29 Limiters - Published Date from: 20130101-20141231
S29	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28
S28	(resource* N2 allocat*)
S27	(managed N2 (care or clinical or network))
S26	((clinical or critical or patient) N1 path*)
S25	(MH "Health Resource Allocation")
S24	(MH "Practice Patterns")
S23	(MH "Disease Management")
S22	(MH "Consumer Satisfaction+")
S21	(MH "Hospitalization+")
S20	quality adjusted life year or quality adjusted life years
S19	qaly or qalys
S18	value and (money or monetary)
S17	fee or fees
S16	financial or finance or finances or financed
S15	price* or pricing*
S14	TI economic* or pharmacoeconomic* or pharmaco-economic*
S13	AB cost* and (effective* or utilit* or benefit* or minimi*)
S12	cost*
S11	budget*
S10	(MH "Budgets")
S9	(MH "Fees and Charges+")
S8	(MH "Economics, Pharmaceutical")
S7	(MH "Economics")
S6	(MH "Costs and Cost Analysis+")
S5	S1 or S2 or S3 or S4
S4	(skin N3 (cancer* or oncolog* or malignan* or neoplasia or neoplasm* or carcinoma* or adenocarcinoma* or tumor* or tumour*))
S3	(MH "Skin Neoplasms")
S2	melanoma*
S1	(MH "Melanoma")

EconLit: Ovid. 1961 to October 2014

1. melanoma$.tw.
2. (skin adj3 (cancer$ or oncolog$ or malignan$ or neoplasia or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.
3. 1 or 2
4. limit 3 to yr="2013 -Current"

Appendix 5: Search strategy for measurement and valuation of health effects (November 2014)

Databases searched:

- Medline and Medline in Process & other non-indexed citations
- Embase
- EconLIT
- Cochrane Library
  - NHS EED
  - Cochrane database of systematic reviews (CDSR)
  - HTA database
  - Dare
- CINAHL

The dates on which the search was conducted are presented in the table below.

Database	**Date searched**
Medline and Medline in Process & other non-indexed citations	25 November 2014
Embase	
EconLIT	
NHS EED	
CDSR	
HTA database	
DARE	
CINAHL	

The span of the search can be found within the search strategies presented below.

The complete search strategies used, including all the search terms and the relationship between the search terms are presented in the tables below.

Medline and Medline In-Process & other non-indexed citations: Ovid. 1946 to present

1. Melanoma/
2. melanoma$.tw.
3. Skin Neoplasms/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or neoplasia or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.
5. or/1-4

6. "Quality of Life"/

7. (qol or (quality adj2 life)).ab,ti.

8. (value adj2 (money or monetary)).tw.

9. value of life/

10. quality adjusted life year/

11. quality adjusted life.tw.

12. (qaly$ or qald$ or qale$ or qtime$).tw.

13. disability adjusted life.tw.

14. daly$.tw.

15. health status indicators/

16. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

17. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

18. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

19. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.

20. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

21. (euroqol or euro qol or eq5d or eq 5d).tw.

22. (hql or hqol or h qol or hrqol or hr qol).tw.

23. (hye or hyes).tw.

24. health$ year$ equivalent$.tw.

25. health utilit$.tw.

26. (hui or hui1 or hui2 or hui3).tw.

27. disutilit$.tw.

28. rosser.tw.

29. (quality adj2 wellbeing).tw.

30. qwb.tw.

31. (willingness adj2 pay).tw.

32. standard gamble$.tw.

33. time trade off.tw.

34. time tradeoff.tw.

35. tto.tw.

36. letter.pt.

37. editorial.pt.

38. comment.pt.

39. 36 or 37 or 38

40. or/6-35

41. 40 not 39

42. 5 and 41

43. limit 42 to yr="2013 -Current"

Embase: Ovid. 1974 to 18 November 2014

1. melanoma/
2. melanoma$.mp.
3. skin tumor/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or neoplasia or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.
5. or/1-4
6. "Quality of Life"/
7. (qol or (quality adj2 life)).ti,ab.
8. (value adj2 (money or monetary)).tw.
9. socioeconomics/
10. quality adjusted life year/
11. (qaly$ or qald$ or qale$ or qtime$).tw.
12. disability adjusted life.tw.
13. daly$.tw.
14. health survey/
15. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
16. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
17. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
18. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
19. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
20. (euroqol or euro qol or eq5d or eq 5d).tw.
21. (hql or hqol or h qol or hrqol or hr qol).tw.
22. (hye or hyes).tw.
23. health$ year$ equivalent$.tw.
24. health utilit$.tw.
25. (hui or hui1 or hui2 or hui3).tw.
26. disutilit$.tw.
27. rosser.tw.
28. (quality adj2 wellbeing).tw.
29. qwb.tw.
30. (willingness adj2 pay).tw.
31. standard gamble$.tw.
32. time trade off.tw.
33. time tradeoff.tw.
34. tto.tw.
35. letter.pt.
36. editorial.pt.
37. comment.pt.

38. 35 or 36 or 37
39. or/6-34
40. 39 not 38
41. 5 and 40
42. limit 41 to yr="2013 -Current"

Cochrane Library

Cochrane database of systematic reviews (CDSR): Wiley Intersceince, 1996-present

Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present

Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present

NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	MeSH descriptor: [Quality of Life] this term only
#2	(qol or (quality next/2 life)):ti,ab,kw
#3	MeSH descriptor: [Value of Life] this term only
#4	value and (money or monetary):ti,ab,kw
#5	MeSH descriptor: [Quality-Adjusted Life Years] this term only
#6	(quality adjusted life):ti,ab,kw
#7	(qaly* or qald* or qale* or qtime*):ti,ab,kw
#8	disability adjusted life:ti,ab,kw
#9	daly*:ti,ab,kw
#10	MeSH descriptor: [Health Status Indicators] explode all trees
#11	sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six:ti,ab,kw
#12	sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six:ti,ab,kw
#13	sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve:ti,ab,kw
#14	sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen:ti,ab,kw
#15	sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty:ti,ab,kw
#16	euroqol or euro qol or eq5d or eq 5deuroqol or euro qol or eq5d or eq 5d:ti,ab,kw
#17	hql or hqol or h qol or hrqol or hr qol:ti,ab,kw
#18	hye or hyes:ti,ab,kw
#19	health* year* equivalent*:ti,ab,kw
#20	health utilit*:ti,ab,kw
#21	hui or hui1 or hui2 or hui3:ti,ab,kw
#22	disutilit*:ti,ab,kw
#23	rosser:ti,ab,kw
#24	qwb:ti,ab,kw
#25	standard gamble*:ti,ab,kw
#26	willingness to pay:ti,ab,kw
#27	quality of wellbeing:ti,ab,kw

#28	time trade off:ti,ab,kw
#29	time tradeoff:ti,ab,kw
#30	tto:ti,ab,kw
#31	letter:pt
#32	editorial:pt
#33	comment:pt
#34	#31 or #32 or #33
#35	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#36	#35 not #34
#37	MeSH descriptor: [Melanoma] this term only
#38	melanoma*:ti,ab,kw
#39	MeSH descriptor: [Skin Neoplasms] this term only
#40	(skin next/3 (cancer* or oncolog* or malignan* or neoplasia or neoplasm* or carcinoma* or adenocarcinoma* or tumor* or tumour*)):ti,ab
#41	#37 or #38 or #39 or #40
#42	#36 and #41 from 2013 to 2014

Cinahl: EBSCO. 1981 to present

S42	S5 AND S41 Limiters - Published Date from: 20130101-20141231
S41	S40 NOT S39
S40	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35
S39	S36 or S37 or S38
S38	PT comment
S37	PT editorial
S36	PT letter
S35	TI tto or AB tto
S34	TI time tradeoff or AB time tradeoff
S33	TI time trade off or AB time trade off
S32	TI standard gamble* or AB standard gamble*
S31	TI willingness N2 pay or AB willingness N2 pay
S30	TI qwb or AB qwb
S29	TI quality N2 wellbeing or AB quality N2 wellbeing
S28	TI rosser or AB rosser
S27	TI disutilit* or AB disutilit*
S26	TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)
S25	TI health utilit* or AB health utilit*
S24	TI health* year* equivalent* or AB health* year* equivalent*
S23	TI (hye or hyes) or AB (hye or hyes)
S22	TI (hql or hqol or h qol or hrqol or hr qol) or AB (hql or hqol or h qol or hrqol or hr qol)
S21	
S20	TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)
S19	TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
	TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or

S18	shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)
S17	TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or
S16	sf twelve or sftwelve or shortform twelve or short form twelve)
	TI quality adjusted life or AB quality adjusted life
S15	TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
	TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
S14	or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or
S13	shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
S12	(MH "Health Status Indicators")
S11	TI daly* or AB daly*
S10	TI disability adjusted life or AB disability adjusted life
S9	TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)
S8	(MH "Quality-Adjusted Life Years")
S7	(MH "Economic Value of Life")
S6	TI value and TI (money or monetary) or AB value and AB (money or monetary)
	TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))
	(MH "Quality of Life")
S5	S1 or S2 or S3 or S4
S4	(skin N3 (cancer* or oncolog* or malignan* or neoplasia or neoplasm* or carcinoma* or adenocarcinoma* or tumor* or tumour*))
S3	(MH "Skin Neoplasms")
S2	melanoma*
S1	(MH "Melanoma")

EconLit: Ovid. 1961 to October 2014

1. melanoma$.tw.
2. (skin adj3 (cancer$ or oncolog$ or malignan$ or neoplasia or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.
3. 1 or 2
4. limit 3 to yr="2013 -Current"

Appendix 6: Search strategies for cost and healthcare resource identification, measurement and valuation (March 2013)

The date on which the search was conducted.

Database	Date searched
Medline	24/05/13
Embase	24/05/13
HTA	24/05/13
DARE	24/05/13
NHS EED	24/05/13
Cinahl	24/05/13
EconLit	22/05/13

Medline and Medline In-Process & Other Non-Indexed Citations: Ovid. 1946 to Present

1. Melanoma/
2. melanoma$.tw.
3. Skin Neoplasms/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
5. or/1-4
6. "Quality of Life"/
7. (qol or (quality adj2 life)).ab,ti.
8. (value adj2 (money or monetary)).tw.
9. value of life/
10. quality adjusted life year/
11. quality adjusted life.tw.
12. (qaly$ or qald$ or qale$ or qtime$).tw.
13. disability adjusted life.tw.
14. daly$.tw.
15. health status indicators/
16. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
17. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
18. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
19. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
20. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
21. (euroqol or euro qol or eq5d or eq 5d).tw.
22. (hql or hqol or h qol or hrqol or hr qol).tw.
23. (hye or hyes).tw.
24. health$ year$ equivalent$.tw.
25. health utilit$.tw.
26. (hui or hui1 or hui2 or hui3).tw.
27. disutilit$.tw.
28. rosser.tw.
29. (quality adj2 wellbeing).tw.
30. qwb.tw.
31. (willingness adj2 pay).tw.
32. standard gamble$.tw.
33. time trade off.tw.
34. time tradeoff.tw.
35. tto.tw.
36. letter.pt.
37. editorial.pt.
38. comment.pt.
39. 36 or 37 or 38
40. or/6-35
41. 40 not 39
42. 5 and 41
43. limit 42 to yr="1970 -Current"

Embase: Ovid. 1974 to 2013 May 08

1. melanoma/
2. melanoma$.tw.
3. skin tumor/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
5. or/1-4

6. "Quality of Life"/
7. (qol or (quality adj2 life)).ti,ab.
8. (value adj2 (money or monetary)).tw.
9. socioeconomics/
10. quality adjusted life year/
11. (qaly$ or qald$ or qale$ or qtime$).tw.
12. disability adjusted life.tw.
13. daly$.tw.
14. health survey/
15. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
16. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
17. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
18. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
19. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
20. (euroqol or euro qol or eq5d or eq 5d).tw.
21. (hql or hqol or h qol or hrqol or hr qol).tw.
22. (hye or hyes).tw.
23. health$ year$ equivalent$.tw.
24. health utilit$.tw.
25. (hui or hui1 or hui2 or hui3).tw.
26. disutilit$.tw.
27. rosser.tw.
28. (quality adj2 wellbeing).tw.
29. qwb.tw.
30. (willingness adj2 pay).tw.
31. standard gamble$.tw.
32. time trade off.tw.
33. time tradeoff.tw.
34. tto.tw.
35. letter.pt.
36. editorial.pt.
37. comment.pt.
38. 35 or 36 or 37
39. or/6-34
40. 39 not 38
41. 5 and 40

Cochrane Library

NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	MeSH descriptor: [Quality of Life] this term only
#2	(qol or (quality next/2 life)):ti,ab,kw
#3	MeSH descriptor: [Value of Life] this term only
#4	value and (money or monetary):ti,ab,kw
#5	MeSH descriptor: [Quality-Adjusted Life Years] this term only
#6	(quality adjusted life):ti,ab,kw
#7	(qaly* or qald* or qale* or qtime*):ti,ab,kw
#8	disability adjusted life:ti,ab,kw
#9	daly*:ti,ab,kw
#10	MeSH descriptor: [Health Status Indicators] explode all trees
#11	sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six:ti,ab,kw
#12	sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six:ti,ab,kw
#13	sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve:ti,ab,kw
#14	sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen:ti,ab,kw
#15	sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty:ti,ab,kw
#16	euroqol or euro qol or eq5d or eq 5deuroqol or euro qol or eq5d or eq 5d:ti,ab,kw
#17	hql or hqol or h qol or hrqol or hr qol:ti,ab,kw
#18	hye or hyes:ti,ab,kw
#19	health* year* equivalent*:ti,ab,kw
#20	health utilit*:ti,ab,kw
#21	hui or hui1 or hui2 or hui3:ti,ab,kw
#22	disutilit*:ti,ab,kw
#23	rosser:ti,ab,kw
#24	qwb:ti,ab,kw
#25	standard gamble*:ti,ab,kw
#26	willingness to pay:ti,ab,kw
#27	quality of wellbeing:ti,ab,kw
#28	time trade off:ti,ab,kw
#29	time tradeoff:ti,ab,kw
#30	tto:ti,ab,kw
#31	letter:pt
#32	editorial:pt
#33	comment:pt
#34	#31 or #32 or #33
#35	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#36	#35 not #34
#37	MeSH descriptor: [Melanoma] explode all trees
#38	melanoma*:ti,ab,kw
#39	MeSH descriptor: [Skin Neoplasms] explode all trees
#40	(skin next/3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*)):ti,ab
#41	#37 or #38 or #39 or #40
#42	#36 and #41 from 1970 to 2013

Cinahl: EBSCO. 1981 to present

S42	S5 AND S41 Limiters - Published Date from: 19700101-20130631
S41	S40 NOT S39
S40	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or

	S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35
S39	S36 or S37 or S38
S38	PT comment
S37	PT editorial
S36	PT letter
S35	TI tto or AB tto
S34	TI time tradeoff or AB time tradeoff
S33	TI time trade off or AB time trade off
S32	TI standard gamble* or AB standard gamble*
S31	TI willingness N2 pay or AB willingness N2 pay
S30	TI qwb or AB qwb
S29	TI quality N2 wellbeing or AB quality N2 wellbeing
S28	TI rosser or AB rosser
S27	TI disutilit* or AB disutilit*
S26	TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)
S25	TI health utilit* or AB health utilit*
S24	TI health* year* equivalent* or AB health* year* equivalent*
S23	TI (hye or hyes) or AB (hye or hyes)
S22	TI (hql or hqol or h qol or hrqol or hr qol) or AB (hql or hqol or h qol or hrqol or hr qol)
S21	TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)
S20	TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
S19	TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)
S18	TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
S17	TI quality adjusted life or AB quality adjusted life
S16	TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
S15	TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
	(MH "Health Status Indicators")
S14	TI daly* or AB daly*
S13	TI disability adjusted life or AB disability adjusted life
S12	TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)
S11	(MH "Quality-Adjusted Life Years")
S10	(MH "Economic Value of Life")
S9	TI value and TI (money or monetary) or AB value and AB (money or monetary)
S8	TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))
S7	(MH "Quality of Life")
S6	S1 or S2 or S3 or S4 (skin N3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*)) (MH "Skin Neoplasms") melanoma*
S5	(MH "Melanoma")
S4	
S3	
S2	
S1	

EconLit: Ovid. 1961 to April 2013

1. melanoma$.tw.
2. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
3. 1 or 2

The inclusion and exclusion criteria.

Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Study Type	Studies reporting costs and resource use	The aim of the review was to identify relevant costs and use of resources
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population
Interventions	There was no restriction to intervention	To ensure all relevant studies were included
Outcomes	Studies reporting the resource use and costs associated with the treatment and ongoing management of advanced melanoma	The aim of the review was to identify relevant costs and data about resource use
Country of Study	UK	Costs and use of resources from a K perspective were required
Exclusion Criteria		
Category	**Exclusion criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of utility studies (although reference lists of these were being hand-searched)	Primary study articles were required

Appendix 7: Search strategy for measurement and valuation of health effects (March 2013)

The date on which the search was conducted.

Database	Date searched
Medline	24/05/13
Embase	24/05/13
HTA	24/05/13
DARE	24/05/13
NHS EED	22/05/13
Cinahl	24/05/13
EconLit	22/05/13

Medline and Medline In-Process & Other Non-Indexed Citations: Ovid. 1946 to Present

1. Melanoma/
2. melanoma$.tw.
3. Skin Neoplasms/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
5. or/1-4
6. "Quality of Life"/
7. (qol or (quality adj2 life)).ab,ti.
8. (value adj2 (money or monetary)).tw.
9. value of life/
10. quality adjusted life year/
11. quality adjusted life.tw.
12. (qaly$ or qald$ or qale$ or qtime$).tw.
13. disability adjusted life.tw.
14. daly$.tw.
15. health status indicators/
16. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
17. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
18. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
19. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
20. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
21. (euroqol or euro qol or eq5d or eq 5d).tw.
22. (hql or hqol or h qol or hrqol or hr qol).tw.
23. (hye or hyes).tw.
24. health$ year$ equivalent$.tw.
25. health utilit$.tw.
26. (hui or hui1 or hui2 or hui3).tw.
27. disutilit$.tw.
28. rosser.tw.
29. (quality adj2 wellbeing).tw.
30. qwb.tw.
31. (willingness adj2 pay).tw.
32. standard gamble$.tw.
33. time trade off.tw.
34. time tradeoff.tw.
35. tto.tw.
36. letter.pt.

37. editorial.pt.
38. comment.pt.
39. 36 or 37 or 38
40. or/6-35
41. 40 not 39
42. 5 and 41
43. limit 42 to yr="1970 -Current"

Embase: Ovid. 1974 to 2013 May 08

1. melanoma/
2. melanoma$.tw.
3. skin tumor/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
5. or/1-4

6. "Quality of Life"/
7. (qol or (quality adj2 life)).ti,ab.
8. (value adj2 (money or monetary)).tw.
9. socioeconomics/
10. quality adjusted life year/
11. (qaly$ or qald$ or qale$ or qtime$).tw.
12. disability adjusted life.tw.
13. daly$.tw.
14. health survey/
15. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
16. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
17. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
18. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
19. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
20. (euroqol or euro qol or eq5d or eq 5d).tw.
21. (hql or hqol or h qol or hrqol or hr qol).tw.
22. (hye or hyes).tw.
23. health$ year$ equivalent$.tw.
24. health utilit$.tw.
25. (hui or hui1 or hui2 or hui3).tw.
26. disutilit$.tw.
27. rosser.tw.
28. (quality adj2 wellbeing).tw.
29. qwb.tw.
30. (willingness adj2 pay).tw.
31. standard gamble$.tw.
32. time trade off.tw.
33. time tradeoff.tw.
34. tto.tw.
35. letter.pt.
36. editorial.pt.
37. comment.pt.
38. 35 or 36 or 37
39. or/6-34
40. 39 not 38
41. 5 and 40

Cochrane Library

NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	MeSH descriptor: [Quality of Life] this term only
#2	(qol or (quality next/2 life)):ti,ab,kw
#3	MeSH descriptor: [Value of Life] this term only
#4	value and (money or monetary):ti,ab,kw
#5	MeSH descriptor: [Quality-Adjusted Life Years] this term only
#6	(quality adjusted life):ti,ab,kw
#7	(qaly* or qald* or qale* or qtime*):ti,ab,kw
#8	disability adjusted life:ti,ab,kw
#9	daly*:ti,ab,kw
#10	MeSH descriptor: [Health Status Indicators] explode all trees
#11	sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six:ti,ab,kw
#12	sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six:ti,ab,kw
#13	sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve:ti,ab,kw
#14	sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen:ti,ab,kw
#15	sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty:ti,ab,kw
#16	euroqol or euro qol or eq5d or eq 5deuroqol or euro qol or eq5d or eq 5d:ti,ab,kw
#17	hql or hqol or h qol or hrqol or hr qol:ti,ab,kw
#18	hye or hyes:ti,ab,kw
#19	health* year* equivalent*:ti,ab,kw
#20	health utilit*:ti,ab,kw
#21	hui or hui1 or hui2 or hui3:ti,ab,kw
#22	disutilit*:ti,ab,kw
#23	rosser:ti,ab,kw
#24	qwb:ti,ab,kw
#25	standard gamble*:ti,ab,kw
#26	willingness to pay:ti,ab,kw
#27	quality of wellbeing:ti,ab,kw
#28	time trade off:ti,ab,kw
#29	time tradeoff:ti,ab,kw
#30	tto:ti,ab,kw
#31	letter:pt
#32	editorial:pt
#33	comment:pt
#34	#31 or #32 or #33
#35	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#36	#35 not #34
#37	MeSH descriptor: [Melanoma] explode all trees
#38	melanoma*:ti,ab,kw
#39	MeSH descriptor: [Skin Neoplasms] explode all trees
#40	(skin next/3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*)):ti,ab
#41	#37 or #38 or #39 or #40
#42	#36 and #41 from 1970 to 2013

Cinahl: EBSCO. 1981 to present

S42	S5 AND S41 Limiters - Published Date from: 19700101-20130631
S41	S40 NOT S39
S40	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or

	S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35
S39	S36 or S37 or S38
S38	PT comment
S37	PT editorial
S36	PT letter
S35	TI tto or AB tto
S34	TI time tradeoff or AB time tradeoff
S33	TI time trade off or AB time trade off
S32	TI standard gamble* or AB standard gamble*
S31	TI willingness N2 pay or AB willingness N2 pay
S30	TI qwb or AB qwb
S29	TI quality N2 wellbeing or AB quality N2 wellbeing
S28	TI rosser or AB rosser
S27	TI disutilit* or AB disutilit*
S26	TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)
S25	TI health utilit* or AB health utilit*
S24	TI health* year* equivalent* or AB health* year* equivalent*
S23	TI (hye or hyes) or AB (hye or hyes)
S22	TI (hql or hqol or h qol or hrqol or hr qol) or AB (hql or hqol or h qol or hrqol or hr qol)
S21	TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)
S20	TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
S19	TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)
S18	TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
S17	TI quality adjusted life or AB quality adjusted life
S16	TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
S15	TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
	(MH "Health Status Indicators")
S14	TI daly* or AB daly*
S13	TI disability adjusted life or AB disability adjusted life
S12	TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)
S11	(MH "Quality-Adjusted Life Years")
S10	(MH "Economic Value of Life")
S9	TI value and TI (money or monetary) or AB value and AB (money or monetary)
S8	TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))
S7	(MH "Quality of Life")
S6	S1 or S2 or S3 or S4 (skin N3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*)) (MH "Skin Neoplasms") melanoma*
S5	(MH "Melanoma")
S4	
S3	
S2	
S1	

EconLit: Ovid. 1961 to April 2013

1. melanoma$.tw.
2. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
3. 1 or 2

The inclusion and exclusion criteria.

Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Study Type	Studies reporting utilities or HRQL data	The aim of the review was to identify relevant utility data
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population
Interventions	There was no restriction to intervention	To identify all relevant papers
Outcomes	Any reported measurement in the form of utilities was included. Also utility values mapped from a measure of HRQL or a measure of HRQL that can be mapped using only published information	The aim of the review was to identify relevant utility studies
Exclusion Criteria		
Category	**Exclusion criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of utility studies (although reference lists of these were being hand-searched)	Primary study articles were required

Appendix 8: Reference of full texts reviewed in the original economic SLR searches and justification for inclusion and exclusion

Table 21: Full text cost effectiveness studies reviewd in the original search (November 2014) and justification for inclusion and exclusion.

Author	Year	Title	Journal/Periodical Title	Included	Reason for exclusion
Daud,A.	2014	Recent advances in melanoma therapy	Journal of Managed Care Medicine	No	Wrong Study Type

Table 22: Full text cost and resource use studies reviewd in the original search (November 2014) and justification for inclusion and exclusion.

Author	Year	Title	Journal/Periodical Title	Included	Reason for exclusion
Curl,P. Vujic,I. van 't Veer,L.J. Ortiz-Urda,S. Kahn,J.G. Curl,Patti Vujic,Igor van 't Veer,Laura J. Ortiz-Urda,Susana Kahn,James G.	2014	Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma	PLoS ONE [Electronic Resource]	No	Not a UK study
Delea,T.E. Amdahl,J. Wang,A. Amonkar,M. Smith,H.W. Balaratnam,S. Stapelkamp,C.	2014	Cost-utility analysis of dabrafenib/trametinib combination (d+t) for BRAFV600 mutation-positive metastatic melanoma (MM) from the united kingdom (UK) national health service (NHS) perspective	Value in Health	No	Not enough information
Hatswell,A.J. Porter,J. Hertel,N. Lee,D.	2014	The cost of costing treatments incorrectly: Errors in the application of drug prices in economic models due to differing patient weights	Value in Health	Yes	
Hauschild,A.	2013	Response to a costly revolution for a subgroup of	British Journal of	No	Does not report

		patients with metastatic melanoma	Dermatology		costs
Jarkowski,A.,III Nestico,J.S. Vona,K.L. Khushalani,N.I. Jarkowski,Anthony Nestico,Jill S. Vona,Karen L. Khushalani,Nikhil I.	2014	Dose rounding of ipilimumab in adult metastatic melanoma patients results in significant cost savings	Journal of Oncology Pharmacy Practice	No	Not a UK study
Lee,D. Porter,J. Hatswell,A.J. Hertel,N. Walker,A.	2014	Cost-effectiveness analysis of ipilimumab in previously untreated patients with unresectable malignant melanoma in Scotland	Value in Health	No	Not enough information
Lee,N.R. Lee,S.H. Kim,J. Son,S.K. Seo,H.J. Park,D.A.	2014	Cost-utility analysis of dabraf enib/trametinib combination (D+T) for Brafv600 mutation-positive metastatic melanoma (MM) from the United Kingdom (UK) National Health Service (NHS) perspective	Value in Health	No	Not enough information
NIHR,H.S.C.	2013	MEK162 for NRAS mutation positive advanced malignant melanoma ? first and second line (Structured abstract)	Health Technology Assessment Database	Yes	
NIHR,H.S.C.	2013	MK-3475 for advanced melanoma ? first or second line, in patients naïve to ipilimumab (Structured abstract)	Health Technology Assessment Database	Yes	
NIHR,H.S.C.	2013	Lambrolizumab for advanced melanoma ? second line; refractory to ipilimumab (Structured abstract)	Health Technology Assessment Database	No	Does not report costs
Semlitsch,T. Zengerer,A. Jeitler,K.	2013	Dabrafenib (Tafinlar®) in previously untreated subjects with BRAF mutation-positive advanced (stage III) or metastatic (stage IV) melanoma (Structured abstract)	Health Technology Assessment Database	No	Not a UK study

Vouk,K. Benter,U. Amonkar,M. Stapelkamp,C.	2014	Economic burden of adverse effects associated with metastatic melanoma (MM) treatments in the United Kingdom	Value in Health	No	Review study

Table 23: Full text health related quality of life studies reviewd in the original search (November 2014) and justification for inclusion and exclusion.

Author	Year	Title	Journal/Periodical Title	Included	Reason for exclusion
	2013	Society for Melanoma Research 2012 Congress	Pigment Cell and Melanoma Research	No	Does not report utilities
Aceituno,S. Canal,C. Paz,S. Gonzalez,P. Marquez-Rodas,I.	2014	Cost-effectiveness of ipilimumab for previously untreated patients with advanced metastatic melanoma in Spain	Value in Health	No	Does not report utilities
Boss,C. Brenner,E. Braumuller,H. Wieder,T. Kayser,S. Feuchtinger,T. Rocken,M.	2014	Clearance of malignant ascites by interferon-induced senescence	Journal of Investigative Dermatology	No	Does not report utilities

Boss,C. Brenner,E. Braumuller,H. Wieder,T. Rocken,M.	2014	Senescence induction in metastatic melanoma during immunotherapy with interferon-alpha	Journal of Investigative Dermatology	No	Not enough information
Brandberg,Y. Johansson,H. Aamdal,S. Bastholt,L. Hernberg,M. Stierner,U. von der,Maase H. Hansson,J. Nordic Melanoma Cooperative Group. Brandberg,Yvonne Johansson,Hemming Aamdal,Steinar Bastholt,Lars Hernberg,Michaela Stierner,Ulrika von der Maase,Hans Hansson,Johan Nordic Melanoma Cooperative Group.	2013	Role functioning before start of adjuvant treatment was an independent prognostic factor for survival and time to failure. A report from the Nordic adjuvant interferon trial for patients with high-risk melanoma	Acta Oncologica	No	Not enough information

Cooper,A.B. Griffin,K.C. Chiang,Y.S. Ross,M.I. Lee,J.E. Gershenwald,J.E. Royal,R.E. Lucci,A. Cormier,J.N.	2014	Do patient-reported quality-of-life responses in melanoma patients vary by stage?	Journal of Clinical Oncology	no	wrong population

Corrie,P.G. Marshall,A. Dunn,J.A. Middleton,M.R. Nathan,P.D. Gore,M. Davidson,N. Nicholson,S. Kelly,C.G. Marples,M. Danson,S.J. Marshall,E. Houston,S.J. Board,R.E. Waterston,A.M. Nobes,J.P. Harries,M. Kumar,S. Young,G. Lorigan,P. Corrie,Pippa G. Marshall,Andrea Dunn,Janet A. Middleton,Mark R. Nathan,Paul D. Gore,Martin Davidson,Neville Nicholson,Steve Kelly,Charles G. Marples,Maria Danson,Sarah J. Marshall,Ernest Houston,Stephen J.	2014	Adjuvant bevacizumab in patients with melanoma at high risk of recurrence (AVAST-M): preplanned interim results from a multicentre, open-label, randomised controlled phase 3 study	Lancet Oncology	No	Not enough information

Board,Ruth E. Waterston,Ashita M. Nobes,Jenny P. Harries,Mark Kumar,Satish Young,Gemma Lorigan,Paul					

Delea,T.E. Amdahl,J. Wang,A. Amonkar,M. Smith,H.W. Balaratnam,S. Stapelkamp,C.	2014	Cost-utility analysis of dabrafenib/trametinib combination (d+t) for BRAFV600 mutation-positive metastatic melanoma (MM) from the united kingdom (UK) national health service (NHS) perspective	Value in Health	No	Not enough information
Drabe,N. Jenewein,J. Weidt,S. Seiler,A. Witzemann,L. Meier,C. Buchi,S. Schad,K. Nunez,D.G.	2014	When it can't been healed: A longitudinal qualitative study of relationship changes in couples facing advanced melanoma	Psycho-Oncology	No	Does not report utilities
Dubravcic,I.D. Brozic,J.M. Aljinovic,A. Sindik,J. Dubravcic,Iva Dumbovic Brozic,Jasmina Maric Aljinovic,Ana Sindik,Josko	2014	Quality of life in Croatian metastatic melanoma patients	Collegium Antropologicum	No	Not enough information

Flaherty,K. Arenberger,P. Ascierto,P.A. De Groot,J.W. Hallmeyer,S. Long,G.V. Lotem,M. Marples,M. Schadendorf,D. Starodub,A. Taylor,M.H. Wolter,P. Yamazaki,N. Wasserman,E. Ford,J. Weill,M. Dummer,R.	2014	NEMO: A phase 3 trial of binimetinib (MEK162) versus dacarbazine in patients with untreated or progressed after first-line immunotherapy unresectable or metastatic NRAS-mutant cutaneous melanoma	Journal of Clinical Oncology	no	Does not report utilities
Fogarty,G.B. Middleton,M.	2013	ANZMTG 01.07 An international Phase III trial of whole brain radiotherapy following local treatment of 1-3 intracranial metastases of melanoma needs the help of British neurological surgeons	British Journal of Neurosurgery	no	wrong population

Grob,J.J. Amonkar,M.M. Martin-Algarra,S. Demidov,L.V. Goodman,V. Grotzinger,K. Haney,P. Kampgen,E. Karaszewska,B. Mauch,C. Miller,W.H.,Jr. Millward,M. Mirakhur,B. Rutkowski,P. Chiarion-Sileni,V. Swann,S. Hauschild,A.					
Grob,J.J. Amonkar,M.M. Martin-Algarra,S. Demidov,L.V. Goodman,V. Grotzinger,K. Haney,P. Kampgen,E. Karaszewska,B. Mauch,C. Miller,W.H.J. Millward,M. Mirakhur,B. Rutkowski,P. Chiarion-Sileni,V. Swann,S.	2014	Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: quality-of-life analyses of the BREAK-3 study comparing dabrafenib with dacarbazine	Annals of Oncology	No	Not enough information

Hauschild,A.					

Harvey,B. Lee,D. Gaudin,A.-F. Gueron,B. Bregman,B. Lebbe,C. Borget,I.	2013	Changes in the quality of life of advanced melanoma patients after 12 weeks of treatment with ipilimumab compared to gp100 in a phase III clinical trial	Journal of Clinical Oncology	No	Not enough information
Hatswell,A.J. Pennington,B. Pericleous,L. Rowen,D. Lebmeier,M. Lee,D.	2014	Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death	Health and Quality of Life Outcomes	Yes	
Kahler,K.C. Egberts,F. Gutzmer,R. Kahler,Katharina C. Egberts,Friederike Gutzmer,Ralf	2013	Palliative treatment of skin metastases in dermato-oncology	Journal der Deutschen Dermatologischen Gesellschaft	No	Does not report utilities
Kovacs,P. Panczel,G. Borbola,K. Juhasz,G. Liszkay,G.	2013	Psychological changes during ipilimumab treatment-first experiences	JDDG - Journal of the German Society of Dermatology	no	Does not report utilities
Martin,R.C.G.	2013	A Phase I evaluation of transcatheter arterial chemoembolization with doxorubicin-loaded LC beads (DEBDOX) in the treatment of liver metastases: A multicenter feasibility trial	Digestive and Liver Disease	No	Does not report utilities

Porter,J. Lee,D. Hertel,N. Hatswell,A.J.	2014	Patient reported utilities in first-line advanced or metastatic melanoma: Analysis of trial CA 184-024	Value in Health	Yes	
Schadendorf,D. Amonkar,M.M. Milhem,M. Grotzinger,K. Demidov,L.V. Rutkowski,P. Garbe,C. Dummer,R. Hassel,J.C. Wolter,P. Mohr,P. Trefzer,U. Lefeuvre-Plesse,C. Rutten,A. Steven,N. Ullenhag,G. Sherman,L. Wu,F.S. Patel,K. Casey,M. Robert,C.	2014	Functional and symptom impact of trametinib versus chemotherapy in BRAF V600E advanced or metastatic melanoma: Quality-of-life analyses of the METRIC stud	Annals of Oncology	No	Not enough information

Shih,V. Ten Ham,R.M.T. Bui,C.T. Tran,D.N. Wilson,L.S.	2014	Braf targeted therapies for the treatment of metastatic melanoma: A cost-effectiveness analysis	Value in Health	No	Not enough information

Table 24: Full text cost and resouce use studies reviewd in the original search (March 2013) and justification for inclusion and exclusion.

					Exclusion				
				Inclusion	Wrong study type/ irrelevant outcomes	Wrong population (disease)	Wrong population (country)	Duplicate/ review	More recent data available
Author	**Date**	**Title**	**Journal**						
B. Arondekar; S. M. Curkendall; M. Monberg; B. Mirakhur; A. K. Oglesby; G. M. Lenhart; N. M. Meyer; B. Arondekar; S. M. Curkendall; M. Monberg; B. Mirakhur; A. K. Oglesby; G. M. Lenhart; N. M. Meyer	2013	Economic burden associated with adverse events in patients with metastatic melanoma	Value in Health	N			X		

C. B. Bares; P. C. Trask; S. M. Schwartz	2002	An exercise in cost-effectiveness analysis: Treating emotional distress in melanoma patients	Journal of Clinical Psychology in Medical Settings	N			X		

E. Bastiaannet; C. Uyl; A. H. Brouwers; E. J. Van De Jagt; O. S. Hoekstr; J. F. Thompson; H. J. Hoekstra	2010	Cost-effectiveness of adding FDG-PET or CT to the diagnostic work-up of melanoma patients stage III	Pigment Cell and Melanoma Research	N			X		

E. Bastiaannet; C. A. Uyl-de Groot; A. H. Brouwers; E. J. van der Jagt; O. S. Hoekstra; W. Oyen; F. Verzijlbergen; O. B. van; J. F. Thompson; H. J. Hoekstra; E. Bastiaannet; C. A. Uyl-de Groot; A. H. Brouwers; E. J. van der Jagt; O. S. Hoekstra; W. Oyen; F. Verzijlbergen; B. van Ooijen; J. F. Thompson; H. J. Hoekstra	2012	Cost-effectiveness of adding FDG-PET or CT to the diagnostic work-up of patients with stage III melanoma	Annals of Surgery	N			X		

I. Chiorean; L. Lupsa; L. Neamtiu; M. Crisan; I. Chiorean; L. Lupsa; L. Neamtiu; M. Crisan	2012	Medicoeconomic index for photo-induced skin cancers	Computational & Mathematical Methods in Medicine	N	X				
E. T. Creagan; E. T. Creagan	1989	Malignant melanoma: cost and reimbursement issues. [Review] [6 refs]	Seminars in Oncology	N	X				
R. A. Diaz; R. Sidhu; J. Robertson; J. Adam; R. A. Diaz; R. Sidhu; J. Robertson; J. Adam	2013	NICE guidance on ipilimumab for previously treated advanced melanoma	Lancet Oncology	N	X				

S. Dixon; S. J. Walters; L. Turner; B. W. Hancock; S. Dixon; S. J. Walters; L. Turner; B. W. Hancock	2006	Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial	British Journal of Cancer	Y					

A. M. Eggermont; A. M. Eggermont	1997	The current EORTC Melanoma Cooperative Group adjuvant trial programme on malignant melanoma: prognosis versus efficacy, toxicity and costs. [Review] [37 refs]	Melanoma Research	N	X				
C. Fellner; C. Fellner	2012	Ipilimumab (yervoy) prolongs survival in advanced melanoma: serious side effects and a hefty price tag may limit its use	P & T	N	X				
B. E. Hillner; J. M. Kirkwood; B. E. Hillner; J. M. Kirkwood	1997	Economic analyses of benefit from interferon-alpha 2B in high-risk melanoma: trade-offs between completeness, simplicity and clarity	European Journal of Cancer	N		X			

B. Hocking	1991	Economic aspects of skin cancer prevention	Journal of Occupational Health and Safety - Australia and New Zealand	N			X		
B. Hocking	1991	Cost-benefit analyses of occupational health and safety in Telecom	Journal of Occupational Health and Safety - Australia and New Zealand	N			X		

H. J. Hoekstra	2010	Cost effectiveness of melanoma follow-up	Pigment Cell and Melanoma Research	N	X				
W. Hoffmann; W. Hoffmann	1998	[Economic analysis of adjuvant interferon-alpha-2-therapy in high risk melanoma patients based on results of the ECOG 1684 Study Group]. [Review] [5 refs] [German]	Strahlentherapie und Onkologie	N	X				

E. Hormbrey; P. Banwell; P. Gillespie; P. Budny; E. Hormbrey; P. Banwell; P. Gillespie; P. Budny	2000	Melanoma follow-up: protocols and practice	British Journal of Dermatology	N	X				

K. Johnston; A. Levy; P. Lorigan; M. Maio; C. Lebbe; M. Middleton; A. Testori; C. Bedane; C. Konto; A. Dueymes; B. M. van	2011	Economic impact of healthcare resource utilisation patterns among patients diagnosed with advanced melanoma in the Uk, Italy, and France: Results from a retrospective, longitudinal survey (melody study)	Value in Health	N					X

K. Johnston; A. R. Levy; P. Lorigan; M. Maio; C. Lebbe; M. Middleton; A. Testori; C. Bedane; C. Konto; A. Dueymes; U. Sbarigia; B. M. van; K. Johnston; A. R. Levy; P. Lorigan; M. Maio; C. Lebbe; M. Middleton; A. Testori; C. Bedane; C. Konto; A. Dueymes; U. Sbarigia; M. van Baardewijk	2012	Economic impact of healthcare resource utilisation patterns among patients diagnosed with advanced melanoma in the United Kingdom, Italy, and France: results from a retrospective, longitudinal survey (MELODY study)	European Journal of Cancer	Y					
M. H. Kanzler; M. H. Kanzler	1999	An estimate of the annual direct cost of treating cutaneous melanoma	Journal of the American Academy of Dermatology	N			X		

B. Krug; R. Crott; I. Roch; M. Lonneux; C. Beguin; J. F. Baurain; A. S. Pirson; B. T. Vander; B. Krug; R. Crott; I. Roch; M. Lonneux; C. Beguin; J. F. Baurain; A. S. Pirson; T. Vander Borght	2010	Cost-effectiveness analysis of FDG PET-CT in the management of pulmonary metastases from malignant melanoma	Acta Oncologica	N			X		

A. Lafuma; B. Dreno; M. Delaunay; C. Emery; F. Fagnani; K. Hieke; J. J. Bonerandi; J. J. Grob; F. C. G. o. Melanoma.; A. Lafuma; B. Dreno; M. Delaunay; C. Emery; F. Fagnani; K. Hieke; J. J. Bonerandi; J. J. Grob; F. C. G. o. Melanoma.	2001	Economic analysis of adjuvant therapy with interferon alpha-2a in stage II malignant melanoma	European Journal of Cancer	N			X		

D. Lee; B. Winn; M. Lebmeier; A. Batty	2012	Modelling the cost-effectiveness of ipilimumab for previouslytreated, metastatic melanoma	Value in Health	Y					

P. Lorigan; M. Maio; M. Middleton; A. Testori; C. Bedane; B. M. van; C. Konto; A. Dueymes; C. Lebbe	2010	Health-care resource utilization in advanced melanoma: An analysis from the melody observational study	Value in Health	Y					

S. Morris; B. Cox; N. Bosanquet; S. Morris; B. Cox; N. Bosanquet	2009	Cost of skin cancer in England	European Journal of Health Economics	Y					
N. Poulios; L. Pinto; R. Carlton; T. Bramley; R. Tierney; J. F. Palma; N. Poulios; L. Pinto; R. Carlton; T. Bramley; R. Tierney; J. F. Palma	2013	Cost analysis model between the cobas braf test and sanger sequencing when treating malignant melanoma based on the presence of v600 mutations	Value in Health	N			X		
J. Smith	2011	NICE rejects ipilimumab, citing cost & lack of follow-up	Oncology Report	N	X				

D. Strens; P. Specenier; M. Peeters	2012	Real world management and costs in metastatic malignant melanoma (MM) patients: A pilot study based on an institutional patient registry	Value in Health	N			X		
A. C. van Akkooi; T. Nijsten; A. C. J. van Akkooi; T. Nijsten	2013	A costly revolution for a subgroup of patients with metastatic melanoma	British Journal of Dermatology	N	X				

F. Vekeman; M. Cloutier; S. Yermakov; M. Amonkar; B. Arondekar; M. S. Duh; F. Vekeman; M. Cloutier; S. Yermakov; M. Amonkar; B. Arondekar; M. S. Duh	2013	Incremental cost of brain metastases among patients with metastatic melanoma	Value in Health	N			X		
F. Witte	2006	Malignant melanoma: Interferon therapy: Cost effectiveness and quality of life	Tumor Diagnostik und Therapie	N				X	
F. Witte	2006	Malignant melanoma: Interferon therapy is not cost-effective and worsens quality of life	Gesundheitsokonomie und Qualitatsmanagement	N				X	

Table 25: Full text health related quality of life studies reviewd in the original search (March 2013) and justification for inclusion and exclusion.

					Inclusion	Reason for Exclusion			
Record	**Author**	**Date**	**Title**	**Journal**		Wrong study type	PopN	Irrelevant QoL outcome	Duplicate/ Review

87	R. L. Askew; R. J. Swartz; Y. Xing; S. B. Cantor; M. I. Ross; J. E. Gershenwald; J. L. Palmer; J. E. Lee; J. N. Cormier; R. L. Askew; R. J. Swartz; Y. Xing; S. B. Cantor; M. I. Ross; J. E. Gershenwald; J. L. Palmer; J. E. Lee; J. N. Cormier	2011	Mapping FACT-melanoma quality-of-life scores to EQ-5D health utility weights	Value in Health	Y				

			Predictors of quality of life in patients with skin melanoma at the dermatology department of the Porto Alegre Teaching Hospital						
120	M. T. Barbato; L. Bakos; R. M. Bakos; R. Prieb; C. D. Andrade; M. T. Barbato; L. Bakos; R. M. Bakos; R. Prieb; C. D. d. Andrade	2011		Anais Brasileiros de Dermatologia	N		X		
121	C. B. Bares; P. C. Trask; S. M. Schwartz	2002	An exercise in cost-effectiveness analysis: treating emotional distress in melanoma patients (Structured abstract)	Journal of Clinical Psychology in Medical Settings.	N	X			

129	V. Barzey; M. B. Atkins; L. P. Garrison; Y. Asukai; S. Kotapati; J. R. Penrod; V. Barzey; M. B. Atkins; L. P. Garrison; Y. Asukai; S. Kotapati; J. R. Penrod	2013	Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis.[Erratum appears in J Med Econ. 2013;16(2):212]	Journal of Medical Economics	Y				

139	A. Batty; B. Winn; M. Lebmeier; D. Rowen; D. Lee	2012	A comparison of patient and general-population utility values for advanced melanoma in health economic modelling	Value in Health	Y				

138	A. J. Batty; D. Fisher; B. Winn; Q. Wang; K. Tolley; D. Rowen	2011	Estimating quality of life in advanced melanoma; A comparison of standard gamble, SF-36 mapped, and eortc QLQ-c30 mapped utilities	Value in Health	Y				

142	G. F. Beadle; P. M. Yates; J. M. Najman; A. Clavarino; D. Thomson; G. Williams; L. Kenny; S. Roberts; B. Mason; D. Schlect	2004	Illusions in advanced cancer: The effect of belief systems and attitudes on quality of life	Psycho-Oncology	N		X		

148	J. R. Beguerie; J. Xingzhong; R. P. Valdez; J. R. Beguerie; J. Xingzhong; R. P. Valdez	2010	Tamoxifen vs. non-tamoxifen treatment for advanced melanoma: a meta-analysis. [Review]	International Journal of Dermatology	N				X

158	C. M. Bender; J. M. Yasko; J. M. Kirkwood; C. Ryan; J. Dunbar-Jacob; T. Zullo; C. M. Bender; J. M. Yasko; J. M. Kirkwood; C. Ryan; J. Dunbar-Jacob; T. Zullo	2000	Cognitive function and quality of life in interferon therapy for melanoma	Clinical Nursing Research	N		X		
179	K. M. Beusterien; S. M. Szabo; S. Kotapati; J. Mukherjee; A. Hoos; P. Hersey; M. R. Middleton; A. R. Levy; K. M. Beusterien; S. M. Szabo; S. Kotapati; J. Mukherjee; A. Hoos; P. Hersey; M. R. Middleton; A. R. Levy	2009	Societal preference values for advanced melanoma health states in the United Kingdom and Australia	British Journal of Cancer	Y				

237	A. Bottomley; C. Coens; S. Suciu; M. Santinami; W. Kruit; A. Testori; J. Marsden; C. Punt; F. Sales; M. Gore; R. Mackie; Z. Kusic; R. Dummer; P. Patel; D. Schadendorf; A. Spatz; U. Keilholz; A. Eggermont; A. Bottomley; C. Coens; S. Suciu; M. Santinami; W. Kruit; A. Testori; J. Marsden; C. Punt; F. Sales; M. Gore; R. Mackie; Z. Kusic; R. Dummer; P. Patel; D. Schadendorf; A. Spatz; U. Keilholz; A. Eggermont	2009	Adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma: a phase III randomized controlled trial of health-related quality of life and symptoms by the European Organisation for Research and Treatment of Cancer Melanoma Group.[Erratum appears in J Clin Oncol. 2009 Sep 20;27(27):4630 Note: Dosage error in published abstract; MEDLINE/PubMed abstract corrected]	Journal of Clinical Oncology	N	X			

254	Y. Brandberg; S. Aamdal; L. Bastholt; M. Hernberg; U. Stierner; M. H. von der; J. Hansson; Y. Brandberg; S. Aamdal; L. Bastholt; M. Hernberg; U. Stierner; H. von der Maase; J. Hansson	2012	Health-related quality of life in patients with high-risk melanoma randomised in the Nordic phase 3 trial with adjuvant intermediate-dose interferon alfa-2b	European Journal of Cancer	N		X		

313	P. N. Butow; A. S. Coates; S. M. Dunn; P. N. Butow; A. S. Coates; S. M. Dunn	1999	Psychosocial predictors of survival in metastatic melanoma	Journal of Clinical Oncology	N			X	

329	L. G. Campana; S. Valpione; V. Chiarion-Sileni; C. R. Rossi	2011	Health-related quality of life outcomes in advanced melanoma patients after palliative treatment with Bleomycin-Based Electrochemotherapy	European Journal of Cancer	N			X	

338	E. D. Capovilla; S. Serpentini; R. Spina; V. Chiarion-Sileni; M. Rastrelli; L. G. Campana; M. Giacobbo	2011	Quality of life and psychological well-being in melanoma survivors	Psycho-Oncology	N			X	

			Individualized quality of life, standardized quality of life, and distress in patients undergoing a phase I trial of the novel therapeutic Reolysin (reovirus)						
346	L. E. Carlson; B. D. Bultz; D. G. Morris	2005		Health and Quality of Life Outcomes	N		X		

356	R. P. Cashin; P. Lui; M. Machado; M. E. Hemels; P. K. Corey-Lisle; T. R. Einarson; R. P. Cashin; P. Lui; M. Machado; M. E. H. Hemels; P. K. Corey-Lisle; T. R. Einarson	2008	Advanced cutaneous malignant melanoma: a systematic review of economic and quality-of-life studies. [Review] [33 refs]	Value in Health	N				X

364	Y. Cemal; S. Jewell; C. R. Albornoz; A. Pusic; B. J. Mehrara	2013	Systematic review of quality of life and patient reported outcomes in patients with oncologic related lower extremity lymphedema	Lymphatic Research and Biology	N		X		

366	P. Ceylan; S. Ozkan	2011	Malignant melanoma patients' anxiety-depression levels and quality of life	Psycho-Oncology	N		X		

442	L. Cohen; P. A. Parker; J. Sterner; M. C. De; L. Cohen; P. A. Parker; J. Sterner; C. De Moor	2002	Quality of life in patients with malignant melanoma participating in a phase I trial of an autologous tumour-derived vaccine	Melanoma Research	N			X	

466	J. N. Cormier; R. L. Askew; J. N. Cormier; R. L. Askew	2011	Assessment of patient-reported outcomes in patients with melanoma. [Review]	Surgical Oncology Clinics of North America	N	X			
467	J. N. Cormier; K. D. Cromwell; M. I. Ross; J. N. Cormier; K. D. Cromwell; M. I. Ross	2012	Health-related quality of life in patients with melanoma: overview of instruments and outcomes. [Review]	Dermatologic Clinics	N				X

468	J. N. Cormier; L. Davidson; Y. Xing; K. Webster; D. Cella	2005	Measuring quality of life in patients with melanoma: Development of the FACT-Melanoma subscale	Journal of Supportive Oncology	N	X			

471	J. N. Cormier; Y. Xing; M. Ding; S. B. Cantor; K. J. Salter; J. E. Lee; P. F. Mansfield; J. E. Gershenwald; M. I. Ross; J. N. Cormier; Y. Xing; M. Ding; S. B. Cantor; K. J. Salter; J. E. Lee; P. F. Mansfield; J. E. Gershenwald; M. I. Ross	2007	Cost effectiveness of adjuvant interferon in node-positive melanoma	Journal of Clinical Oncology	Y				

486	R. Crott; F. Ali; S. Burdette-Radoux; R. Crott; F. Ali; S. Burdette-Radoux	2004	Cost-utility of adjuvant high-dose interferon alpha therapy in stage III cutaneous melanoma in Quebec	Value in Health	N		X		

576	S. Dixon; S. J. Walters; L. Turner; B. W. Hancock; S. Dixon; S. J. Walters; L. Turner; B. W. Hancock	2006	Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial	British Journal of Cancer	Y				
836	K. Y. Graham; A. J. Longman; K. Y. Graham; A. J. Longman	1987	Quality of life and persons with melanoma. Preliminary model testing	Cancer Nursing	N			X	

865	J. Grob; S. M. Algarra; M. M. Amonkar; L. V. Demidov; V. L. Goodman; K. Grotzinger; P. Haney; E. Kampgen; B. Karaszewska; C. Mauch; J. Miller; M. Millward; B. Mirakhur; P. Rutkowski; V. C. Sileni; S. Swann; A. Hauschild	2013	Dabrafenib vs dacarbazine (DTIC) in patients with BRAF V600+ advanced and metastatic melanoma in BREAK-3: Quality of life (QOL) analysis	Pigment Cell and Melanoma Research	N			X	

924	J. Hansson; S. Aamdal; L. Bastholt; M. Hernberg; B. Nilsson; U. K. Stierner; M. H. von der; Y. Brandberg	2011	Health-related quality of life (HRQOL) in the Nordic randomized trial of adjuvant intermediate-dose interferon alfa-2b in high-risk melanoma	Journal of Clinical Oncology	N			X	

970	U. R. Hengge; A. Wallerand; A. Stutzki; N. Kockel; U. R. Hengge; A. Wallerand; A. Stutzki; N. Kockel	2007	Cost-effectiveness of reduced follow-up in malignant melanoma	Journal der Deutschen Dermatologischen Gesellschaft	N	X			

982	B. E. Hillner; B. E. Hillner	1998	Cost-effectiveness assessment of interferon alfa-2b as adjuvant therapy of high-risk resected cutaneous melanoma	European Journal of Cancer	N		X		

989	N. G. Hirst; L. G. Gordon; P. A. Scuffham; A. C. Green; N. G. Hirst; L. G. Gordon; P. A. Scuffham; A. C. Green	2012	Lifetime cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use	Value in Health	Y				

999	D. Hogg; K. Osenenko; S. M. Szabo; M. Schultz; B. M. Donato; S. Lane; A. R. Levy	2010	Standard gamble utilities for advanced melanoma health states elicited from the Canadian general public	Pigment Cell and Melanoma Research	Y				

1101	A. R. Kansal; A. J. Shaul; S. Stern; K. Busam; C. A. Doucet; D. B. Chalfin	2011	Cost-effectiveness of a fluorescence in situ hybridization (FISH) assay for the diagnosis of melanoma in the United States	Pigment Cell and Melanoma Research	N	X			

1135	G. M. Kiebert; D. L. Jonas; M. R. Middleton; G. M. Kiebert; D. L. Jonas; M. R. Middleton	2003	Health-related quality of life in patients with advanced metastatic melanoma: results of a randomized phase III study comparing temozolomide with dacarbazine	Cancer Investigation	N			X	

1142	K. L. Kilbridge; B. F. Cole; J. M. Kirkwood; F. G. Haluska; M. A. Atkins; J. C. Ruckdeschel; D. E. Sock; R. F. Nease Jr.; J. C. Weeks; K. L. Kilbridge; B. F. Cole; J. M. Kirkwood; F. G. Haluska; M. A. Atkins; J. C. Ruckdeschel; D. E. Sock; R. F. J. Nease; J. C. Weeks	2002	Quality-of-life-adjusted survival analysis of high-dose adjuvant interferon alpha-2b for high-risk melanoma patients using intergroup clinical trial data	Journal of Clinical Oncology	N			X	

1143	K. L. Kilbridge; J. C. Weeks; A. J. Sober; F. G. Haluska; C. L. Slingluff; M. B. Atkins; D. E. Sock; J. M. Kirkwood; R. F. Nease; K. L. Kilbridge; J. C. Weeks; A. J. Sober; F. G. Haluska; C. L. Slingluff; M. B. Atkins; D. E. Sock; J. M. Kirkwood; R. F. Nease	2001	Patient preferences for adjuvant interferon alfa-2b treatment	Journal of Clinical Oncology	N		X		

1158	S. M. King; P. Bonaccorsi; S. Bendeck; J. Hadley; K. Puttgen; P. G. Kolm; E. Veledar; D. Lawson; S. C. Chen; S. M. C. King; P. Bonaccorsi; S. Bendeck; J. Hadley; K. Puttgen; P. G. Kolm; E. Veledar; D. Lawson; S. C. Chen	2011	Melanoma quality of life: pilot study using utility measurements	Archives of Dermatology	Y				

1186	C. Y. Ko; M. Maggard; E. H. Livingston; C. Y. Ko; M. Maggard; E. H. Livingston	2003	Evaluating health utility in patients with melanoma, breast cancer, colon cancer, and lung cancer: a nationwide, population-based assessment	Journal of Surgical Research	N		X		

1207	S. Kotapati; S. Francis; B. Sherrill	2011	Health related quality of life (HRQL) of patients receiving ipilimumab with dacarbazine as first-line treatment for unresectable stage III/IV melanoma	Pigment Cell and Melanoma Research	N			X	

1289	D. Lee; B. Winn; M. Lebmeier; A. Batty	2012	Modelling the cost-effectiveness of ipilimumab for previouslytreated, metastatic melanoma	Value in Health	Y				

1349	C. Loquai; I. Schmidtmann; M. Beutel; C. Sunderkotter; S. Grabbe; M. Schiller; D. Nashan; C. Loquai; I. Schmidtmann; M. Beutel; C. Sunderkotter; S. Grabbe; M. Schiller; D. Nashan	2011	Quality of life in melanoma patients during adjuvant treatment with pegylated interferon-2b: patients' and doctors' views	European Journal of Dermatology	N		X		

1351	E. Losina; R. P. Walensky; A. Geller; F. C. Beddingfield III; L. L. Wolf; B. A. Gilchrest; K. A. Freedberg; E. Losina; R. P. Walensky; A. Geller; F. C. Beddingfield; L. L. Wolf; B. A. Gilchrest; K. A. Freedberg	2007	Visual screening for malignant melanoma: a cost-effectiveness analysis	Archives of Dermatology	Y				

1489	M. R. Middleton; J. J. Grob; N. Aaronson; G. Fierlbeck; W. Tilgen; S. Seiter; M. Gore; S. Aamdal; J. Cebon; A. Coates; B. Dreno; M. Henz; D. Schadendorf; A. Kapp; J. Weiss; U. Fraass; P. Statkevich; M. Muller; N. Thatcher; M. R. Middleton; J. J. Grob; N. Aaronson; G. Fierlbeck; W. Tilgen; S. Seiter; M. Gore; S. Aamdal; J. Cebon; A. Coates; B. Dreno; M. Henz; D. Schadendorf; A. Kapp; J. Weiss; U. Fraass; P. Statkevich; M. Muller; N. Thatcher	2000	Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma.[Erratum appears in J Clin Oncol 2000 Jun;18(11):2351]	Journal of Clinical Oncology	N			X	

1510	L. Misery; L. Thomas; D. Jullien; F. Cambazard; P. Humbert; L. Dubertret; L. Dehen; G. Macy; S. Boussetta; C. Taieb	2008	Comparative study of stress and quality of life in outpatients consulting for different dermatoses in 5 academic departments of dermatology	European Journal of Dermatology	N		X		

1520	P. Mohr; A. Hauschild; K. Rass; U. Trefzer; A. Enk; T. Haalck; J. Koller; R. Gutzmer; T. Kuchler	2009	Quality-of-life (QoL) impairment in melanoma patients receiving high-dose interferon alpha 2b (IFNa2b)	Journal of Clinical Oncology	N			X	

1522	P. Mohr; A. Hauschild; U. Trefzer; M. Weichenthal	2009	Quality of life in patients receiving high-dose interferon alfa-2b after resected high-risk melanoma	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	N	X			
1526	F. Mols; C. Holterhues; T. Nijsten; v. d. P.-F. LV.; F. Mols; C. Holterhues; T. Nijsten; L. van de Poll-Franse	2010	Personality is associated with health status and impact of cancer among melanoma survivors	European Journal of Cancer	N		X		

1527	F. Mols; C. Holterhues; T. Nijsten; L. Poll-Franse	2010	Personality affects health status and impact of cancer among melanoma survivors	Psycho-Oncology	N			X	

1528	F. Mols; C. Holterhues; T. Nijsten; L. V. Van De Poll-Franse	2009	Type D personality negatively affects health related quality of life among melanoma patients	Psycho-Oncology	N			X	

1537	M. M. Mooney; C. Mettlin; A. M. Michalek; N. J. Petrelli; W. G. Kraybill; M. M. Mooney; C. Mettlin; A. M. Michalek; N. J. Petrelli; W. G. Kraybill	1997	Life-long screening of patients with intermediate-thickness cutaneous melanoma for asymptomatic pulmonary recurrences: a cost-effectiveness analysis	Cancer	Y				

1555	R. L. Morton; K. Howard; J. F. Thompson; R. L. Morton; K. Howard; J. F. Thompson	2009	The cost-effectiveness of sentinel node biopsy in patients with intermediate thickness primary cutaneous melanoma	Annals of Surgical Oncology	N		X		

1821	I. Quirbt; S. Verma; T. Petrella; K. Bak; M. Charette; M. o. t. M. D. S. G. o. C. C. O. s. P. i. E.-B. Care.; I. Quirbt; S. Verma; T. Petrella; K. Bak; M. Charette; M. o. t. M. D. S. G. o. C. C. O. s. P. i. E.-B. Care.	2007	Temozolomide for the treatment of metastatic melanoma	Current Oncology	N	X			

1880	D. Revicki; S. Kotapati; A. J. van den Eertwegh; P. Lorigan; G. Linette; C. H. Ottensmeier; C. Lebbe; M. Messina; K. Abdallah; S. Wagner	2010	Health related quality of life (HRQL) outcomes of ipilimumab treatment in patients with previously treated unresectable stage III or iv melanoma (USIII/IV MEL)	Annals of Oncology	N			X	

			Impact of ipilimumab on the health-related quality of life (HRQL) of patients with previously treated unresectable stage III or IV melanoma						
1881	D. Revicki; S. Kotapati; I. Villanueva	2009		European Journal of Cancer, Supplement	N			X	

1879	D. A. Revicki; A. J. van den Eertwegh; P. Lorigan; C. Lebbe; G. Linette; C. H. Ottensmeier; S. Safikhani; M. Messina; A. Hoos; S. Wagner; S. Kotapati; D. A. Revicki; A. J. M. van den Eertwegh; P. Lorigan; C. Lebbe; G. Linette; C. H. Ottensmeier; S. Safikhani; M. Messina; A. Hoos; S. Wagner; S. Kotapati	2012	Health related quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment	Health & Quality of Life Outcomes	N			X	

1912	D. W. Robinson Jr.; J. N. Cormier; N. Zhao; C. M. Uhlar; D. A. Revicki; D. Cella; D. W. J. Robinson; J. N. Cormier; N. Zhao; C. M. Uhlar; D. A. Revicki; D. Cella	2012	Health-related quality of life among patients with metastatic melanoma: results from an international phase 2 multicenter study	Melanoma Research	N			X	

1994	D. Schadendorf; M. Milhem; L. V. Demidov; P. Rutkowski; C. Garbe; R. Dummer; J. Hassel; P. Wolter; P. Mohr; U. Trefzer; C. Lefeuvre-Plesse; A. Rutten; N. Steven; G. Ullenhag; K. Grotzinger; M. M. Amonkar; M. Casey; L. J. Sherman; F. S. Wu; C. Robert	2013	Trametinib (T) vs chemotherapy (C) in patients with BRAF V600E+ metastatic melanoma (MM): Quality of life (QOL) analysis	Pigment Cell and Melanoma Research	N			X	

2082	V. Sigurdardottir; C. Bolund; Y. Brandberg; M. Sullivan; V. Sigurdardottir; C. Bolund; Y. Brandberg; M. Sullivan	1993	The impact of generalized malignant melanoma on quality of life evaluated by the EORTC questionnaire technique	Quality of Life Research	N			X	

2083	V. Sigurdardottir; C. Bolund; B. Nilson	1995	Quality of life and ethics: Opinions about chemotherapy among patients with advanced melanoma, next of kin and care-providers	Psycho-Oncology	N			X	

2084	V. Sigurdardottir; C. Bolund; M. Sullivan; V. Sigurdardottir; C. Bolund; M. Sullivan	1996	Quality of life evaluation by the EORTC questionnaire technique in patients with generalized malignant melanoma on chemotherapy	Acta Oncologica	N			X	

2085	V. Sigurdardottir; Y. Brandberg; M. Sullivan; V. Sigurdardottir; Y. Brandberg; M. Sullivan	1996	Criterion-based validation of the EORTC QLQ-C36 in advanced melanoma: the CIPS questionnaire and proxy raters	Quality of Life Research	N			X	

2247	P. C. Trask; A. G. Paterson; K. A. Griffith; M. B. Riba; J. L. Schwartz; P. C. Trask; A. G. Paterson; K. A. Griffith; M. B. Riba; J. L. Schwartz	2003	Cognitive-behavioral intervention for distress in patients with melanoma: comparison with standard medical care and impact on quality of life	Cancer	N		X		

2345	A. Waldmann; S. Nolte; R. Pritzkuleit; E. W. Breitbart; A. Katalinic	2011	Different aspects of self-reported quality of life in 450 German melanoma survivors	Cancers	N		X		

2403	L. S. Wilson; C. M. Reyes; C. Lu; M. Lu; C. Yen; L. S. Wilson; C. M. Reyes; C. Lu; M. Lu; C. Yen	2002	Modelling the cost-effectiveness of sentinel lymph node mapping and adjuvant interferon treatment for stage II melanoma	Melanoma Research	N		X		

2409	J. Winstanley; B. Myles; E. White; E. Paton; M. King; J. Thompson	2010	Improving the measurement of quality of life in melanoma patients	Pigment Cell and Melanoma Research	N			X	
2413	F. Witte	2006	Malignant melanoma: Interferon therapy: Cost effectiveness and quality of life	Tumor Diagnostik und Therapie	N	X			

2414	F. Witte	2006	Malignant melanoma: Interferon therapy is not cost-effective and worsens quality of life	Gesundheitsokonomie und Qualitatsmanagement	N	X			

			Psychosocial outcomes of long-term melanoma survivors						
2466	P. Youl; S. Chambers; J. Aitken; C. Shield; R. Austin	2009		Asia-Pacific Journal of Clinical Oncology	N	X			

2467	A. M. Young; J. Marsden; A. Goodman; A. Burton; J. A. Dunn; A. M. Young; J. Marsden; A. Goodman; A. Burton; J. A. Dunn	2001	Prospective randomized comparison of dacarbazine (DTIC) versus DTIC plus interferon-alpha (IFN-alpha) in metastatic melanoma	Clinical Oncology (Royal College of Radiologists)	N			X	

2487	S. Ziefle; F. Egberts; S. Heinze; M. Volkenandt; M. Schmid-Wendtner; W. Tilgen; R. Linse; J. Boettjer; T. Vogt; K. Spieth; T. Eigentler; N. H. Brockmeyer; A. Heinz; A. Hauschild; M. Schaefer; S. Ziefle; F. Egberts; S. Heinze; M. Volkenandt; M. Schmid-Wendtner; W. Tilgen; R. Linse; J. Boettjer; T. Vogt; K. Spieth; T. Eigentler; N. H. Brockmeyer; A. Heinz; A. Hauschild; M. Schaefer	2011	Health-related quality of life before and during adjuvant interferon- treatment for patients with malignant melanoma (DeCOG-trial)	Journal of Immunotherapy	N		X		

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Association of Dermatologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? **Depends on BRAF status and extent of disease when metastatic. Current available treatments are BRAF inhibitors, ipilimumab, pembrolizumab and standard chemotherapy (dacarbazine).**

Is there significant geographical variation in current practice? **Variation occurs dependent where trials are available.**

Are there differences of opinion between professionals as to what current practice should be? **Generally no but sequencing of treatment can vary.**

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages? **BRAF inhibitors, ipilimumab, pembrolizumab and standard chemotherapy (dacarbazine). BRAF inhibitors can only be given in approx. 50% of patients with a metastatic melanoma who have a BRAF mutation. Ipilimumab can be used for all types of metastatic melanoma but does have significant autoimmune side effects so patients need to be fit. Pembrolizumab is also available for both BRAF positive and negative patients any line.**

Nivolumab plus ipilimumab is more effective than either ipilimumab on its own or nivolumab on its own as per the checkmate 067 trial (Larkin et al, NEJM).

Downsides of the combined treatment include that the toxicity is higher. The data however are not mature and so it is difficult to predict the longer term overall survival. There appears to be however no difference between BRAF positive or negative status. There is no direct comparison to the BRAF inhibitors.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? **NO**

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? **NO**

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? **Secondary care oncology clinics**

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)? **Day care facilities need to be available as the drug is administered intravenously.**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations. **There are new NICE melanoma guidelines but they were produced prior to this technology becoming available.**

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use? **Requires intravenous administration fortnightly until progression of disease. Ipilimumab is a cycle of 4 IV treatments (usually) and the BRAF inhibitors are orally administered.**

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation. **Stop on progression of disease and at present the data on how long it should be carried on for in disease responders is not known in view of toxicity.**

With immunotherapies; particularly ipilimumab, some early CT scans can show differential increase in the size of the disease which is secondary to the immune reaction rather than true progression. Interpretation of these scans can therefore be difficult and review at an MDT with specialist radiologist input is recommended.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice? **Autoimmune side effects are the most reported AE's but not as severe generally as ipilimumab.**

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] **registrar submitting comments on behalf of:**

Name of your organisation: NCRI Skin Cancer Clinical Studies Group/RCP/RCR/ACP

Comments coordinated by: [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Patients with advanced inoperable melanoma have their tumours genotyped to check the BRAF mutation status. Most with BRAF wildtype disease receive first line immunotherapy. Those with BRAF mutation positive disease (around 50%) will also be considered for immunotherapy as a first line treatment with BRAF inhibitors, such as vemurafenib and dabrafenib, later in the treatment pathway. Those with rapidly progressive BRAF mutation positive disease, short life expectancy and poor prognostic features (high disease burden, raised serum lactate dehydrogenase, poor performance status and multiple, symptomatic brain metastases) would be considered for first line BRAF inhibition therapy.

Until very recently immunotherapy was largely with the CTLA4 targeting treatment, ipilimumab. Ipilimumab is approved by NICE as both first and second line treatment for advanced melanoma (TA319 and TA268) and has been widely used as a result. The KEYNOTE-006 study was a direct comparison between the PD1 targeting agent pembrolizumab and ipilimumab and showed prolonged progression free survival (PFS) (46.4% vs 26.5% 6 month PFS) and overall survival (68.4% vs 58.2% 12 month survival) with less high grade toxicity (10.1% vs 19.9% grade 3 or more) with pembrolizumab compared to ipilimumab. NICE has just approved pembrolizumab as a first line treatment option for advanced inoperable melanoma (NICE TA357) and so practice has changed to reflect this. In view of the NICE guidances described above, there is not significant geographical variation in current practice.

Nivolumab, another PD1 targeting immunotherapy, has marketing authorisation in the UK for treating advanced melanoma. Nivolumab monotherapy is currently being considered by NICE as first and second line treatment (ID845) and this may mean that there are two PD1 drugs available to this group of patients. However, further advances on the results obtained with single agent use need to be made and this is why combination immunotherapy is being considered in this STA. Patients will also always be considered for and offered clinical trials for which they are eligible.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

The immunotherapy agents should be used in specialist clinics by oncologists in secondary care with expertise in the systemic treatment of melanoma. Side-effects may require inpatient stays for interventions such as high dose intravenous steroids, administration of immunosuppressants (for example, infliximab for immune-mediated colitis), and respiratory support. Pre-existing pathways need to be in place with other disciplines such as respiratory medicine, endocrinology and gastroenterology to proactively manage these toxicities. Some centres have created immunotherapy multidisciplinary teams to actively treat such events and support oncologists in the safe delivery of these agents.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NICE guidelines for the management of melanoma were published in July 2015, but these do not directly refer to use of immune checkpoint inhibitors.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Administration of the combination is consistent with current alternatives in that both immune checkpoint inhibitors are established single agents. The combination regimen offers an improvement in efficacy based on reported response rate and progression-free survival, but at a cost of significant increase in toxicity: grade 3 or more adverse events were reported in 55% treated patients in the Checkmate 067 trial. In practice, this means that as many as half of treated patients can expect to have a hospital admission for drug-related toxicity. This high frequency of severe and often complex toxicity has implications for patient selection, patient education and specialist management.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The international CHECKMATE-067 study had a UK Chief Investigator (Dr Larkin, the Royal Marsden Hospital) and recruited patients at 10 UK sites. This was a randomised phase III study comparing nivolumab alone versus nivolumab in combination with ipilimumab versus ipilimumab alone. The manuscript, with Dr Larkin as first author, has been recently published and described 945 previously untreated patients with unresectable stage III or IV melanoma who were randomised 1:1:1 to these three treatments. PFS was a co-primary endpoint and was 11.5 months for the combination arm compared with 2.9 months for ipilimumab alone (hazard ratio 0.42; 95% CI, 0.31-0.57; p<0.001) and 6.9 months for nivolumab alone (HR compared with ipilimumab, not powered to compare with the combination. HR 0.57; 99.5% CI 0.43-0.76; p<0.001). Overall survival was the other co-primary endpoint but these results are not yet available as the data remains immature.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The combination arm was associated with increased side effects with grade 3 and above events occurring in 55.0% on the combination, compared with 27.3% on ipilimumab alone and 16.3% on nivolumab alone. The reported side-effects are predominantly immune-related adverse events previously reported with checkpoint inhibitors administered as single agent. The most frequent events are diarrhoea/colitis, fatigue, endocrinopathies (hypophysitis, thyroid dysfunction), increase in transaminases, rash, emesis and pneumonitis. There have been no new toxicities that have come to light which have not been previously described in the context of immunotherapy. All specialist melanoma teams prescribing immune checkpoint inhibitors are now familiar with the occurrence of immune-related adverse events and standard treatment algorithms are readily available to guide their management.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

N/A

Implementation issues

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NHS staff routinely administer ipilimumab and pembrolizumab so further training is not needed for the combination of nivolumab and ipilimumab. Ipilimumab is given as a 90 minute infusion every 3 weeks for 4 cycles only. Nivolumab is given as an infusion every fortnight until progression or unacceptable toxicity – this differs from the 3 weekly administration of pembrolizumab until progression or unacceptable toxicity. Therefore, more treatment visits will be needed.

Increased toxicity rates with the combination of ipilimumab and nivolumab will mean that inpatient and multidisciplinary resources are utilised more frequently. On the other hand, increased toxicity also results in high chance of treatment discontinuation – in Checkmate 067, fewer than half of the patients started on the combination regimen continued treatment beyond the initial 12 weeks.

Education has been key to the safe administration of immunotherapy agents to date and current practice should cover what is needed for the combination.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. *No equality issues have been identified.*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID848]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by Melanoma Focus [] and consequently I will not be submitting a personal statement.

Name: [redacted].....

Signed: .....

Date:
.....18.04.16.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID848]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by the Royal College of Physicians and consequently I will not be submitting a personal statement.

Name: .....

Signed: .....

Date: .....29th March 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID848]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

the experience of having the condition or caring for someone with the condition

the experience of receiving NHS care for the condition

the experience of having specific treatments for the condition

the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)

preferences for different treatments and how they are given

expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

a patient

a carer (who may be voicing views for a patient who is unable to) or

somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

About you

Your name: [redacted]
Name of your nominating organisation:Melanoma UK
Do you know if your nominating organisation has submitted a statement?

☐ Yes ☒ No

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

a patient with the condition?

x☐ Yes ☐ No

a carer of a patient with the condition?

☐ Yes ☐ No

a patient organisation employee or volunteer?

☐☒ Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☐☒ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Living with the condition

What is your experience of living with the condition as a patient or carer?

I first had malignant melanoma in 1995, a year later it progressed to the lymph nodes in my groin making me stage 3. I was told then that my life expectancy was two years because there were no treatments available. I was one of the lucky ones and was free of evident disease for 18 years. Unfortunately it recurred in autumn of 2014 with two new primaries and a local recurrence. At that point my local hospital, Shrewsbury , had to hand me on to a specialist melanoma centre. I elected to have treatment at the Royal Marsden because of some melanoma vaccine trials I'd had at St Georges In Tooting in the late 90s. During 2015 I had three rounds of surgery on seven sites to perform WLE or remove in–transit metastases. My last ct scan at the end of December 2015 showed disease progression to distant lymph nodes making me stage 4. In January 2016 I started monotherapy pembrolizumbab. So far I've had 4 infusions. My two subcutaneous metastases have disappeared and my LDH has trended down from 150 to 105 so I hope that I'm a responder. I'm lucky that I've only had minor side effects and can lead a relatively normal life.

Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

To any patient, survival is usually the most important outcome. Quality of life comes a poor second. Although I appear to be responding to pembrolizumab, on average only about 40% of patients do respond. Checkpoint 67, the comparison of monotherapy ipilimumab and monotherapy nivolumab with the combination therapy of ipilimumab plus nivolumab showed significantly higher response rates for the combination (60%) and longer survival. This result is crucial for patients.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I am very pleased with the care that I have received at the Marsden. In an ideal world I would have liked to have had adjuvant immunotherapy during

2015 before my disease spread. However, there are no immunotherapy adjuvant treatments on the NHS and I was excluded from a trial because of my history with a melanoma vaccine in the late 90s. Monotherapy ipilimumab was available as a treatment to me when I progressed to stage 4 but I was advised that the anti PD1 drugs worked better and with less side effects. Combination ipilimumba and nivolumab was not available on the nhs.

What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

the course and/or outcome of the condition

physical symptoms

pain

level of disability

mental health

quality of life (such as lifestyle and work)

other people (for example, family, friends and employers)

ease of use (for example, tablets rather than injection)

where the treatment has to be used (for example, at home rather than in hospital)

any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

The main potential benefit is living longer if one responds. 60% patients responding is a huge benefit but the combination does have significant riask of side effects. Some patients would opt for the combo despite the risk of side effects whilst others would choose monotherapy anti PD1. The key point is that approving the combination would give patients and clinicians more choice.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

More responders and longer survival.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

As mentioned above the significant risk of side effects could result in some patients not choosing the combination.

What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

aspects of the condition that the treatment cannot help with or might make worse

difficulties in taking or using the treatment (for example, injection rather than tablets)

side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

where the treatment has to be used (for example, in hospital rather than at home)

impact on others (for example, family, friends and employers)

financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)

any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

Although clinicians are becoming more skilled in managing side effects, my understanding is that some patients have died from the side effects and that a significant number have had to be hospitalized for treament.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

People who do not mind about the risk of side effects.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

No.

Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☒ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

No data.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, as stated above the 65% response rate is crucial.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular

groups of people, who they are and why.

Other issues

Do you consider the treatment to be innovative?

☐X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Dual therapy uses both anti PD1 and CTLA4 tecnology.

Is there anything else that you would like the Appraisal Committee to consider?

Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

Significantly higher response rate for combo versus monotherapy

Significantly longer survival data

Substanial risk of side effects associated with ipilimumab

Approval would give patients more choice in their treatment plan.

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 15/06/13

BMJ Technology Assessment Group

Title: Nivolumab in combination with ipilimumab for advanced, unresectable melanoma

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Steve Edwards	Project lead: supervised the production of the final report; critical appraisal of the company's submission; critical appraisal of the clinical evidence; and critical appraisal of the economic evidence
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary and clinical results sections
Andrea Berardi	Critical appraisal of the company's submission; critical appraisal of the economic model; cross-checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the summary and economic sections
Michelle Helena van Velthoven	Critical appraisal of the company's submission; and critical appraisal of the clinical evidence; and drafted the clinical sections
Fatima Salih	Critical appraisal of the company's submission; critical appraisal of the economic evidence; cross-checking of company's search strategies; and drafted the economic sections

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

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Abbreviation	Description
AE	Adverse event
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ASCO-GU	American Society of Clinical Oncology-Genitourinary
AUC	Area under the curve
BIC	Bayesian Information Criterion
BMS	Bristol-Myers Squibb Pharmaceuticals Ltd
BNF	British National Formulary
BSC	Best supportive care
CC	Complication or comorbidity
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMH	Cochran–Mantel–Haenszel
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CTC	Common terminology criteria
CXR	Chest x-ray
DARE	Database of Abstracts and Reviews of Effects
DC	Discontinuation
DMC	Data monitoring committee
DOR	Duration of response
DR	Distant recurrence
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DTIC	Dacarbazine
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EMA	European Medicines Agency
EOL	End of life
EORTC-QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC-8D	European Organisation for Research and Treatment of Cancer 8-dimension
EQ-5D	European Quality of Life 5-dimension
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology

FKSI-15	15 item Functional Assessment of Cancer Therapy Kidney Symptom Index
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms
GCP	Good clinical practice
GI	Gastrointestinal
GP	General practitioner
HCHS	Hospital & community health services
HDI	High-dose interferon alpha
HR	Hazard ratio
HRG	Health-related group
HRQoL, HRQL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
INB	Incremental net benefit
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LR	Local recurrence
LY	Life year
LYG	Life year gained
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloane Kettering Cancer Centre
MTA	Multiple Technology Appraisal
mTOR	Mammalian target of rapamycin
NE	Not estimable
NED	No evidence of disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-Small Cell Lung Cancer
ONS	Office of National Statistics
OP	Outpatient
OPATT	Outpatient attendance
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD-1	Programmed death receptor 1
PD-L1	Programmed death receptor ligand 1
PD-L2	Programmed death receptor ligand 2

PET	Positron-emission tomography
PFS	Progression-free survival
PH	Proportional hazards
PLD	Patient-level data
PPS	Post-progression survival
PR	Partial response
PrePS	Pre-progression survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life-year
QoL	Quality of life
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank-preserving structural failure time
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SG	Standard gamble
SGA LoT	Subgroup analysis for line of therapy
SNP	Single nucleotide polymorphisms
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TKI	Tyrosine kinase inhibitor
TNM	Tumour Node Metastasis
TOC	Total other currencies
ToT	Time on treatment
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
TSD	Technical support document
TTD	Time to treatment discontinuation
TTO	Time trade-off
TTP	Time-to-progression
Tx	Treatment
ULN	Upper limit of normal
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	Von Hippel-Lindau
WTP	Willingness-to-pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company, Bristol Myers Squibb, submitted clinical and economic evidence in support of the effectiveness of nivolumab and ipilimumab combination immunotherapy (hereafter referred to as combination immunotherapy) for the treatment of advanced melanoma, to the National Institute for Health and Care Excellence (NICE).

At the time of writing of the Evidence Review Group's (ERG) report, nivolumab and ipilimumab combination immunotherapy does not have a European licence for use in advanced (metastatic or unresectable) melanoma; also, no opinion from the Committee for Medicinal Products for Human Use (CHMP) has been issued.

CheckMate 067 and CheckMate 069 are the key trials forming the basis of the direct clinical evidence submitted by the company. Both trials assessed the efficacy and safety of combination immunotherapy compared to ipilimumab in adults with previously untreated, unresectable stage III or stage IV melanoma. The ERG considers the intervention in CheckMate 067 and CheckMate 069 to be consistent with the anticipated licence and the NICE final scope[(1)] for this STA. The trial populations were largely in line with the final scope issued by NICE, although slightly narrower as the trials were limited to patients with a specific performance status and without prior systemic anticancer treatments.

The final scope issued by NICE[(1)] lists comparators of interest as ipilimumab, pembrolizumab, and the BRAF inhibitors dabrafenib and vemurafenib (for people with $BRAF^{+}$ melanoma). The company did not include pembrolizumab as a comparator in the submission. According to the company, pembrolizumab is not established standard of care for advanced melanoma in NHS England and thus it is not a relevant comparator to combination immunotherapy. The company did not identify any direct evidence comparing combination immunotherapy to either of the BRAF inhibitors dabrafenib or vemurafenib. The company therefore performed a covariate-adjusted "indirect" comparison using data from the trial BRIM-3 (vemurafenib versus dacarbazine). Combination immunotherapy was not compared directly to dabrafenib, instead the company assumed that vemurafenib and dabrafenib have approximately equal efficacy. The ERG considers that the CS does not fully address the scope issued by NICE based on the omission of the comparator pembrolizumab, and inclusion of dabrafenib only by making an assumption of equivalence with vemurafenib.

All clinically relevant outcomes were reported within the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

CheckMate 067 and CheckMate 069 are multicentre, double-blind, parallel-group randomised controlled trials. CheckMate 067 is a phase III trial including 629 patients randomised 1:1 to combination immunotherapy and ipilimumab. In the phase II trial CheckMate 069, 142 patients were randomised 2:1 to combination immunotherapy and ipilimumab.

In both trials, patients in the combination immunotherapy arm received nivolumab 1mg/kg plus ipilimumab 3mg/kg every three weeks by intravenous (IV) infusion for four doses followed by nivolumab 3mg/kg every two weeks until disease progression, discontinuation due to toxicity or any other reason. Patients who had a clinical benefit and were tolerating treatment, as determined by the investigator, were allowed to be treated after disease progression. Patients in the ipilimumab group received ipilimumab 3mg/kg every three weeks by IV infusion for four doses and a nivolumab-matched placebo.

In CheckMate 067 and CheckMate 069, combination immunotherapy was associated with a statistically significant improvement in PFS (HR 0.42, 95% CI: 0.31 to 0.57, and HR 0.39, 95% CI: 0.25 to 0.63, respectively). PFS was defined as the time between the date of randomisation and the first date of documented progression or death due to any cause (investigator-assessed). OS (defined as time between the date of randomisation and the date of death) data were immature for both CheckMate 067 and CheckMate 069, with median survival not reached in either intervention or comparator arm in either trial. An interim analysis of CheckMate 069 showed no statistically significant difference in OS for combination immunotherapy versus ipilimumab (HR 0.73, 95% CI: 0.39 to 1.36). No OS data was presented for CheckMate 067 in the CS. [redacted]

Objective response rate (ORR) was defined as the number of patients with a best objective response of complete or partial remission divided by the number of randomised patients (investigator-assessed). Combination immunotherapy was associated with a statistically significant ORR compared to ipilimumab in both CheckMate 067 (OR 6.11, 95% CI: 3.59 to 10.38) and CheckMate 069 (OR 12.19, 95% CI: 4.41 to 33.68). In both CheckMate 067 and CheckMate 069 time to response did not differ significantly between treatment arms, with the majority of all responses observed at the time of the first scan at 12 weeks.

Data from CheckMate 067 and CheckMate 069 indicate that a substantial proportion of patient experience continued clinical response after discontinuation of treatment with combination immunotherapy, and a substantial proportion of patient in both trials were treated beyond RECIST defined progression because they showed continued clinical benefit and could tolerate the treatment.

There were no clinically meaningful differences in HRQoL between combination immunotherapy and ipilimumab in either trial.

According to the company, the safety profile of combination immunotherapy was consistent with the mechanisms of action of nivolumab and ipilimumab monotherapy. The rates of grade 3-4 AE were considerably higher among patients treated with combination immunotherapy compared to ipilimumab. The proportion of discontinuation due to any grade or grade 3-4 AEs were higher in the combination immunotherapy arm compared to the ipilimumab arm in both trials. The most common treatment related serious adverse effects (frequency ≥2%) associated with combination immunotherapy were diarrhoea, colitis, pyrexia, increased transaminases, nausea and hypophysitis. Select AEs were defined as AEs with a potential immunological cause. In both trials, there were a higher proportion of all and grade 3-4 select AEs in the combination immunotherapy arm compared to the ipilimumab group for the endocrine, gastrointestinal, hepatic, pulmonary, renal and skin categories.

The company used covariate-adjusted data to produce comparative efficacy estimates for combination immunotherapy, ipilimumab and BRAF inhibitors to extrapolate survival data that were used in the economic model. Due to the immaturity of OS data from CheckMate 067 and 069, the difference in efficacy of combination immunotherapy compared to ipilimumab was estimated using patient level data (PLD) from CheckMate 067 (combination immunotherapy and ipilimumab arms) for PFS, and PLD from CheckMate 066 (nivolumab arm) and MDX010-20 (ipilimumab arms) as proxy for OS. The difference in efficacy of combination immunotherapy compared to BRAF inhibitors was similarly estimated using PLD from CheckMate 067, CheckMate 066 and MDX010-20, together with aggregate data from BRIM-3 (vemurafenib arm) to form an indirect comparison. The PLD were adjusted for the following covariates: treatment, trial, baseline ECOG, LDH, M stage, history of brain metastases, age, gender, and subsequent ipilimumab therapy.

[redacted]

1.3 Summary of cost effectiveness evidence submitted by the company

The company developed a single *de novo* three-state cost-effectiveness model in Microsoft Excel® for the analysis in the $BRAF^-$ and $BRAF^+$ subpopulations. Combination immunotherapy (i.e. nivolumab in addition to ipilimumab; referred to as "the Regimen" in the CS) was compared to ipilimumab monotherapy in the $BRAF^-$ subpopulation. The comparators included in the $BRAF^+$ analysis were ipilimumab monotherapy, dabrafenib and vemurafenib. The company used the same three-state model structure but a different approach to modelling the effectiveness of immunotherapies (i.e. combination immunotherapy and ipilimumab) and BRAF inhibitors (i.e. vemurafenib and dabrafenib). All patients started in the progression-free survival (PFS) health state, and could at any time progress to the post-progression survival (PPS) health state or die and transition to the absorbent death health state. From the PPS health state, patients could either die or remain in the same health state. Weekly cycles, using a half-cycle correction were applied in the model. The company discounted both costs and health effects accrued at 3.5% rate.

A semi-Markov approach was adopted for immunotherapies, modelling directly the transitions between health states. In the semi-Markov approach, mortality was modelled differently for progressed and non-progressed patients, and was determined by PPS and pre-progression survival (PrePS), respectively. Transitions from the PFS to the PPS health state was regulated by time to progression (TTP). TTP, PrePS and PPS concurred to estimate PFS and OS associated to the immunotherapies. The company reported assuming equal mortality in post-progression for combination immunotherapy and ipilimumab. As mortality rates were substantially lower in pre-progression compared to post-progression, an extension in the time spent in the PFS health state would translate in a survival benefit. Transition probabilities were estimated based on non-parametric (i.e. Kaplan Meier curves) and parametric models.

An AUC approach was adopted for the BRAF inhibitors, modelling directly the proportions of patients in the three health states (i.e. PFS, PPS, OS) rather than the transitions between them. Under this approach, the OS was modelled explicitly, and was not dependent on TTP or PFS as in the semi-Markov approach. Effectiveness data were based on pseudo-patient level data (PLD) extracted from the results of the phase III BRIM-3 pivotal trial for vemurafenib.[2, 3]

Survival models were adjusted for a pre-specified set of baseline characteristics. These were set equal to the ones observed in the CheckMate 067 trial in the $BRAF^-$ subpopulation and to the patients' characteristics of the BRIM-3 trial in the $BRAF^+$ analysis. This was because PLD were available only for combination immunotherapy and ipilimumab, and not for the BRAF inhibitors. In the $BRAF^+$ analysis the survival models used to model and extrapolate the effectiveness of immunotherapy were adjusted for the baseline characteristics observed in the BRIM-3 trial. This adjustment allowed

comparing immunotherapies and BRAF inhibitors based on the indirect comparison carried out by the company.

The data sources used and the methodologies applied to model treatment effectiveness of immunotherapies for the three outcomes in the company's model were:

- TTP, modelled separately for the two time periods individuated before and after 84 days into the CheckMate 067 trial. This was because of an observed cluster of progression events occurring at the first scheduled assessment of progression:
    - TTP pre-84 days: Kaplan Meier curves from the CheckMate 067 trial, adjusted for the patients' baseline characteristics based on the estimates of a Cox proportional hazards model;
    - TTP post-84 days: log-normal parametric model estimated based on the post-84 days CheckMate 067 trial data. Treatment effect was based on the model estimate, assuming proportionality of the hazards;
- PrePS:
    - PrePS from model inception to end of observed follow-up in the CheckMate 067 trial: Kaplan Meier curves from the CheckMate 067 trial, adjusted for the patients' baseline characteristics based on the estimates of a Cox proportional hazards model. The treatment effect estimated in the Cox model was not considered in the adjustment, and it was accounted for by the difference in the area under the Kaplan Meier curves. The maximum follow-up periods differed between the two model arms and were equal to 551 days and 513 days for combination immunotherapy and ipilimumab, respectively;
    - PrePS from end of maximum follow-up in the CheckMate 067 trial to end of time horizon: patients were assumed to die at the same rate of the general population. The age-specific mortality was based on the UK life tables;
- PPS:
    - PPS from model inception to year 3: log-logistic model estimated based on the nivolumab arm of the CheckMate 066 trial and the pooled ipilimumab and ipilimumab plus gp100 arms of the MDX010-20 trial.

- PPS from year 3 to end of time horizon: Gompertz parametric model estimated based on the pooled ipilimumab data reported by Schadendorf *et al.*[4]

The effectiveness of BRAF inhibitors was modelled based on two outcomes:

- PFS, based on a generalised gamma parametric model estimated based on pseudo-PLD generated from the BRIM-3 trial. The OS was set as upper bound for the PFS;
- OS, based on the log-normal parametric model based on pseudo-PLD generated from the BRIM-3 trial results until model year 3. A Weibull parametric model fitted on pseudo-PLD extracted from the AJCC registry for melanoma-specific mortality, in addition to age- and gender-matched English general population mortality.

Pharmacological resource use for immunotherapies was based on the data collected from the CheckMate 067 RCT. Patients were assumed to receive nivolumab within combination immunotherapy based on the time on treatment (ToT) observed in the trial up to 2 years since initiation, at which point all patients were to discontinue treatment. The company also assumed that, based on the trial relative dose intensity, only 90.16% of the target dose of nivolumab would be received by patients at each treatment administration over the maximum treatment duration of 2 years. A separate parametric model, independent of PFS but limited by OS, was used because the clinical stopping rule of nivolumab within combination immunotherapy allowed for treatment following disease progression.

The proportion of patients that would receive each of the four planned doses of ipilimumab was also based on the CheckMate 067 trial. Simple proportions of patients were used to model ToT rather than survival analysis. The company assumed that patients on BRAF inhibitors would be treated while in the PFS health state.

In the company's model patients could receive subsequent therapies after progression and discontinuation or failure of the model first-line treatment. Subsequent therapies were based on data collected in the CheckMate trial for combination immunotherapy and ipilimumab, in the BRIM-3 trial for vemurafenib and in BREAK-3 for dabrafenib. The company assumed that different proportion of patients would receive subsequent therapies across treatment arms. In particular, ipilimumab was associated with the lowest proportion of patients who would not receive subsequent therapy. The cost of subsequent treatment was applied as a one-off quantity at treatment progression.

Follow-up resource use was based on time since treatment initiation and time to death. Resource use data were largely on the UK subset of patients from a longitudinal observational study on healthcare resource utilisation associated with the treatment of melanoma in Italy, France and UK. Resource use

including outpatient and inpatient visits, laboratory tests and radiological examinations was accounted for at treatment initiation, then regularly during the first, second, and third and subsequent years. Costs associated to resources used in palliative and terminal care were also attributed to patients for the 12 weeks before death.

The company only looked at treatment-related adverse events (TRAEs) when assessing the comparative toxicity profile of the interventions. The considered TRAEs were: endocrine disorders of any grade); diarrhoea of grade 2 or higher; other TRAEs of grade 3 or higher. TRAEs data were taken from the CheckMate 067 trial for immunotherapies. The rates were based on the pivotal trials for each of the two the BRAF inhibitors, i.e. BRIM-3 for vemurafenib and BREAK-3 for dabrafenib. Among the four compared interventions, combination immunotherapy was considered the more toxic one, with the highest percentage of patients experiencing all TRAE included and the highest percentage of patients hospitalised across all TRAEs. The treatment-specific costs associated to TRAE management were front-loaded at treatment initiation and then re-applied at week 54, which was the mean follow-up for patients in the CheckMate 067 trial. The total TRAE costs estimates were £1,628 for combination immunotherapy, £929 for ipilimumab, £624 for dabrafenib and £973 for vemurafenib.

Patients' health-related quality of life (HRQoL) was based on the analysis of the EQ-5D CheckMate 067 trial data. The valuation method applied was not reported. The company used the results of a longitudinal mixed-effects linear model including baseline EQ-5D, progression status and treatment received as covariates. The treatment effect was assumed to account for HRQoL disutilities associated to TRAE. A total of 5,244 visits involving 827 study patients across the three treatment arms of the trial (i.e. nivolumab monotherapy, ipilimumab monotherapy and combination immunotherapy) were used in the model. The utility scores applied by progression status were 0.76 and 0.73 for progression-free and progressed patients in both the combination immunotherapy and ipilimumab arms. A comparable HRQoL profile to nivolumab monotherapy was assumed for the BRAF inhibitors, applying utility scores of 0.80 and 0.76 to the PFS and PPS health states, respectively.

Patient access schemes (PAS) are in place for ipilimumab, dabrafenib, vemurafenib and pembrolizumab. The company therefore produced two price scenarios, one based on list prices for all drugs and one based on PAS prices. The PAS for ipilimumab is known to the company; the PASs for dabrafenib, vemurafenib and pembrolizumab were based on assumptions.

In the BRAF^{-} analysis, the company estimated that combination immunotherapy would cost £22,826 more than ipilimumab while increasing the per-patient quality-adjusted life years (QALY) by 2.19. The estimated incremental cost-effectiveness ratio (ICER) was £10,433 per QALY gained. [redacted]

In the BRAF^{+} subpopulation, the incremental analysis compared combination immunotherapy, as the most expensive and effective intervention, against dabrafenib, the next most efficient comparator. Vemurafenib and ipilimumab resulted both extendedly dominated. Combination immunotherapy was estimated to cost £35,085 more than dabrafenib while increasing the total QALYs accrued by 3.11. The ICER was equal to £11,284. [redacted]

Results from the deterministic sensitivity analyses showed that the most influential factors were related to treatment efficacy, as the comparative cost-effectiveness profiles were largely driven by assumptions and parameter estimations around treatment effectiveness. The probabilistic sensitivity analysis did not highlight non-linear behaviours in the distribution of the simulations; the results were in line with the deterministic ones. However, key parameters such as the baseline characteristics, which influenced all efficacy models as covariates were not varied stochastically.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

The ERG considers CheckMate 067 and CheckMate 069 to be well-designed, good quality trials, and considers the results of the submitted evidence to be relevant to the decision problem that is the focus of this STA.

Economic

The economic evaluation was well-presented, with the inputs and assumptions reported clearly in the CS. The electronic model design was sound, and the ERG did not encounter any major difficulty to check and confirm the methodologies applied as stated in the CS and as implemented in the economic model.

The economic evaluation was based on evidence from a phase III RCT, and resource use was based on a robust longitudinal study. The ERG considers each piece of the analyses performed to be reasonable and justified when assessed individually.

1.4.2 Weaknesses and areas of uncertainty

Clinical

There is a lack of data showing potential differences in response kinetics between combination immunotherapy and ipilimumab and BRAF inhibitors.

No evidence for the comparison of combination immunotherapy and pembrolizumab was searched for or presented in the CS, as the company did not consider pembrolizumab to be a relevant comparator to combination immunotherapy. [redacted]

No direct evidence was identified for the comparison of combination immunotherapy to either of the BRAF inhibitors dabrafenib and vemurafenib. Also, the OS data from both CheckMate 067 and CheckMate 069 were immature at the time of submission. The company therefore performed "indirect" comparisons using covariate adjusted data. The ERG has concerns around the transparency of the choice of trials to inform the indirect comparisons of combination immunotherapy versus ipilimumab and BRAF inhibitors, which may impact on the results of the economic models. However, it was not possible for the ERG to estimate the size or direction of the impact.

The ERG also has concerns that the indirect comparison approach presented by the company requires several assumptions which may not be justified. The evidence presented by the company, in support of some of these assumptions does not definitively demonstrate their validity (e.g. the effect of line of treatment and the equivalence of BRAF inhibitor efficacy). The effect of previous treatments is likely a conservative estimate of OS for combination immunotherapy and ipilimumab. However, if the efficacy of the BRAF inhibitors is not equivalent, no estimate of combination immunotherapy versus dabrafenib is available. Also, no reliable long-term survival data were available for either of the BRAF inhibitors.

By using the covariate adjusted approach, the intrinsic advantages of using results from randomised controlled trials are lost. The company could only adjust for the observed prognostic covariates. Any unobserved prognostic covariates could not have been accounted for. This isn't a problem when using a method that preserves randomisation since the randomisation should provide balanced groups within each trial. Although the company adjust the data for several prognostic factors and other covariates, the company did not present any validation of the covariate adjusted approach in the CS. It is unclear if all relevant covariates were captured and adjusted for in the indirect comparisons, in particular it is unclear what was captured in the trial covariate. It is also unclear if the adjustments of the included covariates were sufficient. Hence, it is not possible for the ERG to comment on the validity of the results.

Economic

The ERG identified few weaknesses in the economic evaluation. However, those that were identified were on assumptions around effectiveness modelling and comparability, which had a significant influence on the results and/or on their plausibility of the comparisons carried out.

The main area of uncertainty on the economic results is associated to and intrinsic to the modelling approach taken for immunotherapies. The semi-Markov approach with a different mortality for patients in pre- and post-progression implicitly assumes surrogacy between TTP (or PFS) and OS. This is because using this modelling structure a difference in TTP, *coeteris paribus*, translates directly into a difference in survival. While the benefits of combination immunotherapy on OS and PFS times were demonstrated over ipilimumab in the CheckMate 067 RCTs (among other trials), the company failed to provide evidence to support the surrogacy assumption.

Furthermore, the ERG did not agree with the company's modelling approach for both PrePS and PPS in the immunotherapies comparison. The company assumed a difference in PrePS between combination immunotherapy and ipilimumab based on the difference in the Kaplan Meier curves observed in the CheckMate 067 RCT, which was assumed to persist over the entire time horizon. However, the treatment effect was not found to be significantly non-null when tested, and the company's use of the poorly informative tails of the Kaplan Meier curves as a basis for extrapolation was considered inappropriate by the ERG. The ERG also considers unlikely that the survival rates of patients with advanced melanoma would be in line with the survival of the age- and gender-matched general English population, but could not find an alternative data source as mortality data are not commonly reported separately by disease progression status.

The ERG found that the methodology used to nest the short- and long-term mortality in the PPS health state produced implausible results based on the assumptions stated in the CS. The company's approach to the nesting of the two curves resulted in substantial differences in expected survival for patients based on time of progression since treatment initiation. A difference of about 13 years of life spent in the PPS health state was observed for patients progressing in the first weeks of the model (approximately 3 undiscounted life years on average) and patients progressing after 3 years since treatment initiation (approximately 16 undiscounted years on average). This difference was dictated by how the two evidence sources were synthesised rather than the data themselves. As the TTP were times different between the immunotherapies, and the PPS was modelled dependent on TTP, the company's stated assumption of equal PPS for combination immunotherapy and ipilimumab did not hold due to the modelling approach taken. The company did not state or explain this discrepancy to their assumption that the same post-progression mortality was applied to the two immunotherapies. The ERG considers the company's modelling of post-progression mortality to produce intermediate results which negated internal validity and to be based on an unstated and unjustified assumption.

Due to these issues with PrePS and PPS mortality, the ERG considers the survival benefit of combination immunotherapy over ipilimumab is likely to have been overestimated by an unknown quantity. This quantity could not be estimated because of the modelling approach taken, which implicitly assumes surrogacy between TTP (or PFS) and OS. As the presence of OS and PFS benefits

for combination immunotherapy over ipilimumab were supported by robust phase III randomised evidence, it was impossible for the ERG to separate the benefit resulting by the use and extrapolation of the clinical data and the benefit resulting from the unjustified surrogacy assumption.

A second key weakness of the company's submitted economic evidence was about the comparability between immunotherapies and BRAF inhibitors in the $BRAF^+$ subpopulation. The company modelled the two immunotherapies using a semi-Markov model, and the two BRAF inhibitors using an AUC model. These two models were very different, as the first one assumed implicitly surrogacy between TTP (or PFS) and OS, with very different mortality rates over time between PFS and PPS; on the other hand, in the AUC approach PFS and OS were modelled independently. Given the limited follow-up times of the available clinical data, and therefore the difficulties associated to validate long-term modelling assumptions, the ERG does not consider the evidence submitted to be sufficient to provide robust results for the comparison between immunotherapies and BRAF inhibitors. The ERG expects the underlying assumptions of the different modelling approaches to provide incomparable results on the long-term time horizon set for the analysis. The ERG provided the results of an exploratory analysis based on a substantially shorter time horizon of 5 years between the immunotherapies and the BRAF inhibitors. However, these results should be interpreted with extreme caution as the assumptions about the long-term mortality associated to immunotherapies were changed from the company's base case to increase the internal validity of the comparison between combination immunotherapy and ipilimumab. This expected gain in internal validity might have not propagated to the comparison between immunotherapies and BRAF inhibitors.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG carried out additional scenario analyses to provide more reliable results in light of the analysis of the assumptions which were considered inappropriate in the company's model. The key areas of uncertainty identified by the ERG, granting exploration through scenario analyses, were:

- Dependency on time of progression of post-progression mortality rates for immunotherapies. The ERG's preferred assumption was to remove the long-term data nesting and base the extrapolation of post-progression mortality only on clinical trial data;

- Treatment effect on pre-progression mortality for immunotherapies. As a beneficial treatment effect of combination immunotherapy on PrePS was not demonstrated, the ERG assumed equal pre-progression mortality between combination immunotherapy and ipilimumab by averaging the Kaplan Meier curves. This removed the assumption of a PrePS benefit of combination immunotherapy over ipilimumab equal to the difference in the tails of the

Kaplan Meier curves for the two therapies which was assumed to persist over the entire time horizon;

- Treatment dosage assumptions for combination immunotherapy. The ERG did not find the company's justification around the assumption of a constant reduction over time in the nivolumab resource use and cost to be sufficient to grant a reduction in costs equal to approximately 10% of the total costs associated with the drug acquisition costs of nivolumab;

- Second-line treatments received in post progression. The ERG could not verify the company's assumptions regarding the treatment-specific proportions of patients accessing different subsequent treatments. The ERG explored a scenario comparing combination immunotherapy and ipilimumab over the entire population, irrespective of BRAF mutation status, in line with the patient population analysed in the CheckMate 067 trial. [redacted]

The ERG's preferred base case was based on a revised company's base case model, after the correction of two inputs which determined a negligible difference in results, and on the application of all four alternative assumptions explored in scenario analyses. The results represent the ERG's preferred set of assumptions around the company's base case for the comparison between combination immunotherapy and ipilimumab irrespective of BRAF mutation status. The ICER for this comparison resulted in £19,322 per QALY gained using list prices, [redacted]. However, the ERG notes that substantial uncertainty around the results is caused by the surrogacy assumption between TTP and OS, which determines the entire survival benefit of combination immunotherapy over ipilimumab in the ERG's preferred base case.

The ERG's exploratory analysis in the $BRAF^{+}$ subpopulation was based on the same set of assumptions as for the preferred base case regarding immunotherapies, with the exception of the application of the alternative set of probabilities of receiving subsequent therapies. Assuming a 5-year model time horizon, combination immunotherapy resulted in the longest expected survival among the compared interventions, with 2.20 (discounted) life years. The BRAF inhibitors and ipilimumab resulted in a similar life expectancy, equal to 1.62 and 1.54 discounted life years respectively. The incremental analysis for this explorative scenario compared the most expensive and effective intervention, combination immunotherapy, to the next most efficient comparator, which was dabrafenib. The ICER was estimated equal to £101,779 per QALY gained using list prices, [redacted]

[redacted]. The ERG considers these results exploratory and associated with a high amount of uncertainty. As such, they should be interpreted with caution.

The company did not provide a comparison against pembrolizumab in the CS, as detailed in the NICE Final Scope. A supplemental scenario analysis was requested by the ERG at the clarification stage and provided by the company as part of the responses to the clarification questions. However, the ERG does not find the comparison to be sufficient to base the comparative cost-effectiveness profile between combination immunotherapy and pembrolizumab. This is because of the following reasons:

- The model outcomes were based on the results of the ipilimumab arm in the company's base case. However, the ERG found an unreasonable modelling assumption around the integration of short- and long-term post-progression mortality which resulted in implausible intermediate outcomes for ipilimumab;

- The model assumed constant proportionality of the hazards over the entire time horizon for PFS and OS between ipilimumab and combination immunotherapy and ipilimumab and pembrolizumab. The HRs were estimated based on relatively short-term follow-up, with no evidence supporting the assumption for the entire time horizon;

- Assuming HRs for the OS in the model assumed that, in addition to melanoma-specific mortality, pembrolizumab and combination immunotherapy would also reduce the portion of mortality determined by age- and gender-match general population mortality compared to ipilimumab, over the entire time horizon. This translates in assuming that the mortality rates for patients in the PFS health states beyond 3 years in the combination immunotherapy and pembrolizumab arms would have death rates lower than the rates of the English general population. This is considered an unreasonable assumption by the ERG;

- The assumption of a different OS derives from a naïve comparison of the HRs between ipilimumab, combination immunotherapy and pembrolizumab. However, [redacted] the network meta-analysis (NMA) performed by the company and replicated by the ERG between pembrolizumab and combination immunotherapy;

- The ERG agrees with the company that the exploratory NMA [redacted]. However, the analysis is not probative of a treatment difference, and as such the comparative efficacy results should be considered with extreme caution.

Overall, the ERG considers the company's submitted evidence to be sufficient to inform the comparison between combination immunotherapy and ipilimumab for adult patients with advanced

melanoma. The ERG finds the company's economic evaluation to be overcomplicated and to rely on too many key assumptions. The ERG considers that more parsimonious economic and statistical modelling approaches, with fewer assumptions to justify and fewer model parameters to estimate based on relatively short-term data, would have greatly benefitted the robustness, validity and interpretation of the results.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

In the company submission (CS, Section 3.1 and 3.3) the company provides an overview of key aspects of melanoma including incidence, prevalence, presentation and symptoms, and prognosis.

Melanoma is described by the company as an aggressive type of skin cancer originating from melanocytes.[5, 6] It only makes up 4% of all skin cancer cases in the UK, with around 12,800 new cases in 2010. However, melanoma is accounting for 90% of skin cancer-related deaths; in 2011 there were 2,200 melanoma-related deaths in the UK.[5, 7]

The majority of melanoma cases are estimated to be caused by ultraviolet (UV) radiation.[8, 9] There has been a step increase in the incidence of melanoma over the last few decades, which is thought to be linked to lifestyle changes leading to more UV radiation exposure.[8] According to the CS the incidence rates are expected to continue to rise by around 3.5% per year.[10] Compared to other cancers, a relatively high proportion of melanoma cases occur in younger patients.[11] The incidence of melanoma is roughly equal in men and women; although, melanoma is more common in women than men in the younger age groups, a pattern that is reverses in older people.[7] Overall the incidence does increase with age.

The company's description of presentation and possible symptoms of melanoma is reproduced in Box 1. All information presented in boxes is taken directly from the CS, unless otherwise stated, and the references have been renumbered.

Box 1 Presentation and symptoms of melanoma (CS, pg 22, Section 2.1)

> Often the first visible indication of melanoma is typically a mole that has changed in shape, colour, size or feel (cutaneous melanoma). Melanoma can also originate from other sources, e.g. ocular and mucosal. In these cases the initial signs and symptoms may be less obvious. Initially, melanoma is normally asymptomatic and, if detected early, can be cured by surgical removal. If it goes undetected, melanoma can invade and destroy nearby tissue, and thereafter may metastasise. When this occurs, symptoms become more severe.[12] Specific symptoms will depend on the sites to which melanoma has spread, but patients may typically experience pain and fatigue that affect their physical and mental well-being, weight loss, loss of appetite, nausea and shortness of breath.[12, 13]

The severity of melanoma is divided into stages based on how widespread the disease is, using the American Joint Committee on Cancer (AJCC) staging system.[12, 14] Advanced and unresectable melanoma, which is the focus of this STA, is classified as AJCC stage III or IV. The majority of people are diagnosed at an early stage of the disease, however approximately 10% of melanoma patients are not diagnosed until the disease has reached stage III or IV.[15, 16]

The company's overview of the many prognostic factors that can influence disease progression is presented in Box 2.

Box 2. Prognostic factors in melanoma

There are also a number of prognostic factors in melanoma, the most significant of which include speed of diagnosis, staging and location of metastasis, lactate dehydrogenase (LDH) levels, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale at diagnosis and age.[13, 14, 17-21] Stage IV (metastatic) disease and poor performance status at diagnosis have the poorest prognosis, particularly when brain metastases are present.[13, 14, 17-19, 22]

As mentioned, the prognosis for people with advanced melanoma is generally poor; for people with stage IV melanoma the one-year survival was 10-35%, decreasing to 8-25% for five-year survival in 2010.[7] However, life expectancy may have improved more recently due to the availability of new treatments.

Around 50% of melanoma patients have a mutation in their BRAF gene ($BRAF^+$); a serine/threonine protein kinase, which activates the MAP kinase/ERK-signalling pathway.[23] A BRAF mutation may affect the prognosis in terms of having a poorer prognosis of overall survival.[24] However, the main difference for $BRAF^+$ and $BRAF^-$ patients is the treatment options available to the patients, which does affect the prognosis of their disease.

Based on expert clinical advice, the Evidence Review Group (ERG) considers the company's overview of the underlying health problem to be appropriate and relevant to the decision problem that is the focus of this Single Technology Appraisal (STA).

2.2 Critique of company's overview of current service provision

In the CS the company gives an overview of the current clinical pathway and treatment options for patients with advanced melanoma (CS, Section 3.2). The company also provides a list of issues with current clinical practice (CS, Section 3.5), a list of relevant clinical guidelines and NICE guidance (CS, Section 3.4), and expected changes to the current service provision that will be needed for the use of combination immunotherapy (CS, Section 2.4).

$BRAF^+$ melanoma patients have a greater number of treatment options than $BRAF^-$ patients. Until recently treatment for $BRAF^-$ patients was limited to ipilimumab. If ipilimumab could not be tolerated, the disease was very fast paced or progressed, the options for $BRAF^-$ patients were limited to clinical trial enrolment or palliative care. The first-line treatment for $BRAF^+$ patients were ipilimumab or one of the BRAF inhibitor dabrafenib or vemurafenib, depending on whether a patient was assessed as high risk. The ERG notes that according to the National Comprehensive Cancer Network (NCCN) guidelines patients would be classified as high risk if a clinical deterioration is

anticipated within 12 weeks.[25] According to the company, patients' risk status is assessed based on tumour burden, performance status (symptom burden), prognosis and pace of disease. A fast-paced disease was confirmed by the ERG clinical experts as one of the main criteria for considering treatment options according to the high risk profile. High risk patients would not be suitable for ipilimumab monotherapy because of the delayed response kinetics compared to the BRAF inhibitors.[2, 26, 27] Therefore, high risk $BRAF^-$ patients were generally offered palliative care or clinical trials, and high risk $BRAF^+$ patients are likely to be treated with a BRAF inhibitor as first-line therapy. $BRAF^+$ patients who progress on BRAF inhibitor therapy can subsequently receive ipilimumab monotherapy and $BRAF^+$ patients who progress on ipilimumab can subsequently receive BRAF inhibitor therapy. The therapeutic intent for low risk patients, who are anticipated to be clinically stable for more than 12 weeks according to NCCN guidelines, is long-term survival.[25]

After the mentioned options of systemic treatments have been tried, patients' last option is palliative care, for which the ERG notes that the company does not give any further details.

The company lists several issues with current clinical practice (CS, Section 3.5) including:

- 50% of melanoma patients being $BRAF^-$ with limited treatment options;
- Long-term survival benefit has not been demonstrated with BRAF inhibitors;
- Development of resistance to BRAF inhibitors;
- Low response rate to ipilimumab;
- Long-term survival is only achieved in 20% of patients on ipilimumab;
- Slow response time with ipilimumab.

The ERG notes that the company's description of the current clinical pathway was in accordance with NICE guidance on systemic anticancer treatments. The company acknowledges that more recently several new therapies have received market authorisation for treatment of advanced melanoma including the PD-1 checkpoint inhibitors nivolumab and pembrolizumab, and the BRAF/MEK inhibitor combination therapies dabrafenib + trametinib and vemurafenib + cobimetinib. NICE recently recommended both pembrolizumab (November 2015[28]) and nivolumab (February 2016[29]). The ERG notes that the BRAF/MEK inhibitor combination therapies are both being assessed by NICE with recommendations expected later in 2016.

In the CS Section 3.2 the company describes the anticipated treatment pathway including nivolumab plus ipilimumab combination therapy (hereafter referred to as combination immunotherapy) and recently recommended PD-1 checkpoint inhibitors. Combination immunotherapy is anticipated by the company to be first-line therapy for all patients, regardless of BRAF mutation status, as PD-1

checkpoint inhibitors do not have the delayed response kinetics observed with ipilimumab.[30] Hence, the first consideration would be whether the patient is likely to tolerate combination therapy, i.e. tolerate the side effects of the treatment. The company acknowledges eligibility for combination immunotherapy to be a subjective assessment. Clinicians may base this judgement on a combination of factors such as the presence of brain metastases, performance status, or disease volume. Patients who are not considered eligible for combination immunotherapy are likely to receive pembrolizumab or nivolumab monotherapy as first-line treatment, irrespective of BRAF status and risk of metastases. Subsequent lines of therapy will include ipilimumab and BRAF inhibitors based on BRAF status and risk, similar to current clinical practice. According to the company patients who receive combination immunotherapy as first-line treatment are unlikely to receive either nivolumab or ipilimumab in subsequent lines of treatment.[30]

Based on clinical expert advice the ERG notes that, combination immunotherapy may become the preferred choice for first-line treatment of advanced melanoma. However, the ERG clinical expert also points out that the group of patients that may benefit the most from combination immunotherapy as first-line treatment are those with high risk and/or large tumour burden disease. The preferred first-line treatment for some patients may be PD-1 inhibitor monotherapy (pembrolizumab or nivolumab) because of the better side effect profile compared to combination immunotherapy. Also, if either of the BRAF/MEK inhibitor combination therapies are recommended by NICE later this year (2016) they may become the preferred first-line treatment option for some $BRAF^+$ patients, as they also have a fast response time, but may have a better response rate and be better tolerated than combination immunotherapy.

The ERG recognises the importance for patients with advanced melanoma to have a wide range of effective treatment options. According to the company the two groups of patients likely to have the greatest need for combination immunotherapy are $BRAF^-$ patients and $BRAF^+$ patients who fail to respond to BRAF inhibitor therapy at first-line. The ERG notes that the latter group is expected to be small if most patients follow the suggested treatment pathway with combination immunotherapy as first-line treatment.

The company estimates the number of new cases of advanced (unresectable or metastatic) melanoma, which constitutes the patient group defined in the NICE final scope[1] for this STA, to 1,304 in 2016 (CS, Section 3.3). The company does not give an estimate of the proportion of this population who may be eligible to treatment with combination immunotherapy. The ERG's clinical experts agree the importance of combination immunotherapy for a group of patients with advanced and unresectable melanoma. However, they also note that a substantial proportion of patients will not be able to tolerate the toxicity of combination therapy.

The company also gives a description of possible changes in service provision and management needed when combination immunotherapy is used in clinical practice (CS Section 2.4). The company anticipates existing staffing and infrastructure for administration and monitoring of cancer treatments to be utilised for the use of combination immunotherapy. The company states that the main additional resource associated with the use of combination immunotherapy is the more frequent administration schedule; after the first four doses of nivolumab and ipilimumab, which are 3-weekly, nivolumab is administered every two weeks whereas e.g. pembrolizumab is given every three weeks. However, the company also notes that, "the additive toxicity of administering nivolumab and ipilimumab concurrently may increase monitoring requirements" (CS, pg 26, Section 2.4).

The ERG clinical expert notes that both the incidence of and the management needed for side effects of treatment may increase with the introduction of combination immunotherapy in clinical practice. More monitoring and administration resources will be needed which is not accounted for in the current infrastructure.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provides a summary of the final decision problem issued by NICE (CS, Section 1.1) together with a brief description of the rationale for any deviation from the decision problem (Table 1).

Table 1. Summary of decision problem as outlined in the CS (reproduced from CS Table 1, pg 14)

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	Adults with advanced (unresectable or metastatic) melanoma	Adults with advanced (unresectable or metastatic) melanoma	-
Intervention	Nivolumab in combination with ipilimumab	Nivolumab in combination with ipilimumab	-
Comparator(s)	• Ipilimumab • Pembrolizumab • BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma	• Ipilimumab • BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma	The current standard of care is ipilimumab and/or the BRAF inhibitors (for those with BRAF mutation-positive disease only). Pembrolizumab is not included in the current clinical pathway of care having only been recommended by NICE for use in NHS England after disease progression with ipilimumab in October 2015; and for use in patients not previously treated with ipilimumab in November 2015. Recent prescribing data indicate that there is virtually no pembrolizumab usage in a first-line setting and it is not in routine use in clinical practice. Pembrolizumab is not therefore established standard of care for advanced melanoma in NHS England and thus is not a relevant comparator to the Regimen [combination immunotherapy].
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	-
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per	A cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	life year is presented. A lifetime time horizon of 40 years is used in the base case analysis. Costs are considered from a National Health Service and Personal Social Services perspective. The availability of patient access schemes for the comparator technologies has been taken into account in a confidential appendix, list prices are used within the submission document as requested by NICE.	
Subgroups to be considered	None specified.	None specified.	-
Special considerations including issues related to equity or equality	None specified.	None specified.	-

3.1 Population

CheckMate 067[31] and CheckMate 069[32] are the key trials that form the basis of the direct clinical evidence submitted by the company. The eligibility criteria for enrolment were similar in the two trials (Table 2): adults (≥18 years of age) with unresectable stage III or stage IV melanoma (AJCC staging) and ECOG PS of 0 or 1. However, to be eligible for Checkmate 067, patients needed to have a known BRAF mutation status and prior radiotherapy (non-systemic) completed ≥4 weeks before study drug administration, in contrast to the CheckMate 069 RCT where this was not required.

The ERG considers the trial populations to be largely in line with the final scope issued by NICE[1], although the scope did not specify patients with a specific performance status or without prior systemic anticancer treatments.

Table 2. Eligibility criteria for participants in CheckMate 067 and CheckMate 069 (adapted from CS, pg 47, Table 11)

	CheckMate 067	**CheckMate 069**
Location	Patients were treated across 137 sites in Australia, Europe, Israel, New Zealand and North America, including 7 sites in the United Kingdom	Patients were treated across 21 sites in France and North America.
Eligibility criteria for participants	Men and women aged ≥18 years who signed informed consent and met the following main disease criteria upon screening were enrolled: Untreated, histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging PD-L1-positive, PD-L1-negative or PD-L1-intermediate classification according to recent biopsy from an unresectable or metastatic site Known BRAF mutation status Prior radiotherapy (non-systemic) completed ≥4 weeks before study drug administration Measurable disease by RECIST v1.1 criteria ECOG PS of 0 or 1 Patients who met any of the following key criteria were excluded from study eligibility: Active brain metastases or leptomeningeal metastases Ocular melanoma Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured Active, known or suspected autoimmune disease Conditions requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration Prior treatment with an anti-PD-1, anti-PD-	Men and women aged ≥18 years who signed informed consent and met the following main disease criteria upon screening were enrolled: Histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging No prior systemic anticancer therapy for unresectable or metastatic melanoma. Note that prior adjuvant or neoadjuvant melanoma therapy was permitted if it was completed at least 6 weeks prior to first dose and all related AEs have either returned to baseline or stabilised. Measurable disease by RECIST v1.1 criteria ECOG PS of 0 or 1 Patients who met any of the following key criteria were excluded from study eligibility: Active brain metastases or leptomeningeal metastases Ocular melanoma Active, known or suspected autoimmune disease Conditions requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration Prior randomisation in an ipilimumab study trial Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody or any antibody or drug specifically targeting T-cell co-stimulation or checkpoint

	L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibody or any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways	pathways
Pre-planned subgroups	Subgroup analyses assessing the impact of age, gender, race, region, baseline ECOG PS, PD-L1 expression status, BRAF mutation status, M stage at study entry, history of brain metastases, smoking status, baseline LDH and AJCC stage on clinical efficacy outcomes were pre-planned.	Subgroup analyses assessing the impact of M stage at study entry, AJCC stage, age, gender, race, region, baseline ECOG performance status, history of brain metastases, smoking status, and baseline LDH on clinical efficacy outcomes were pre-planned for patients with BRAF mutation-negative and BRAF mutation-positive tumours.
Abbreviations in table: AJCC, American Joint Committee on Cancer; CD137, cluster of differentiation 137 (a member of the tumour necrosis factor family); CTLA-4, cytotoxic T-lymphocyte associated antigen 4; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand-1; PS, performance score; RECIST, Response Evaluation Criteria in Solid Tumors. **Source**: CheckMate 067 CSR[33]; CheckMate 069 CSR[34]; Larkin *et al*. 2015[31]; Postow *et al*. 2015.[32]		

In both trials there were several pre-planned subgroups, the results of which the company presents in CS Section 4.8. No subgroups were identified in the scope issued by NICE.[1] The ERG notes that the omission of subgroups from the final scope is in line with the anticipated clinical pathway if combination immunotherapy is recommended by NICE. The ERG also notes that the subgroups presented by the company include important prognostic factors and factors that may guide treatment choice.

CheckMate 069 was carried out at several sites in France and North America, and CheckMate 067 at sites in Australia, Israel, New Zealand, North America and Europe, including 66 patients (10.5%) from seven sites in the United Kingdom. In both trials randomisation was stratified by BRAF mutation status. However, the proportion of $BRAF^-$ patients in the trials was substantially higher (68-78%) than in the general patient population with advanced melanoma where around 50% are $BRAF^-$.

In summary, the ERG's clinical experts stated that the characteristics of the patient population enrolled in CheckMate 067 and 069 are representative of patients with metastatic or unresectable melanoma in England and Wales, however, an eligibility criteria for enrolment in these trials was an ECOG of 0 or 1, whereas in clinical practice the performance status of patients will be mixed, with some patients with ECOG 2.

3.2 Intervention

The company provides an overview of the technology (CS Section 2.1), the regulatory status (CS Section 2.2) and draft Summary of Product Characteristics (SmPC) of nivolumab, ipilimumab and the combination of the two.

Ipilimumab and nivolumab are both human monoclonal antibodies that act as inhibitors of T-cell receptors known as checkpoints, i.e. checkpoint inhibitors. Ipilimumab and nivolumab inhibit

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) respectively, which are both involved in T-cell differentiation and function. The company description of the mechanism of action of nivolumab and ipilimumab is presented in Box 3.

Box 3 nivolumab and ipilimumab mechanism of action (CS, pg 22, Section 2.1)

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) are immune checkpoints involved in T-cell differentiation and function:

•CTLA-4 is specifically involved in inhibiting constant T-cell production to avoid 'self-damage' in the priming and activation (early) stage of the immune response. This pathway 'switches off' the immune response to tumour antigens stopping production of activated T-cells in human malignancy.

•PD-1 is specifically involved in inhibiting T-cell destruction of healthy, 'self-cells' at the effector (later) stage of the immune response. Tumour cells can exploit this pathway by up-regulating proteins that engage PD1 to limit the activity of T-cells at the tumour site.

Ipilimumab and nivolumab are both fully human, monoclonal immunoglobulin antibodies (IgG1k and IgG4 HuMab, respectively) that act as checkpoint inhibitors of CTLA-4 and PD-1 at their distinct, yet complementary, positions within the T-cell response pathway:

•Ipilimumab stops the immune response from being 'switched off' which allows the production of active T-cells to continue, increasing the number of activated T-cells surrounding the tumour.

•Nivolumab stops the inactivation of T-cells at the tumour site, allowing the active T-cells to infiltrate and destroy the tumour.

The Regimen [combination immunotherapy] therefore potentiates immune-mediated tumour destruction; stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes.

Nivolumab and ipilimumab combination immunotherapy does not currently have a UK marketing authorisation for the treatment of advanced melanoma. The company anticipates the European Medicines Agency's (EMA) Committee for Human Medicinal Products (CHMP) to give its opinion on the combination immunotherapy early 2016. At the time of writing no CHMP opinion has been published. Combination immunotherapy of nivolumab and ipilimumab has been approved in the US for the treatment of unresectable or metastatic melanoma in $BRAF^{-}$ patients.

Nivolumab and ipilimumab monotherapy both have been granted marketing authorisation by the FDA and the EMA for use in North America and Europe, respectively, for the treatment of advanced melanoma in adults. Nivolumab also has a marketing authorisation for the treatment of squamous non-small cell lung cancer after previous chemotherapy in adults. The ERG notes that in November

2015 nivolumab also received marketing authorisation in the US for treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy.[35]

Nivolumab plus ipilimumab combination therapy is administered through intravenous infusion in a hospital or clinic setting. The recommended dose of nivolumab is 1mg/kg of body weight plus 3mg/kg of body weight of ipilimumab given every three weeks for four doses followed by nivolumab 3mg/kg of body weight bi-weekly. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated, for a maximum duration of two years. Hence, in the key clinical trials, CheckMate 067[31] and CheckMate 069[32], combination immunotherapy was given according to the draft SmPC recommendation and treatment after disease progression was permitted for patients who had a clinical benefit and were tolerating treatment, as determined by the investigator.

To summarise, the ERG considers the intervention in the CS to be consistent with the anticipated licence and the NICE final scope for this STA.[1]

3.3 Comparators

The final scope issued by NICE[1] lists comparators of interest as:

- ipilimumab;
- pembrolizumab;
- BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma.

The company does not include pembrolizumab as a comparator in the CS and gives the following reasons (Table 1):

- "[pembrolizumab] is not included in the current clinical pathway of care having only been recommended by NICE for use in NHS England after disease progression with ipilimumab in October 2015; and for use in patients not previously treated with ipilimumab in November 2015. Recent prescribing data indicate that there is virtually no pembrolizumab usage in a first-line setting and it is not in routine use in clinical practice. Pembrolizumab is not therefore established standard of care for advanced melanoma in NHS England and thus is not a relevant comparator to the Regimen [combination immunotherapy]." (CS, pg 14, Section 1.1)
- "at the time of systematic review initiation, pembrolizumab was not recommended for use in the NHS by NICE and was not included in either the draft or pre-invitation scope for this appraisal; therefore pembrolizumab was not included as an intervention of interest." (CS, pg 39, Section 4.1)

The ERG does not consider the company's justification for omitting pembrolizumab from its submission to be valid. Pembrolizumab is a licensed comparator that has been approved for use by NICE in this indication, and was specifically requested by NICE in the final scope for this STA.

The company carried out a systematic literature review to identify studies that could inform the comparisons of combination immunotherapy to ipilimumab and BRAF inhibitors. CheckMate 067[31] and CheckMate 069[32] evaluated combination immunotherapy versus ipilimumab. CheckMate 067 also included a nivolumab monotherapy treatment arm, however, this falls outside the scope of this STA.

Due to the immaturity of the survival data in CheckMate 067 and CheckMate 069, the company performed an indirect comparison to estimate survival outcomes for combination immunotherapy versus ipilimumab using a covariate adjusted data approach. The company used PFS data from CheckMate 067 (combination immunotherapy and ipilimumab arm) and data from CheckMate 066[36] (nivolumab arm) and MDX010-20[26] (ipilimumab and ipilimumab+gp100 arms) as a proxy for OS, assuming equal post-progression survival (PPS) efficacy for ipilimumab, nivolumab and combination immunotherapy. The assumption of equal PPS efficacy for the immunotherapies is discussed in Section 4.4.1.

The company did not identify any direct evidence comparing combination immunotherapy to either of the BRAF inhibitors dabrafenib or vemurafenib. The company therefore performed an indirect comparison using parametric survival modelling of patient level data from CheckMate 067, CheckMate 066, and MDX010-20, as combination immunotherapy versus ipilimumab, and using summary data from BRIM-3[27] (vemurafenib versus dacarbazine). Combination immunotherapy was not compared directly to dabrafenib. Instead, the company assumed that vemurafenib and dabrafenib have approximately equal efficacy. The assumption of equal efficacy for dabrafenib and vemurafenib is discussed in Section 4.4.2.

The ERG's clinical experts indicated that, though there are differences across the populations included in the identified trials, the differences do not preclude an indirect comparison.

In summary, the ERG considers that the CS does not fully address the scope issued by NICE based on the omission of the comparator pembrolizumab and inclusion of dabrafenib only by making an assumption of equivalence with vemurafenib.

3.4 Outcomes

In Section 4.7 of the CS the company provides direct evidence on the outcomes listed in the final scope issued by NICE,[1] which were:

- overall survival (OS);
- progression free survival (PFS);
- objective response rate (ORR);
- adverse effects (AE) of treatment;
- health-related quality of life (HRQoL).

The primary outcomes in CheckMate 067[31] were OS (defined as time between the date of randomisation and the date of death) and PFS (defined as the time between the date of randomisation and the first date of documented progression or death due to any cause). Secondary outcomes included:

- ORR (defined as the number of patients with a best overall response [BOR] of complete response [CR] or partial response [PR] divided by the number of randomised patients (investigator-assessed);
- OS, PFS and ORR difference between the two experimental arms;
- OS based on PD-L1 expression level (PD-L1 status assessed using a verified assay with ≥5% tumour cell membrane expression cut-off); and
- HRQoL measured by mean changes from baseline in the EORTC QLQ-C30 scales.

In CheckMate 069[32] the primary outcome was ORR in $BRAF^-$ patients. ORR was defined as the number of patients with a BOR of CR or PR divided by the number of randomised patients. Secondary outcomes included:

- duration of response (DOR), defined as the time between the date of first response to the date of first documented tumour progression or death due to any cause (investigator-assessed);
- time to response (TTR), defined as the time from randomisation to the date of the first documented CR or PR (investigator-assessed);
- PFS in $BRAF^-$ patients;
- ORR in $BRAF^+$ patients;
- PFS in $BRAF^+$ patients;
- HRQoL (measured by mean changes from baseline in the EORTC QLQ-C30 scales).

In both trials tumour response was assessed according to the RECIST, version 1.1.[37] Tumour assessments began 12 weeks (±1 week) from first dose and continued every six weeks (±1 week) for

the first 12 months and every 12 weeks (±1 week) thereafter, until disease progression was documented or treatment was discontinued.

Both trials also captured several exploratory outcomes including:

- percent change in tumour volume;
- safety and tolerability: measured by the incidence of AEs, SAEs, deaths and laboratory abnormalities;
- HRQoL: assessed using EuroQol-five dimensions questionnaire (EQ-5D) and WPAI:GH;
- biomarker assessment.

3.5 Other relevant factors

The company has not identified any equality issues related to the use of combination immunotherapy. The ERG clinical experts agree with this statement.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

This section describes and critiques the systematic review methods, in terms of searching, inclusion/exclusion, data extraction, and quality assessment of trials informing both the company's direct and indirect comparisons. This section also covers the evidence synthesis of head-to-head trials, however the methods for the indirect comparisons are described and critiqued in Section 4.4.

The company presents a full systematic review of the direct evidence for clinical efficacy of combination immunotherapy from identified RCTs (company submission [CS] Section 4.1, and 4.6).

4.1.1 Searches

The company performed a systematic search for RCTs assessing the clinical efficacy of combination immunotherapy, ipilimumab and BRAF inhibitors in patients with advanced (metastatic and unresectable) melanoma (search strategies presented in CS Appendix 3). The search informed both the direct and indirect evidence in the CS (CS Section 4.1).

Searched databases listed in the CS are:

- MEDLINE and MEDLINE In-Process;
- EMBASE;
- The Cochrane Library, including the following:
    - The Cochrane Database of Systematic Reviews (CDSR);
    - The Cochrane Central Register of Controlled Trials;
    - The Database of Abstracts of Reviews of Effects (DARE);
    - The Health Technology Assessment (HTA) database.

The CS also specifies dates when searches were performed (September 2015), the coverage of and specific search terms for each database. The search strategies included terms for melanoma, nivolumab, ipilimumab, vemurafenib, dabrafenib, and a search filter for RCTs, but no search terms for pembrolizumab. The company also hand-searched the last three years of relevant conference proceedings:

- The American Society of Clinical Oncology (ASCO, 2013-2015);

- European Society for Medical Oncology (ESMO, 2013-2015);
- The Society for Immunotherapy of Cancer (2013-2015);
- The Society for Melanoma Research (SMR, 2013-2015).

The database searches were complemented by searching reference lists of systematic reviews, clinical guidelines and previous health technology assessments identified through the systematic search. Unpublished data held by the company were also reviewed.

No systematic search for data on safety and tolerability or for non-RCT evidence was presented. At the clarification stage, the company explained that, "Non-RCT evidence is presented for the Regimen [combination immunotherapy] only to supplement RCT data." and "A systematic search for non-RCT evidence of the Regimen [combination immunotherapy] was not required as this treatment is not available outside of BMS (the company, Bristol Myers Squibb) sponsored clinical trial programmes in the European Union (EU) and only recently became available outside the EU" (Clarification response A1). However, data on efficacy, safety and tolerability from one non-RCT (CheckMate 004[38]) were presented in the CS.

In summary, the ERG considers that the company conducted a comprehensive search strategy, which was appropriate for the decision problem with the exception of the exclusion of pembrolizumab. All RCTs relevant to the clinical effectiveness of combination immunotherapy in the treatment of advanced melanoma are likely to have been identified, however, the ERG notes that it is unclear if CheckMate 004 is the only non-RCT of combination immunotherapy or if there may be other observational trials not reported in the CS.

4.1.2 Inclusion criteria

The company applied inclusion and exclusion criteria summarised in Table 3 to identify RCTs to inform both direct and indirect evidence on the clinical effectiveness of combination immunotherapy.

Table 3. Eligibility criteria used in the search strategy (reproduced from CS, pg 39, Table 8)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Adult patients with advanced (Stage III or IV unresectable or metastatic) melanoma • Treatment naïve and/or treatment exposed	• Patients with Stage I or II melanoma • Patients with Stage III resectable melanoma • Paediatric melanoma patients • Patients with non-melanoma malignancy/disease
Intervention	• Nivolumab plus ipilimumab	Any other

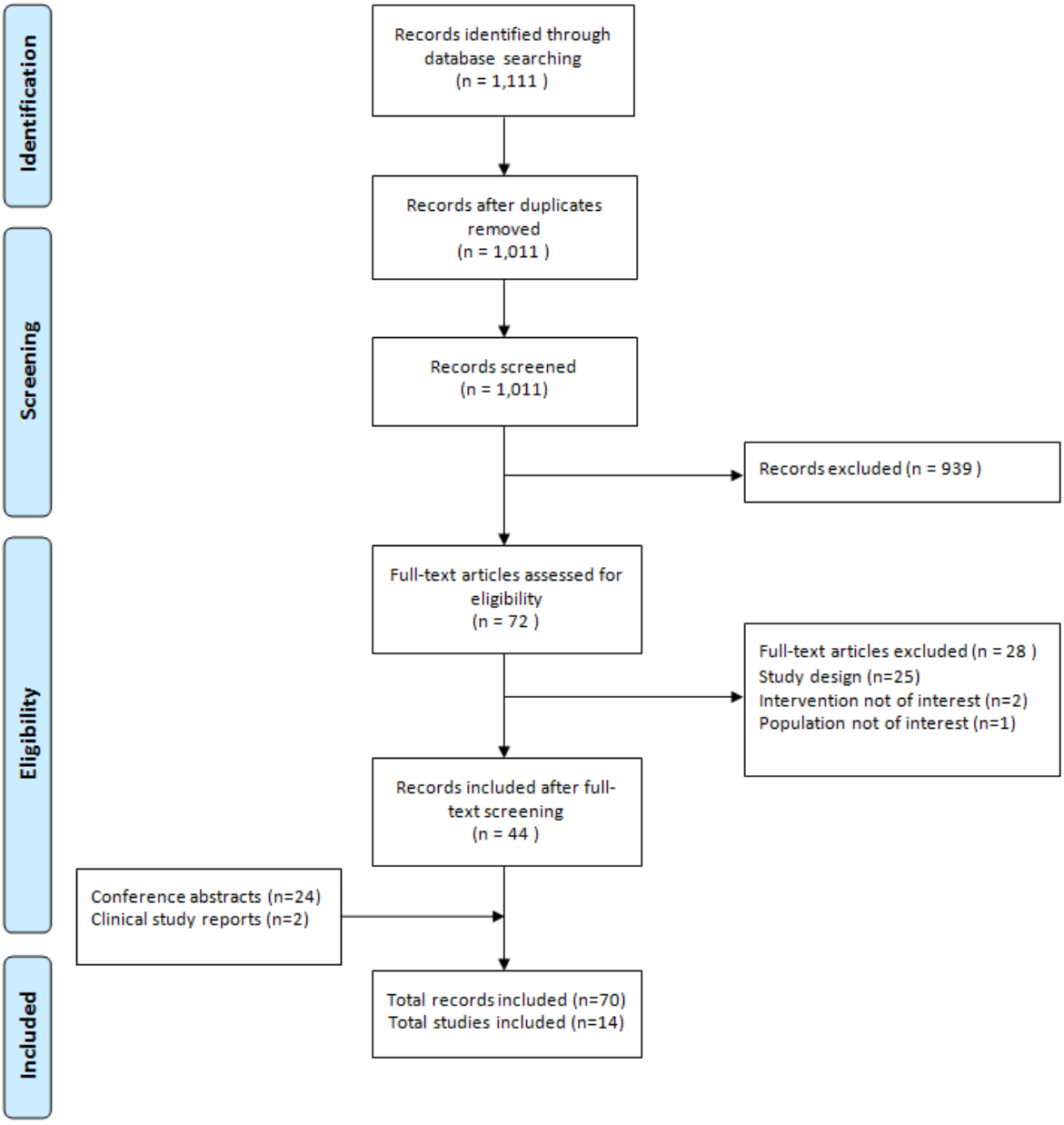
Clinical effectiveness	Inclusion criteria	Exclusion criteria
	• Ipilimumab 3mg/kg • Dabrafenib 150mg • Vemurafenib 960mg	
Comparators	• Active therapy • Palliative care • Best supportive care • Placebo	None
Outcomes	• Overall survival • Progression-free survival • Objective response • Safety and tolerability • HRQL	None
Study design	• Randomised controlled trials • Systematic reviews/meta-analyses[a]	• Non-randomised controlled trials • Single-arm trials • Observational studies • Database analyses • Pooled data analyses • Non-systematic reviews • In-vitro studies • Preclinical studies • Case reports/series • Commentaries/letters/editorials
Language restrictions	None	None
Abbreviations in table: HRQL, health-related quality of life; kg, kilogram; mg, milligram. Notes: [a] included for reference review only.		

The ERG notes that the inclusion and exclusion criteria are in line with the scope issued by NICE[(1)] for this single technology appraisal (STA) with the exception of the exclusion of pembrolizumab as a comparator.[(1)] To inform any indirect comparison of combination immunotherapy and the comparators in the NICE scope, the ERG considers it appropriate to include additional interventions outside the NICE scope, such as nivolumab monotherapy, to facilitate the development of a complete network.

The methods applied by the company to identify relevant studies for inclusion in the review were in line with recommended practice for carrying out systematic reviews, as outlined by the Centre for Reviews and Dissemination.[(39)] Two reviewers independently assessed each reference (title and abstract) identified in the literature searches against the inclusion and exclusion criteria in Table 3. Citations meeting basic study selection criteria (or in cases of disagreement between the two reviewers) were obtained in full and independently assessed (secondary screening). In the event of disagreement between the two reviewers, a third reviewer independently assessed the paper and

applicability of selection criteria attained by consensus. The number of included and excluded studies at each stage is captured in the PRISMA diagram in Figure 1.

Figure 1. PRISMA flow diagram of the literature search process (reproduced from CS Figure 6)



Abbreviations in figure: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Of 14 trials meeting the inclusion criteria (reported in 14 primary publications and 56 secondary publications), two provided direct evidence on the clinical efficacy of combination immunotherapy versus ipilimumab: CheckMate 067[31] and CheckMate 069[32] (Table 4). No trials were identified that provided direct evidence on the clinical efficacy of combination immunotherapy versus either of the BRAF inhibitors (vemurafenib and dabrafenib).

Table 4: Included trials (adapted from CS, pg 42, Table 9)

Trial	Comparator(s)	Primary study reference
Studies investigating nivolumab + ipilimumab combination therapy		
CheckMate 067 (CA209-067)	Ipilimumab 3 mg/kg Nivolumab 3 mg/kg	Larkin *et al*. 2015[31]
CheckMate 069 (CA209-069)	Ipilimumab 3 mg/kg	Postow *et al*. 2015[32]
Studies investigating ipilimumab 3 mg/kg monotherapy		
CA184-004	Ipilimumab 10 mg/kg	Hamid *et al*. 2011[40]
CA184-022	Ipilimumab 0.3 mg/kg Ipilimumab 10 mg/kg	Wolchok *et al*. 2010[41]
MDX010-08	Ipilimumab 3 mg/kg + dacarbazine	Hersh *et al*. 2011[42]
MDX010-20	Ipilimumab 3 mg/kg + gp-100 gp-100	Hodi *et al*. 2010[26]
Keynote 006	Pembrolizumab 10 mg/kg q2w Pembrolizumab 10 mg/kg q3w	Robert *et al*. 2015[43]
Studies investigating dabrafenib 150 mg monotherapy		
BREAK-3	dacarbazine	Hauschild *et al*. 2012[2]
COMBI-d	Dabrafenib + trametinib	Long *et al*. 2014[44]
BRF113220	Dabrafenib + trametinib	Flaherty *et al*. 2012[45]
Studies investigating vemurafenib 960 mg monotherapy		
BRIM-3	dacarbazine	Chapman *et al*. 2011[27]
COMBI-v	Dabrafenib + trametinib	Robert *et al*. 2015[46]
coBRIM	Vemurafenib + cobimetinib	Larkin *et al*. 2014[47]
Grippo *et al.* 2014	Vemurafenib 240 mg Vemurafenib 480 mg Vemurafenib 720 mg	Grippo *et al*. 2014[48]
Abbreviations in table: gp-100, glycoprotein-100; q2w, every 2 weeks; q3w, every 3 weeks.		

As a result of immature overall survival data from the key trials, CheckMate 067 and CheckMate 069, the company supported the head-to-head data, with more mature survival data from two other trials, MDX010-20[26] (ipilimumab arm) and CheckMate 066[36] (nivolumab arm), assuming equivalence between combination immunotherapy, nivolumab and ipilimumab for long-term predictions of survival (discussed in Section 4.4.1). MDX010-20 was identified in the systematic search, however, CheckMate 066 was a post hoc addition as it did not meet the intervention inclusion criteria.

A network meta-analysis (NMA), combining combination immunotherapy with the comparators in the scope, was not deemed appropriate by the company (discuss in Section 4.4). To inform the indirect comparison of combination immunotherapy and BRAF inhibitors, the company modelled progression and survival based on covariate adjusted survival data from CheckMate 067, MDX010-20 and CheckMate 066 (as above) with data from BRIM-3[27] (vemurafenib arm), identified in the systematic search.

The ERG notes that the choice of trials informing the long-term survival data for combination immunotherapy and ipilimumab, and the indirect comparison to BRAF inhibitors is justified by the

company based on, e.g. length of follow up and availability of individual patient data, but the selection criteria and process were not specified in the CS (discussed in Section 4.4.1 and 4.4.2).

In summary, the ERG considers it likely that the company identified and included all relevant RCTs with direct evidence on the clinical efficacy of combination immunotherapy versus the comparators listed in the NICE scope. The company has also likely identified all potentially relevant RCTs of ipilimumab, vemurafenib and dabrafenib, which could be relevant for the company's approach to indirect comparison. However, the selection of trials for the indirect comparisons is unclear in the CS and a potential source for bias.

4.1.3 Data extraction

The ERG notes that the methods used for data extraction were not reported in the CS. However, at the clarification stage the company stated that, "One reviewer extracted data items from RCTs meeting the eligibility criteria (CS, Table 8) as required for statistical analyses and completion of the NICE submission template. All extracted data was verified against the original source by a second reviewer." Data extraction in a systematic review is undertaken by two reviewers who independently extract data using standardised data extraction forms, as outlined by the Centre for Reviews and Dissemination.[39] As a minimum, one reviewer should extract the data with a second reviewer independently checking the data extraction forms for accuracy and detail. If disagreements occur between assessors, they should be resolved according to a predefined strategy using consensus and arbitration by a third reviewer. The company also lists the sources for the extracted data (CS Table 9). In the CS a summary of trial methods is presented (CS Section 4.3) including: trial design and setting, intervention and comparator, patient eligibility, outcomes, subgroups, a description of the statistical methods for the trials (CS Section 4.4), and an overview of the patient flow in the trials (CS Section 4.4). These sections in the CS are summarised in Section 4.2 of this report.

4.1.4 Quality assessment

Quality assessment of RCTs informing the direct evidence

The company critically appraised the two key RCTs: CheckMate 067[31] (Table 6) and CheckMate 069[32] (Table 5). The assessment appears to be based on NICE-recommended checklist for RCT assessment of bias.[49]

The ERG independently validated the company's assessment and notes that some aspects are missing in the company's quality assessment of the RCTs (Table 5 and Table 6). The ERG largely agrees with the company's quality assessment and judged the literature related to each of the trials (protocol, primary publication, CS Appendix or CSR) to mostly answer the quality assessment questions adequately.

Both CheckMate 069 and CheckMate 067 randomised participants according to BRAF mutation status (V600 mutation–positive versus wild-type) and CheckMate 067 also stratified according to tumour PD-L1 status (positive versus negative or indeterminate), and American Joint Committee on Cancer (AJCC) metastasis stage (M0, M1a, or M1b versus M1c). Both RCTs used an interactive voice response system for allocation of patients to the treatment and control arm and the patients, investigator, site staff and sponsor were blinded to the drug administered. There were no major differences in baseline characteristics between the intervention and control arms in both RCTs.

In CheckMate 069 there was a higher discontinuation rate in the combination immunotherapy arm (76.6%) compared with the ipilimumab arm (69.6%). In Checkmate 067 there were imbalances in drop-outs between the arms and it is unclear whether these were expected. More participants in the ipilimumab compared to the combination immunotherapy arm discontinued treatment.

Outcomes appeared to be reported with sufficient detail and valid methodology seemed to have been used for assessment. However, the company reports that patients were allowed to receive treatment beyond RECIST-defined progression to reflect clinical practice (Box 4).

Box 4. Outcomes RCTs for quality assessment (CS, pg 62, Section 4.6)

Outcome assessments were all conducted in accordance with trial validated methodology. However, in recognition of the limitations of validated RECIST criteria for assessing immuno-oncology drugs (see Section 4.3), patients were allowed to receive treatment beyond RECIST-defined progression to better reflect clinical practice. Indeed, both trials are thought to reflect routine clinical practice in England in respect of population, comparator choice, treatment administration and outcomes being assessed.
Abbreviations in box: RECIST, Response Evaluation Criteria in Solid Tumors.

Power calculations and intention-to-treat analysis appeared to be undertaken appropriately in both RCTs.

Table 5. Quality assessment of CheckMate 069 (Adapted from CS, pg 62-63, Section 4.6, Table 14 and Appendix 6, Table 6)

Question	Company's assessment	ERG's assessment
Was randomisation carried out appropriately?	Yes, randomisation performed by permuted blocks method and stratified according to BRAF mutation status.	Yes, 1:1:1 ratio and stratification used; quote: "Randomization was stratified according to BRAF mutation status (V600 wild-type versus mutation-positive)."
Was the concealment of treatment allocation adequate?	Yes, enrolment and randomisations performed through IVRS.	Yes; quote: "Patients were randomised in a 2:1 ratio through an IVRS."
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, patient demographics well balanced with no key differences between the two groups.	Yes, no major differences in age, sex, disease stage at study entry, ECOG performance status, metastasis stage at study entry, lactate dehydrogenase, history

Question	Company's assessment	ERG's assessment
		of brain metastases, and BRAF V600 mutation.
Did the comparison groups receive the same care apart from the intervention(s) studied?	Not assessed	Yes, nivolumab plus ipilimumab versus ipilimumab plus placebo; quote: "ipilimumab (3 mg per kilogram of body weight) combined with either nivolumab (1 mg per kilogram) or placebo once every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram) or placebo every 2 weeks until the occurrence of disease progression or unacceptable toxic effects"
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, the sponsor, subjects, investigator and site staff were blinded to study drug administration until progression of disease and treatment discontinuation.	Yes; quote CSR: "The subjects, investigator, site staff and BMS were blinded to the study drug administered (ipilimumab plus placebo or nivolumab plus ipilimumab).
Were all groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)?	Not assessed	Unclear, minimum follow-up of 11 months.
Were there any unexpected imbalances in drop-outs between groups?	No, but reported in CS Section 4.6, pg 62 that "In CheckMate 069, treatment discontinuation rates were higher in the Regimen [combination immunotherapy] group."	Unclear, higher discontinuation rate in combination therapy group (76.6%) compared with ipilimumab group (69.6%; Appendix)
Were the groups comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)?	Not assessed	Yes, best overall response rates that could not be determined are similar between the groups (13% nivolumab plus ipilimumab; 10% ipilimumab).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not assessed	No.
Did the study have an appropriate length of follow-up?	Not assessed	Yes, minimum follow-up of 11 months.
Did the study use a precise definition of outcome?	Not assessed	Yes; quote: "The primary end point was the rate of investigator-assessed, confirmed objective response among patients with BRAF V600 wild-type tumors."
Was a valid and reliable method used to determine the outcome?	Not assessed	Yes; quote: "Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1,18 at the following time points: 12 weeks after the first treatment, every 6 weeks thereafter for the first year, then every 12 weeks until disease progression or discontinuation of treatment."
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to	Yes, primary efficacy analysis was performed according to the intention-to-treat principle.	Yes.

Question	Company's assessment	ERG's assessment
account for missing data?		
Was statistical powering such to detect a significant difference between treatment groups?	Yes	Yes; quote: "Given a two-sided alpha level of 0.05, we calculated that the sample of 100 patients with BRAF wild-type tumors would give the study approximately 87% power to detect a significant difference in the objective response rate between the combination group and the ipilimumab-monotherapy group, assuming an objective response rate of 40% versus 10%."
How closely do the RCT(s) reflect routine clinical practice	Population, treatment arms, administration and outcomes all relevant to clinical practice in NHS England.	ERG's clinical expert opinion: fairly reflective, but in practice there are more patients with poorer performance status; BRAF +ve patients are under-represented compared to clinical practice where they constitute 50% of patients, this is due to the fact that doctors may be reluctant to put them in trial as they would respond better to BRAF inhibitors or to a combination of BRAF and MEK inhibitors.
Abbreviations in table: BMS, Bristol-Myers Squibb; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; NHS, National Health Service; RCT, randomised controlled trial. Quotes are from Postow *et al*. 2015[30] unless stated otherwise. Source: Postow *et al*. 2015[32], CheckMate 069 CSR[34]		

Table 6. Quality assessment of CheckMate 067 (Adapted from CS, pg 62-63, Section 4.6, Table 14 and Appendix 6, Table 5)

Question	Company's assessment	ERG's assessment
Was randomisation carried out appropriately?	Yes, randomisation performed by permuted blocks method and stratified according to PD-L1 status, BRAF mutation status and AJCC metastasis stage.	Yes, 1:1:1 ratio and stratification used. Quote: "Randomization was stratified according to tumor PD-L1 status (positive versus negative or indeterminate), *BRAF* mutation status (V600 mutation–positive versus wild-type), and American Joint Committee on Cancer metastasis stage (M0, M1a, or M1b versus M1c)."
Was the concealment of treatment allocation adequate?	Yes, enrolment and randomisations performed through IVRS.	Yes, interactive voice response system used; quote protocol: "After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number."
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, patient demographics well balanced with no key differences between the two groups.	Yes, no major differences in age, sex, ECOG performance status, metastasis stage, lactate dehydrogenase, brain metastases, PD-L1 status, and *BRAF* status.
Did the comparison groups receive the same care apart from the intervention(s) studied?	Not assessed	Yes, nivolumab-plus-ipilimumab compared to nivolumab mono plus placebo and ipilimumab mono plus placebo; quote: "enrolled patients were randomly assigned in a 1:1:1 ratio to receive one of the following regimens: 3 mg of nivolumab per kilogram of body weight every 2 weeks (plus ipilimumab-matched placebo); 1 mg of nivolumab per kilogram every 3 weeks plus 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses, followed by 3 mg of nivolumab per kilogram every 2 weeks for cycle 3 and beyond; or 3 mg of ipilimumab

Question	Company's assessment	ERG's assessment
		per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, the sponsor, subjects, investigator and site staff were blinded to study drug administration until progression of disease and treatment discontinuation.	Yes; quote CSR: "The subjects, investigator, site staff and BMS were blinded to the study drug administered (nivolumab plus placebo, ipilimumab plus placebo, or nivolumab plus ipilimumab)."
Were all groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)?	Not assessed	Yes; quote: "The database lock occurred on February 17, 2015. At a median follow-up ranging from 12.2 to 12.5 months across the three groups."
Were there any unexpected imbalances in drop-outs between groups?	No	Unclear; there were imbalances in drop-outs between the groups but it is unclear whether these were expected. More participants in the ipilimumab compared to the nivolumab-plus-ipilimumab and nivolumab groups dropped out. The CS states, "the majority discontinued due to disease progression, which is accounted for within efficacy assessments" (CS, pg 62, Section 4.6) Quote: "At a median follow-up ranging from 12.2 to 12.5 months across the three groups, 117 of 313 patients (37.4%) in the nivolumab group, 93 of 313 (29.7%) in the nivolumab-plus-ipilimumab group, and 50 of 311 (16.1%) in the ipilimumab group were continuing study treatment (Table S1 in the Supplementary Appendix). The most frequent reason for discontinuation was disease progression in the nivolumab and ipilimumab monotherapy groups (154 of 313 patients [49.2%] and 202 of 311 [65.0%], respectively) and toxic effects of the study drug in the nivolumab-plus-ipilimumab group (120 of 313 [38.3%])."
Were the groups comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)?	NA	Yes, best overall response rates that could not be determined are similar between the groups (7.9% nivolumab; 6.7% nivolumab plus ipilimumab; 10.2% ipilimumab).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No.
Did the study have an appropriate length of follow-up?	Not assessed	Yes, patients were followed for a minimum of 9 months.
Did the study use a precise definition of outcome?	Not assessed	Yes; quote: "Progression-free survival was defined as the time between the date of randomization and the date of documented progression or death, whichever occurred first. Patients treated after progression were considered to have had progressive disease at the time of the initial progression event,

Question	Company's assessment	ERG's assessment
		as assessed by the investigator, regardless of subsequent tumor responses."
Was a valid and reliable method used to determine the outcome?	Not assessed	Yes; quote: "Patients were assessed for tumor response, according to RECIST, version 1.1,[15] at 12 weeks after randomization, then every 6 weeks for 49 weeks, and then every 12 weeks until progression or treatment discontinuation, whichever occurred later."
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, primary efficacy analysis was performed according to the intention-to-treat principle.	Yes.
Was statistical powering such to detect a significant difference between treatment groups?	Yes	Yes; quote: "For the comparison of progression-free survival, we estimated that the number of events that was projected to be observed at a follow-up of at least 9 months would give the study approximately 83% power to detect an average hazard ratio of 0.71 at a type I error rate of 0.005 (twosided) for all comparisons."
How closely do the RCT(s) reflect routine clinical practice	Population, treatment arms, administration and outcomes all relevant to clinical practice in NHS England.	ERG's clinical expert opinion: fairly reflective, but in practice there are more patients with poorer performance status; BRAF +ve patients are under-represented compared to clinical practice where they constitute 50% of patients, this is due to the fact that doctors may be reluctant to put them in trial as they would respond better to BRAF inhibitors or to a combination of BRAF and MEK inhibitors.
Abbreviations in table: AJCC, American Joint Committee on Cancer; ITT, intention-to-treat; IVRS, interactive voice response system; NHS, National Health Service; RCT, randomised controlled trial. Quotes are from Larkin *et al*. 2015[31] unless stated otherwise. Source: Larkin *et al*. 2015[31], Protocol Larkin *et al*. 2015[50], CheckMate 067 CSR[33].		

Quality assessment of RCTs in indirect comparisons

The company critically appraised the three RCTs included in the indirect comparisons (CS Appendix 6): CheckMate 066[36], MDX010-20[26], BRIM-3[27], and one additional trial not included in the indirect comparison, BREAK-3[2] based on NICE-recommended checklist for RCT assessment of bias.[49]

As previously mentioned for the quality assessment of the RCTs informing the direct evidence, some aspects are missing in the company's quality assessment of the RCTs and the ERG independently validated the company's assessment (Appendix 9.1). The ERG largely agrees with the company's quality assessment and judged the literature related to each of the trials (protocol, primary study publication or CS Appendix) to mostly answer the quality assessment questions adequately.

CheckMate 066 and MDX010-20 were double-blind, while BRIM-3 and BREAK-3 were open-label. Therefore, patients, investigators, study site monitors, site pharmacist and sponsors were not blinded

to the study treatment assignment. In BREAK-3 a masked independent review committee (IRC) reviewed all scans and, per protocol, had to confirm progression before patients crossed over from dacarbazine to dabrafenib. However, the ERG agrees with the company that the risk of bias related to the open-label nature of the studies is reduced because the primary outcomes were not patient-reported outcomes.

Quality assessment of non-RCTs

The company critically appraised CheckMate 004[38] (Appendix 9.1). The company stated, "Quality assessment of CheckMate 004 has been conducted by assessing risk of common types of bias (selection, performance, attrition and detection) as well as the applicability of study results to the decision problem." (CS, pg 106-107, Section 4.11).

The ERG notes that most of the assessments of performance, attrition and detection bias, which are part of the NICE-recommended checklist for non-controlled trials, are missing in the company's quality appraisal of CheckMate 004 and that the company has mostly focused on assessing the applicability of the study to the decision problem (Table 1).[49] The ERG independently validated the company's assessment based on the CSR[38] as the only other reference provided for the trial was a poster[51] (Appendix 9.1).

4.1.5 Evidence synthesis

The company initially did not conduct any meta-analyses of data from CheckMate 067[31] and CheckMate 069[32] stating that, "Meta-analysis was not conducted as data is available from a large Phase III trial (CheckMate 067) to inform outcomes and outcomes from the Phase II trial are consistent with those in the Phase III trial" (CS, pg 78, Section 4.9). The ERG disagrees with the company's rationale for not conducting a meta-analysis of the available comparable trials. As a point of principle, the results of studies (comparable or not) should not influence the decision to combine results in a meta-analysis. In this case the trials appear to be sufficiently comparable in terms of patient population, intervention, comparator, outcomes and study design. Therefore, pooling the data in a meta-analysis may provide increased statistical power and strengthen the interpretation of the results of the individual RCTs.

At the clarification stage, the company performed meta-analyses of CheckMate 067 and CheckMate 069 for PFS and ORR. The analyses were performed using the R package 'metafor'. PFS was analysed using the inverse variance method with log hazard ratios and standard errors for the log hazard ratios. Response rates (overall, complete and partial) were analysed using a random effects model.

4.1.6 Summary of review methods

The search for relevant RCTs was comprehensive and systematic, although it could have included additional comparators, like nivolumab although outside the scope, to facilitate indirect comparisons through an NMA or the approach presented by the company (covariate adjusted method). Instead CheckMate 066, which was not identified through the systematic search, was included and used in the indirect comparisons. The inclusion of trials was in line with the scope, though only a selection of the included studies were described and used in any analysis. The selection of these trials was not clear from the CS and may have introduced bias affecting the results. Although the key trials (CheckMate 067 and 069) were described in great detail, several of the trials used in the indirect comparisons were not, and the methods for data extraction were not specified in the CS. The quality assessments of the included trials were partially done in accordance to standard criteria recommended by NICE as several quality assessment criteria were not included. Evidence synthesis included meta-analyses of results from the key trials.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The company's systematic review identified two ongoing randomised controlled trials (RCTs) evaluating the effectiveness of nivolumab plus ipilimumab (combination immunotherapy) in the treatment of advanced, unresectable melanoma: CheckMate 067 and CheckMate 69 (Table 7). Both RCTs directly compare the clinical efficacy and safety of combination immunotherapy with ipilimumab 3mg/kg monotherapy. The company reasons that, "this is the most appropriate comparator of those referenced in the decision problem as (like the Regimen [combination immunotherapy]) it can be administered to all advanced melanoma patients, irrespective of BRAF status" (CS, pg 44, Section 4.2).

Table 7. List of relevant RCTs (reproduced from CS, pg 44, Table 10)

Trial name (NCT number)	Phase	Population	Intervention	Comparator	Primary study reference
CheckMate 067 (NCT01844505)	III	Advanced (unresectable or metastatic) melanoma patients who are treatment naïve.	Nivolumab plus ipilimumab	Ipilimumab 3mg/kg monotherapy Nivolumab 3mg/kg monotherapy[a]	Larkin *et al.* 2015[(31)]
CheckMate 069 (NCT01927419)	II	Advanced (unresectable or metastatic) melanoma patients who are treatment naïve.	Nivolumab plus ipilimumab	Ipilimumab 3mg/kg monotherapy[b]	Postow *et al.* 2015[(32)]

[a] results of this treatment arm are not presented as they are not the subject of this submission
[b] patients could receive nivolumab monotherapy upon disease progression and after unblinding.

The company provides an overview of the published primary study references and conference abstracts for the head-to-head trials (Box 5) and states that data are taken from clinical study report (CSR) for each trial.

Box 5 Overview of references related to CheckMate 067 and CheckMate 069

CheckMate 067

- Larkin *et al*. 2015 Efficacy and safety in key patient subgroups of nivolumab alone or combined with ipilimumab versus ipilimumab alone in treatment-naïve patients with advanced melanoma (Checkmate 067). Presented at ECC 2015.[52]
- Schadendorf *et al*. 2015 Patient reported outcomes from a Phase 3 study of nivolumab alone or combined with ipilimumab vs ipilimumab in patients with advanced melanoma: CheckMate 067. Presented at SMR 2015.[53]
- Wolchok *et al*. 2015 Efficacy and safety results from a phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment naïve patients (pts) with advanced melanoma (MEL) (CheckMate 067). Presented at ASCO 2015.[54]

CheckMate 069

- Abernethy *et al*. 2015 Effect of nivolumab (NIVO) in combination with ipilimumab (IPI) versus IPI alone on quality of life (QoL) in patients (pts) with treatment-naive advanced melanoma (MEL): Results of a Phase II study (CheckMate 069). Presented at ASCO 2015.[55]
- Hodi *et al*. 2015 Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study. Presented at ASCO 2015.[56]

Abbreviations in box: ASCO, American Society of Clinical Oncology; ECC, European Cancer Congress.

In addition, the company identified one non-RCT relevant to the decision problem: CheckMate 004 (Table 8). CheckMate 004 assessed the safety and efficacy of nivolumab and ipilimumab given concurrently or sequentially.[38] The trial included patients with advance melanoma irrespective of BRAF status or treatment history. One patient cohort (cohort 8) received combination immunotherapy dosing in line with the expected licence: nivolumab 1mg/kg plus ipilimumab 3mg/kg every three weeks for four doses followed by nivolumab 3mg/kg every two weeks (CS, pg 102-103, Section 4.11).

Table 8. List of relevant non-randomised and non-controlled evidence (reproduced from CS, Table 33, Section 4.11)

Trial name (NCT number)	Objective	Population	Intervention	Primary study reference	Justification for inclusion
CheckMate 004 (NCT01024231)	To investigate the safety and efficacy of	Advanced (unresectable or metastatic)	Concurrent nivolumab and	Wolchok *et al*. 2013[57]	Provides survival data in both treatment naïve

Trial name (NCT number)	Objective	Population	Intervention	Primary study reference	Justification for inclusion
	combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively).	melanoma patients.	ipilimumab or Ipilimumab followed by nivolumab		and treatment exposed patients. Trial design included treatment discontinuation at 96 weeks.
Abbreviations in table: CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death-1.					

No head-to-head data were identified comparing combination immunotherapy with BRAF inhibitor therapy in patients with $BRAF^{+}$ melanoma. Therefore an indirect comparison was used for this comparison, which is presented and discussed in Section 4.4 of this report.

4.2.1 Trial conduct

CheckMate 067 is a phase III, double-blind, multicentre (137 sites including seven in the UK) RCT evaluating the efficacy and safety of combination immunotherapy or nivolumab monotherapy in comparison with ipilimumab in patients with previously untreated metastatic melanoma (Table 9). A description and critique of the nivolumab monotherapy arm in CheckMate 067 is not presented in this report as nivolumab monotherapy is not part of the final scope of this STA. Patients in the combination immunotherapy arm (n=314) received nivolumab 1mg/kg plus ipilimumab 3mg/kg every three weeks by intravenous (IV) infusion for four doses followed by nivolumab 3mg/kg every two weeks until disease progression, discontinuation due to toxicity or any other reason. Patients who had a clinical benefit and were tolerating treatment, as determined by the investigator, were allowed to be treated after disease progression. Patients in the ipilimumab arm (n=315) received ipilimumab 3mg/kg every three weeks by IV infusion for four doses and a nivolumab-matched placebo. Subsequent therapies post progression included anti-PD1s, ipilimumab and BRAF inhibitors (CS, Table 18, Section 4.10). Primary outcomes were:

- overall survival (OS; defined as time between the date of randomisation and the date of death); and
- progression-free survival (PFS; defined as the time between the date of randomisation and the first date of documented progression or death due to any cause, investigator-assessed).

The company assessed survival continuously during treatment and every three months during follow-up.

Secondary outcomes were:

- objective response rate (ORR; defined as the number of patients with a best objective response [BOR] of complete remission [CR] or partial remission [PR] divided by the number of randomised patients, investigator-assessed);
- tumour response (according to the Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1);
- OS, PFS and ORR difference between the two experimental arms;
- OS based on Programmed death-ligand 1 [PD-L1] expression level: defined as OS based on PD-L1 status using a verified assay with ≥5% tumour cell membrane expression cut-off); and
- health-related quality of life (HRQL; measured by mean changes from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core [EORTC QLQ-C30] scales).

CheckMate 067 started on 11th June 2013 and is currently ongoing. Data in the CS are presented at a clinical database lock of 17th February 2015 (CS, pg 45, Section 4.3). [redacted] In the protocol is reported that the total duration of the study is expected to be 44.1 months (17 months of accrual + 27.1 months of follow-up) and additional survival follow-up continues for up to five years from the primary analysis of OS with the study finalising when survival follow-up has concluded.[50]

Checkmate 069 is a phase II, double-blind, multicentre (21 sites in France and North-America) RCT comparing combination immunotherapy with ipilimumab as a first-line treatment in patients with previously untreated metastatic melanoma (Table 9).

When patients randomised to ipilimumab therapy progressed, they could be unblinded and given nivolumab monotherapy. Patients in the combination immunotherapy arm (n=95) received nivolumab 1mg/kg plus ipilimumab 3mg/kg every three weeks by IV infusion for four doses followed by nivolumab 3mg/kg every two weeks until disease progression, discontinuation due to toxicity or any other reason. Patients who had a clinical benefit and were tolerating treatment, as determined by the investigator, were allowed to be treated after disease progression. Patients in the ipilimumab arm (n=47) received ipilimumab 3mg/kg every three weeks by IV infusion for four doses and a nivolumab-matched placebo. Primary outcomes were:

- ORR in patients with $BRAF^-$ tumours (defined as the number of patients with a BOR of CR or PR divided by the number of randomised patients, investigator-assessed); and
- tumour response assessed according to the RECIST (version 1.1).

Secondary outcomes were:

- duration of response (DOR, defined as the time between the date of first response to the date of first documented tumour progression or death due to any cause, investigator-assessed);
- time to treatment response (TTR, defined as the time from randomisation to the date of the first documented CR or PR, investigator-assessed);
- PFS in patients with $BRAF^-$ tumours (defined as the time between the date of randomisation and the first date of documented progression or death due to any cause, investigator-assessed);
- ORR in patients with $BRAF^+$ tumours.
- PFS in patients with $BRAF^+$ tumours.
- HRQL (measured by mean changes from baseline in the EORTC QLQ-C30 scales).

CheckMate 069 started on 23rd August 2013 and is ongoing. Data in the CS are presented at a clinical database lock of 30th January 2015 (CS, pg 45, Section 4.3). The study protocol reports that the follow-up phase starts when patients discontinue treatment after which they are followed up every three months for survival.(58)

In both CheckMate 067 and CheckMate 069 patients who progressed according to the RECIST criteria could continue study treatment if, according to clinical judgement, they benefitted from treatment and were tolerating the drug (Box 6).

Box 6 Treatment continuation beyond RECIST criteria (CS, pg 46, Section 4.3).

Of note, patients could continue treatment beyond initial Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression (where progression is assessed based on tumour size and/or the appearance of new lesions) if they were considered by the investigator to be experiencing clinical benefit and tolerating the study drug. This design is based on accumulating clinical evidence indicating that some patients treated with immune system-stimulating agents show disease progression, as defined by conventional RECIST criteria, before demonstrating subsequent clinical objective responses and/or stable disease (see [CS] Section 2.1). Patients treated beyond initial RECIST-defined progression discontinued study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumour burden volume from time of initial progression. In clinical practice, when assessing immuno-oncology therapies, response to therapy will largely be based on clinical judgement, with consideration given to the potential of response despite an initial increase in tumour burden or the presence of new lesions. It is important to note that progression assessments of immuno-oncology therapies against RECIST criteria for tumour progression in clinical trials therefore provide a conservative estimate of benefit from therapy compared to clinical practice assessment of immuno-oncology treatment effect.
Abbreviations in box: RECIST, Response Evaluation Criteria in Solid Tumors.

Tumour assessments started 12 weeks from the first dose and were then undertaken every six weeks for the first 12 months and thereafter every 12 weeks (all ±1 week). Tumour assessments stopped when both disease progression had occurred and treatment had been discontinued, i.e. patient who were treated beyond progression were assessed until they discontinued treatment and patients who discontinued treatment before progression were still assessed until they had progressed.

Differences between the two RCTs include that CheckMate 067 randomised patients in a 1:1 ratio while CheckMate 069 assigned patients 2:1 to combination immunotherapy and ipilimumab respectively. To be eligible for Checkmate 067, patients needed to have a known BRAF mutation status and prior radiotherapy (non-systemic) completed ≥4 weeks before study drug administration in contrast to the CheckMate 069 RCT where this was not required.

Table 9 Comparative summary of RCT methodology (reproduced from CS, pg 47-51, Table 11 and company Clarification response A14)

Aspects	CheckMate 067	CheckMate 069
Location	Patients were treated across 137 sites in Australia, Europe, Israel, New Zealand and North America, including 7 sites in the United Kingdom	Patients were treated across 21 sites in France and North America.
Trial design	Phase III, randomised, double-blind, active-controlled, multi-centre clinical trial. Patients were randomised in a 1:1:1 ratio through an IVRS. Randomisation was stratified by PD-L1 status, BRAF mutation status and metastatic stage. The sponsor, patients, investigator and site staff were blinded to treatment assignment until progression of disease and treatment discontinuation.	Phase II, randomised, double-blind, active-controlled, multi-centre clinical trial. Patients were randomised in a 2:1 ratio through an IVRS. Randomisation was stratified by BRAF mutation status. The sponsor, patients, investigator and site staff were blinded to treatment assignment until progression of disease and treatment discontinuation.
Eligibility criteria for participants	Men and women aged ≥18 years who signed informed consent and met the following main disease criteria upon screening were enrolled: • Untreated, histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging • PD-L1-positive, PD-L1-negative or PD-L1-intermediate classification according to recent biopsy from an unresectable or metastatic site • Known BRAF mutation status • Prior radiotherapy (non-systemic) completed ≥4 weeks before study drug administration • Measurable disease by RECIST v1.1 criteria • ECOG PS of 0 or 1 Patients who met any of the following key criteria were excluded from study eligibility: • Active brain metastases or leptomeningeal metastases • Ocular melanoma • Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured • Active, known or suspected autoimmune disease • Conditions requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibody or any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways	Men and women aged ≥18 years who signed informed consent and met the following main disease criteria upon screening were enrolled: • Histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging • No prior systemic anticancer therapy for unresectable or metastatic melanoma. Note that prior adjuvant or neoadjuvant melanoma therapy was permitted if it was completed at least 6 weeks prior to first dose and all related AEs have either returned to baseline or stabilised. • Measurable disease by RECIST v1.1 criteria • ECOG PS of 0 or 1 Patients who met any of the following key criteria were excluded from study eligibility: • Active brain metastases or leptomeningeal metastases • Ocular melanoma • Active, known or suspected autoimmune disease • Conditions requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration • Prior randomisation in an ipilimumab study trial • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody or any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

Aspects	CheckMate 067	CheckMate 069
Settings and locations where the data were collected	Local laboratory assessments were arranged by site. An independent DMC was established to provide oversight of safety and efficacy considerations and to provide advice regarding necessary actions for the continuing protection of enrolled patients.	Local laboratory assessments were arranged by site. ICON Laboratories were responsible for management of local laboratory results from the site. ICON entered, reviewed, queried, and transferred the results, from the local laboratory reports received from sites to the BMS Oracle Clinical Database. An independent DMC was established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio.
Trial drugs	Combination immunotherapy group (n=314): nivolumab 1mg/kg plus ipilimumab 3mg/kg q3w by IV infusion for 4 doses followed by nivolumab 3mg/kg q2w Ipilimumab group (n=315): ipilimumab 3mg/kg q3w by IV infusion for 4 doses (plus nivolumab-matched placebo) Nivolumab group (n=316): nivolumab 3mg/kg q2w by IV infusion (plus ipilimumab-matched placebo) Nivolumab treatment continued until there was disease progression or discontinuation due to toxicity or any other reason. Treatment after disease progression was permitted for patients who had a clinical benefit and were tolerating treatment, as determined by the investigator. Drug reductions or dose escalations were not permitted. Dose delays were permitted for all AEs related to trial drugs (regardless of which treatment was attributed to the event).	Combination immunotherapy group (n=95): nivolumab 1mg/kg plus ipilimumab 3mg/kg q3w by IV infusion for 4 doses followed by nivolumab 3mg/kg q2w Ipilimumab group (n=47): ipilimumab 3mg/kg q3w by IV infusion for 4 doses (plus nivolumab-matched placebo) Nivolumab treatment continued until there was disease progression or discontinuation due to toxicity or any other reason. Treatment after disease progression was permitted for patients who had a clinical benefit and were tolerating treatment, as determined by the investigator. Patients initially treated with ipilimumab could be given the option to receive nivolumab 3mg/kg q2w upon disease progression and after unblinding. Drug reductions or dose escalations were not permitted. Dose delays were permitted for all AEs related to trial drugs (regardless of which treatment was attributed to the event).
Permitted and disallowed concomitant medication	Immunosuppressive agents, systemic corticosteroids >10mg daily prednisone equivalent or any concurrent antineoplastic therapy were prohibited during the study (unless utilised to treat a drug-related AE). Palliative radiotherapy and surgical resection were permitted if the lesion being considered for such treatment was not a target lesion, the patient was considered to have progressed at the time of palliative therapy, and the case was discussed with the medical monitors. Patients were permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) and a brief course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by contact allergen) was allowed.	Immunosuppressive agents, systemic corticosteroids or any concurrent antineoplastic therapy (including radiotherapy and surgical resection) were prohibited during the study (unless utilised to treat a drug-related AE). Patients were permitted to use inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalent in the absence of active immune disease; or a brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions. Supportive care for disease-related symptoms was also allowed for all patients on the trial.
Primary outcomes	OS: defined as time between the date of randomisation and the date of death. PFS: defined as the time between the date of randomisation and the first date of documented progression or death due to any cause. Investigator-assessed.	ORR in patients with BRAF mutation-negative tumours: defined as the number of patients with a BOR of CR or PR divided by the number of randomised patients. Investigator-assessed. Tumour response was assessed according to the RECIST, version 1.1. Tumour assessments began 12 weeks (±1 week) from first dose and continued

Aspects	CheckMate 067	CheckMate 069
	Assessments for survival were performed continuously during treatment and every 3 months during follow-up.	every 6 weeks (±1 week) for the first 12 months and every 12 weeks (±1 week) thereafter, until disease progression was documented or treatment was discontinued.
Secondary outcomes	ORR: defined as the number of patients with a BOR of CR or PR divided by the number of randomised patients. Investigator-assessed. Tumour response was assessed according to the RECIST, version 1.1. Tumour assessments began 12 weeks (±1 week) from first dose and continued every 6 weeks (±1 week) for the first 12 months and every 12 weeks (±1 week) thereafter, until disease progression was documented or treatment was discontinued. OS, PFS and ORR difference between the two experimental arms. OS based on PD-L1 expression level: defined as OS based on PD-L1 status using a verified assay with ≥5% tumour cell membrane expression cut-off. HRQL: measured by mean changes from baseline in the EORTC QLQ-C30 scales. HRQL was assessed on Days 1, 15, 22 and 29; 9 weeks from randomisation; every 6 weeks thereafter for the first 12 months; and at follow-up visits 1 and 2.	DOR: defined as the time between the date of first response to the date of first documented tumour progression or death due to any cause. Investigator-assessed. TTR: defined as the time from randomisation to the date of the first documented CR or PR. Investigator-assessed. PFS in patients with BRAF mutation-negative tumours: defined as the time between the date of randomisation and the first date of documented progression or death due to any cause. Investigator-assessed. ORR in patients with BRAF mutation-positive tumours. PFS in patients with BRAF mutation-positive tumours. HRQL: measured by mean changes from baseline in the EORTC QLQ-C30 scales. HRQL assessment began prior to first dose and continued every 6 weeks for the first 6 months.
Key exploratory outcomes	DOR: defined as the time between the date of first response to the date of first documented tumour progression or death due to any cause. Investigator-assessed. TTR: defined as the time from randomisation to the date of the first documented CR or PR. Investigator-assessed. Percent change in tumour volume: defined as the percent decrease in tumour volume from baseline to nadir, observed up until the date of progression, the date of subsequent anticancer therapy, or death. Safety and tolerability: measured by the incidence of AEs, SAEs, deaths and laboratory abnormalities. Severity of AEs was graded according to the NCI CTCAE, version 4.0. Safety assessments were made continuously during the treatment phase and up to 100 days after the last dose of study drug. HRQL: measured by mean changes from baseline in health status, assessed using the EQ-5D tool and by changes in work and activity impairment, assessed using the WPAI:GH tool. EQ-5D assessments were conducted in the on treatment period and during survival follow-up.	OS: defined as time between the date of randomisation and the date of death. Assessments for survival were performed continuously during treatment and every 3 months during follow-up. Percent change in tumour volume: defined as the percent decrease in tumour volume from baseline to nadir, observed up until the date of progression, the date of subsequent anticancer therapy, or death. Safety and tolerability: measured by the incidence of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, Select AEs, laboratory abnormalities, and vital sign measurements. AEs were coded using the MedDRA, version 16.1. Severity of AEs was graded according to the NCI CTCAE, version 4.0. Safety assessments were made continuously during the treatment phase. HRQL: measured by mean changes from baseline in health status, assessed using the EQ-5D tool. Biomarker assessment: exploration of the potential association between biomarker (e.g. PD-L1) expression and efficacy endpoints (response, survival [OS, PFS] and/or safety).
Pre-planned subgroups	Subgroup analyses assessing the impact of age, gender, race, region, baseline ECOG PS, PD-L1 expression status, BRAF mutation status, M stage at study entry, history of brain metastases, smoking status, baseline LDH and AJCC stage on clinical efficacy outcomes were pre-	Subgroup analyses assessing the impact of M stage at study entry, AJCC stage, age, gender, race, region, baseline ECOG performance status, history of brain metastases, smoking status, and baseline LDH on clinical efficacy outcomes were pre-planned for patients with BRAF mutation-negative and

Aspects	CheckMate 067	CheckMate 069
	planned.	BRAF mutation-positive tumours.

Abbreviations in table: AE, adverse event; AJCC, American Joint Committee on Cancer; BOR, best overall response; CD137, cluster of differentiation 137 (a member of the tumour necrosis factor family); CR, complete response; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; DMC, data monitoring committee; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D, EuroQol-five dimension; HRQL, Health-related quality of life; IV, intravenous; IVRS, interactive voice response system; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PR, partial response; q2w, every 2 weeks; q3w, every 3 weeks; PS, performance score; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TTR, time to treatment response; WPAI:GH, Work Productivity and Activity Impairment Questionnaire: General Health.

Source: CheckMate 067 CSR[33]; CheckMate 069 CSR[34]); Larkin *et al*. 2015[31]; Postow *et al*. 2015[32]

[redacted]

Table 10 Protocol amendments in CheckMate 067 (reproduced from CheckMate 067 CSR, pg 83-84, Table 4.5.1)

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

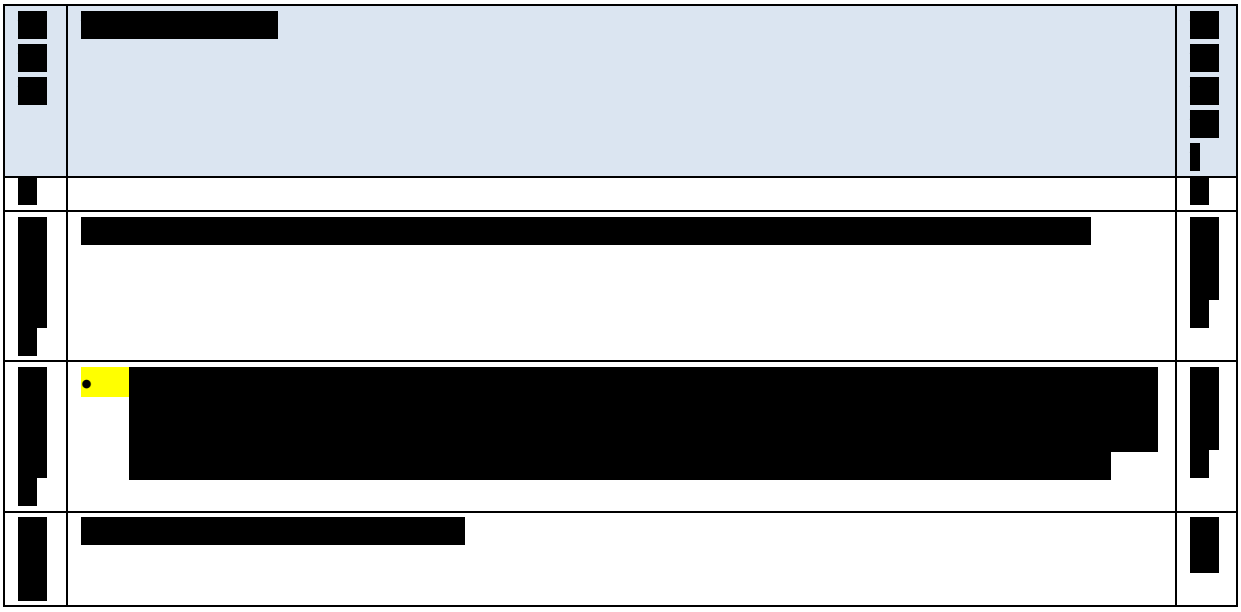
[redacted]

Table 11 [redacted]

[redacted]

Table 11 Protocol amendments and administrative letters in CheckMate 069 (reproduced from CheckMate 069 CSR, pg 70, Table 4.5.1)

[redacted]



The ERG notes that seemingly large changes to the CheckMate 069 protocol were made, particularly under protocol amendment two, but this appears to be reasonable as no patients were recruited at the time of the amendments.

The ERG considers the Checkmate 067 and Checkmate 069 RCTs to be well conducted phase II and III double-blind RCTs. Therefore, these RCTs provide high-quality evidence to inform part of the decision problem: combination immunotherapy compared with ipilimumab.

CheckMate 004 is a phase I trial that aimed to assess the safety and efficacy of different doses of ipilimumab and nivolumab in advanced melanoma.[38] As previously mentioned, cohort 8 in the trial included patients who were treated with combination immunotherapy according to dosing outlined the decision problem (Box 7).

Box 7 Summary of CheckMate 004 methodology

Successive cohorts of patients were treated with escalating doses of nivolumab and ipilimumab but doses were kept constant within each cohort. The trial was initially planned to evaluate various concurrent regimen schedules (cohorts 1 to 5) and two sequenced regimen schedules (cohorts 6 and 7) with eligible patients assigned to a dose cohort in the order they entered the study. Due to maximum tolerated dose (MTD) being exceeded in cohort 3, no patients were enrolled in cohorts 4 or 5 and an alternate dose escalation scheme was added (cohort 2a). Based on data from cohorts 1 to 3, the Regimen [combination immunotherapy] schedule was selected for Phase II/III trials. An expansion treatment group matching the Regimen [combination immunotherapy] was subsequently implemented in CheckMate 004 (cohort 8); patients were enrolled to this cohort from November 2013.

Table 12 outlines the protocol-specified dose levels for the concurrent, sequential and combination immunotherapy groups.

Table 12. Dose levels in planned patient cohorts of CheckMate 004 (reproduced from CS, Table 34, Section 4.11)

Group	Cohort	Nivolumab dose (mg/kg)	Ipilimumab dose (mg/kg)
Concurrent (n=53) Nivolumab and ipilimumab q3w for 4 doses followed by nivolumab q3w for 4 doses followed by nivolumab and ipilimumab q12w for a maximum of 84 weeks (maintenance)	1	0.3	3
	2	1	3
	2a	3	1
	3	3	3
	4	10	3
	5	10	10
Sequential (n=33) Prior standard ipilimumab therapy (resulting in controlled disease) followed by nivolumab q2w for a maximum of 96 weeks	6	1	3
	7	3	3
Combination (n=41) Nivolumab plus ipilimumab q3w for 4 doses followed by nivolumab q2w for a maximum of 96 weeks	8	1 (dose 1-4) 3 (dose 5+)	3
Abbreviations in table: q2w, every 2 weeks; q3w, every 3 weeks; q12w, every 12 weeks. Source: CheckMate 004 CSR[59]			

In CheckMate 004, the primary objective was to assess the safety and tolerability of ipilimumab and nivolumab; assessment of AEs was coded with the Medical Dictionary for Regulatory Activities version 15.1 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (CS, pg 104, Section 4.11). Secondary objectives were to assess:

- safety and tolerability of combination immunotherapy specifically (cohort 8);
- preliminary efficacy of combination immunotherapy;
- immunogenicity to nivolumab and ipilimumab; and
- pharmacokinetics.

Efficacy measures included:

- tumour response, assessed as per modified World Health Organisation (mWHO) criteria and by immune-related response criteria (irRC);
- PFS;
- OS rate; and
- OS.

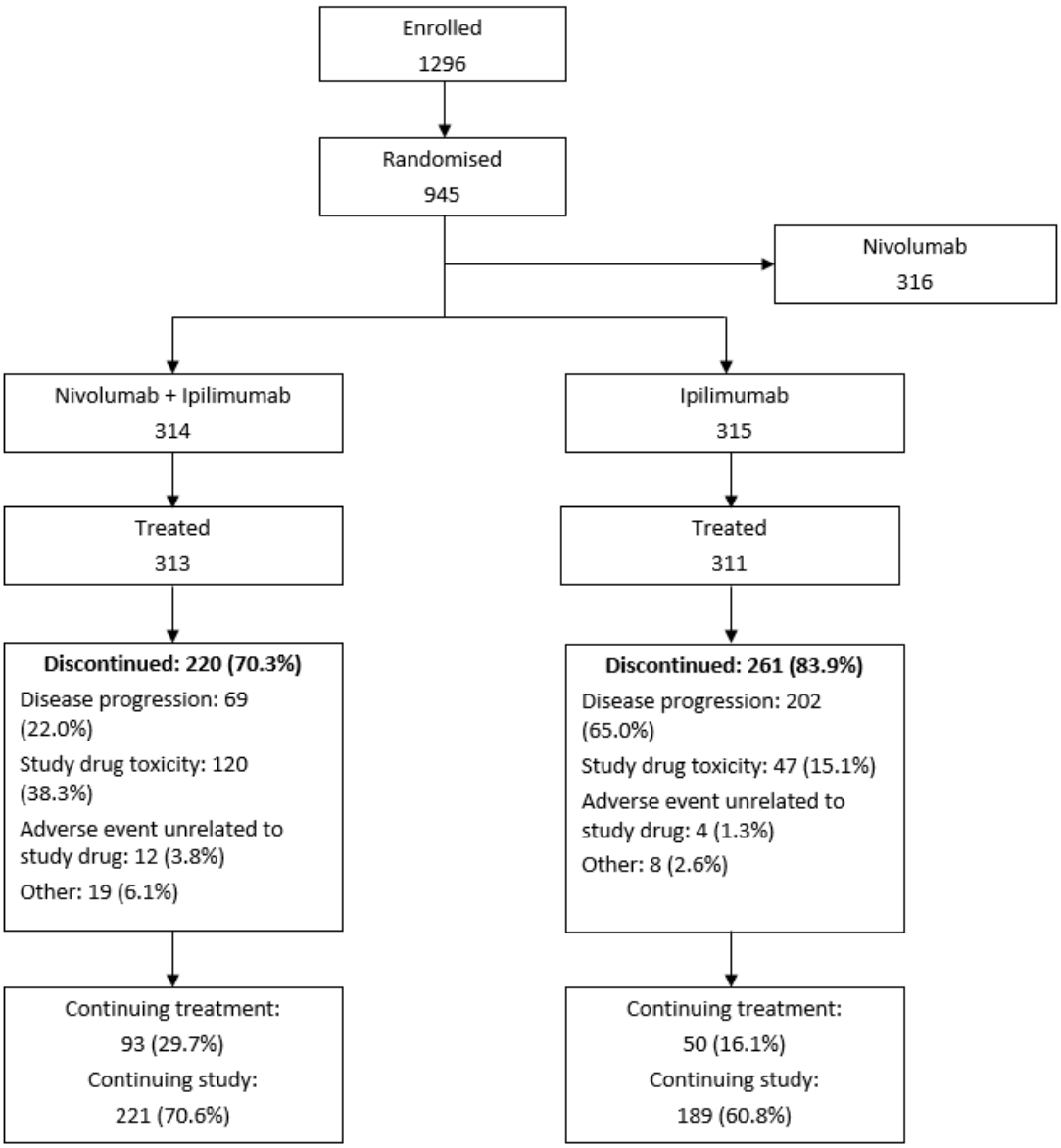
Tumour assessments were undertaken at weeks 12, 18, 24, 30, 36. Thereafter, tumour assessments were conducted every 12 weeks in concurrent groups and every eight weeks from week eight in the

sequential and combination immunotherapy groups. Survival assessments were undertaken every 12 weeks through telephone. After the initiation of therapy patients were followed up for safety up to 5.5 years, survival up to three years, and response measures up to 2.5 years (CS, pg 104, Section 4.11).

4.2.2 Baseline characteristics

CheckMate 067 enrolled 1,296 patients and included 314 participants in the combination immunotherapy arm and 315 participants in the ipilimumab arm (Figure 2). One patient in the combination immunotherapy arm and four patients in the ipilimumab arm withdrew from the study before starting treatment. At the time of database lock (17th February 2015), 220 of 313 (70.3%) patients who began treatment with combination immunotherapy had discontinued to receive study treatment; the main reasons for discontinuation were study drug toxicity (38.3%) and disease progression (22.0%). In the ipilimumab arm, 261 of 311 (83.9%) patients who began therapy had discontinued in the treatment period of the study; the main reason for discontinuation was disease progression (65.0%).

Figure 2: CONSORT diagram of participant flow at the time of the current database lock in CheckMate 067 (reproduced from CS, pg 56, Figure 7)



Abbreviations in figure: CONSORT, Consolidated Standards of Reporting Trials.
Continuing treatment means patients are continuing to receive study drug; continuing study means patients have discontinued study drug but are still being followed for survival analysis.
Source: CheckMate 067 CSR[33]

Baseline characteristics were similar between the treatment arms in CheckMate 067 (Table 13). About half of participants were European (n=347) and 66 patients were from seven UK centres. The ERG's clinical experts agree that the baseline characteristics of the treatment arm are mostly well balanced. The ERG notes there was a lower proportion of patients with elevated LDH in the combination immunotherapy arm (28.0%) versus the ipilimumab arm (36.5%; Table 13).

Table 13 Characteristics of participants in CheckMate 067 RCT (CS, pg 60-61, Table 13)

	Combination immunotherapy (ITT population, n=314)	**Ipilimumab (ITT population, n=315)**
Age, median years (range) Age, mean years (SD)	61 (18-88) 59.3 (13.9)	62 (18-89) 60.8 (13.2)
Gender, male n (%)	206 (65.6)	202 (64.1)
Race, Caucasian n (%)	310 (98.7)	303 (96.2)
Region, n (%)	US: 64 (20.4) EU: 177 (56.4) UK: 30 (9.6) Australia: 40 (12.7) Rest of World: 33 (10.5)	US: 75 (23.8) EU: 170 (54.0) UK: 36 (11.4) Australia: 37 (11.7) Rest of World: 33 (10.5)
ECOG PS, n (%)	0: 230 (73.2) 1: 83 (26.4) 2: 0 Not available: 1 (0.3)	0: 224 (71.1) 1: 91 (28.9) 2: 0
Metastasis stage, n (%)	M0-M1B: 133 (42.4) M1C: 181 (57.6)	M0-M1B: 132 (41.9) M1C: 183 (58.1)
Common metastasis site, n (%)	Lymph node: 174 (55.4) Lung: 184 (58.6) Liver: 93 (29.6)	Lymph node: 196 (62.2) Lung: 184 (58.4) Liver: 92 (29.2)
Elevated LDH, n (%)	88 (28.0)	115 (36.5)
History of brain metastases, yes n (%)	11 (3.5)	15 (4.8)
Disease duration, median years (range)	1.87 (0.1-32.5)	1.95 (0.1, 24.7)
PD-L1-positive[a], n (%)	68 (21.7)	75 (23.8)
BRAF mutation-negative (wild-type), n (%)	213 (67.8)	218 (69.2)

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1; PS, performance status; SD, standard deviation.

[a] PD-L1 not quantifiable in 36 patients randomised to combination immunotherapy and 38 patients randomised to ipilimumab. Validated assay values reported (verified assay values reported in the CSR)

[b] PD-L1 not quantifiable in 15 patients randomised to combination immunotherapy and 9 patients randomised to ipilimumab.

Source: CheckMate 067 CSR[33]; CheckMate 069 CSR[34]; Larkin *et al*. 2015[31]; Postow *et al*. 2015[32]

At the clarification stage, the company kindly supplied baseline characteristics for the UK population in CheckMate 067 (Table 14). The baseline characteristics were fairly balanced between the treatment arms. However, the ERG notes that in the UK trial population a larger proportion of patients had ECOG status 1, elevated LDH, and a smaller proportion were PD-L1positive compared to the full trial populations. Median disease duration was also longer in the UK compared to the full trial population. The difference in ECOG status and elevated LDH levels indicate a worse performance status in the UK trial population compared to the full trial population. Although the ERG notes that, the UK trial population constituted a relatively small proportion of the full trial population in CheckMate 067

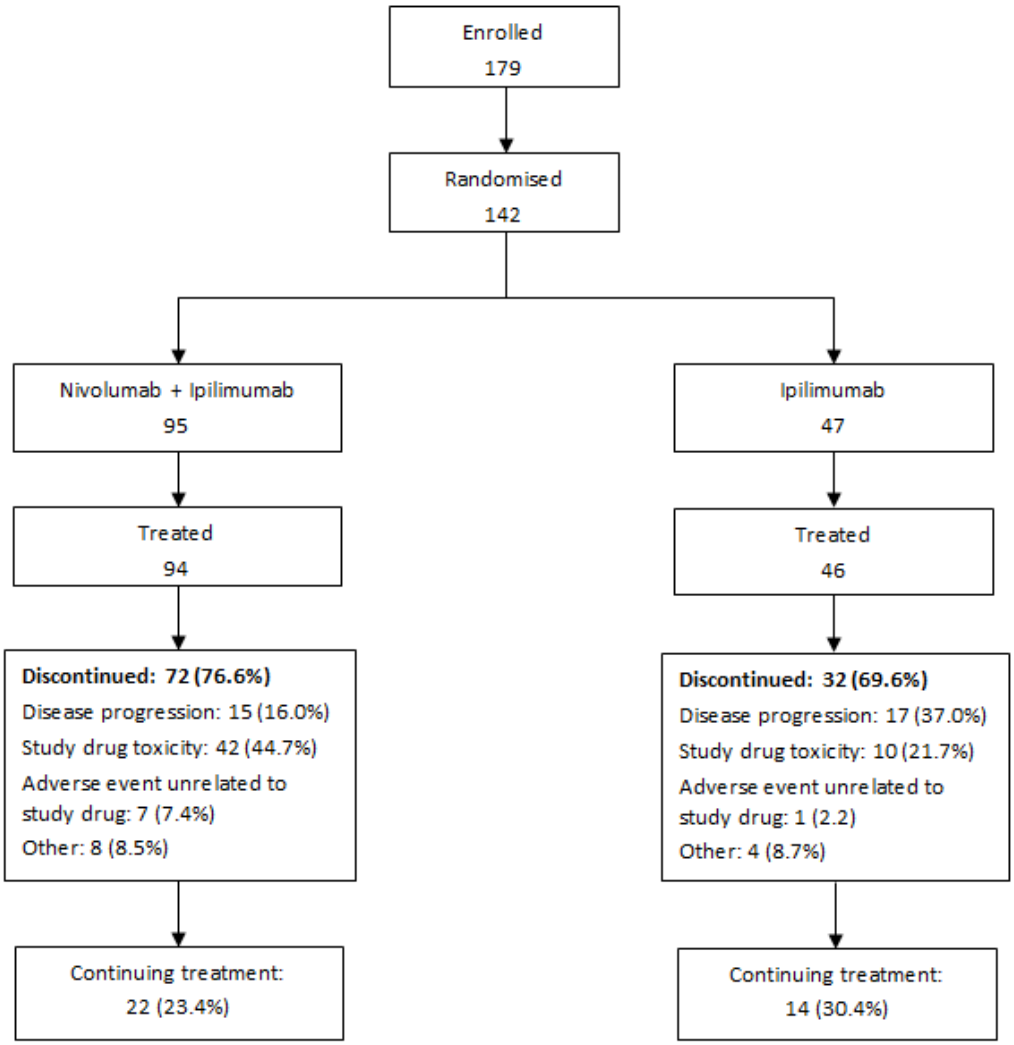
Table 14 Patient characteristics for the UK population subgroup in CheckMate 067 (Clarification response A10)

Characteristics	**Combination immunotherapy (ITT population, n=30)**	**Ipilimumab (ITT population, n=36)**
Age, median years (range) Age, mean years (SD)	57.0 (25,78) 54.9 (14.14)	62.5 (18,83) 60.3 (13.01)
Aged under 65 years old (n/N)	21/30	19/36
Gender, male n (%)	18 (60%)	21 (58.3%)
Race, caucasian n (%)	30 (100%)	36 (100%)
Region, n (%)	UK subpopulation only	
ECOG PS, n (%)	0: 16 (53.3%) 1: 14 (46.7%) 2: 0 Not available: 0	0: 20 (55.6%) 1: 16 (44.4%) 2: 0 Not available: 0
Metastasis stage at study entry (IVRS), n (%)	M0-M1B: 11 (36.7%) M1C: 19 (63.3%)	M0-M1B: 12 (33.3%) M1C: 24 (66.7%)
Common metastasis site, n (%)	Lymph node: 17 (56.7) Lung: 17 (56.7) Liver: 10 (33.3)	Lymph node: 17 (47.2) Lung: 21 (58.3) Liver: 11 (30.6)
Elevated LDH (> ULN), n (%)	16 (53.3%)	15 (41.7%)
History of brain metastases, yes n (%)	1 (3.3%)	1 (2.8%)
Disease duration, median years (range)	2.79 (0.2-16.3)	3.29 (0.1-20.2)
PD-L1-positive, n (%)	12 (40%)	19 (52.8%)
BRAF mutation-negative (IVRS, wild-type), n (%)	20 (66.7%)	23 (63.9%)
[redacted]	[redacted]	[redacted]

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; IVRS, interactive voice response system; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1; PS, performance status; SD, standard deviation; ULN, upper limit of normal.

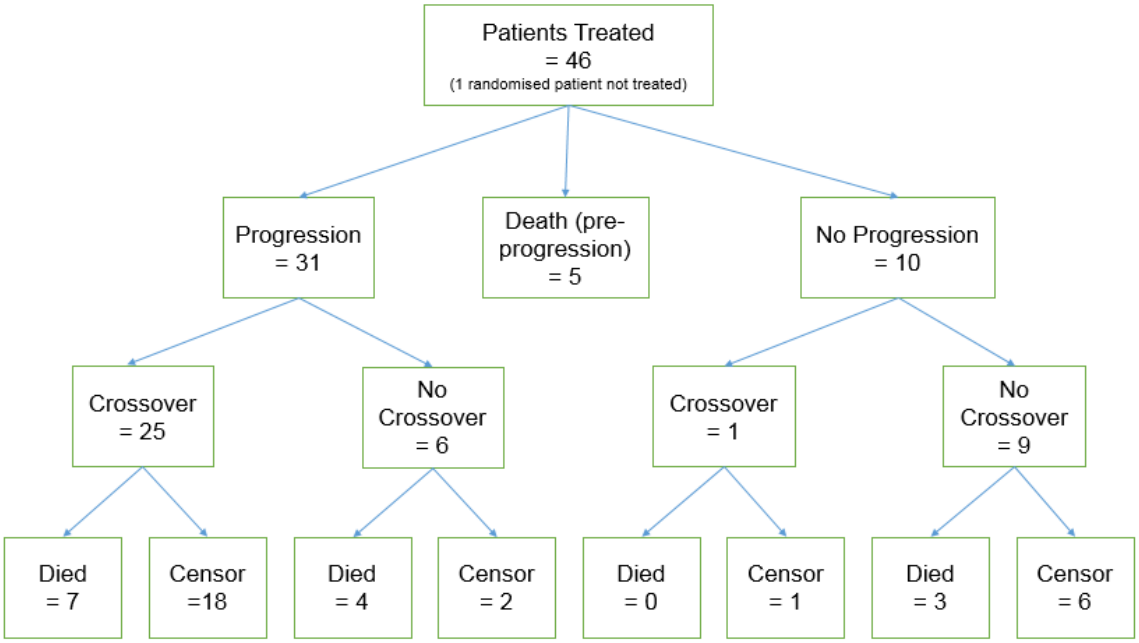
CheckMate 069 included 95 participants in the combination immunotherapy arm and 47 participants in the ipilimumab arm (Figure 3). In both arms, one patient withdrew from the study before starting treatment. At the time of the primary database lock (30th January 2015), 22 of 94 (23.4%) patients treated continued to receive nivolumab plus ipilimumab; the most frequent reason for discontinuation was study drug toxicity (44.7%). In the ipilimumab arm, 14 of 46 (30.4%) participants who were treated continued to receive treatment drug; the most frequent reason for discontinuation was disease progression (37.0%). Of 31 patients who progressed on ipilimumab, 25 crossed over to nivolumab therapy (Figure 4).

Figure 3: CONSORT diagram of participant flow at the time of the current database lock in CheckMate 069: ITT population (CS, pg 57, Figure 8)



Abbreviations in figure: CONSORT, Consolidated Standards of Reporting Trials.
Source: Postow *et al*. 2015[32]

Figure 4. Flow diagram for crossover in CheckMate 069: use of nivolumab subsequent to ipilimumab (CS, pg 58, Figure 9)



Baseline characteristics were similar between arms in CheckMate 069 (Table 15). The median age of the ITT study population was 64 (range 27 to 87) in the combination immunotherapy arm versus 67 (range 31 to 80) in the ipilimumab arm (Table 15). Around two-third of ITT study participants in the combination immunotherapy arm (66.3%) and the ipilimumab arm (68.1%) were male. The company states, "Two patients assigned to the Regimen [combination immunotherapy] presented with an ECOG performance status of 2 at randomisation and were thus identified as a protocol deviation." (CS, pg 58, Section 4.5).

Table 15 Characteristics of participants in CheckMate 069 RCT (CS, pg 60-61, Table 13)

	Combination immunotherapy		**Ipilimumab**	
	ITT population (n=95)	**BRAF mutation-negative population (n=72)**	**ITT population (n=47)**	**BRAF mutation-negative population (n=37)**
Age, median years (range) Age, mean years (SD)	64 (27-87) 63.3 (11.0)	66 (27-87) 65.4 (10.3)	67 (31-80) 64.5 (10.2)	69 (46-80) 66.5 (8.9)
Gender, male n (%)	63 (66.3)	48 (66.7)	32 (68.1)	23 (62.2)
Race, Caucasian n (%)	92 (96.8)	69 (95.8)	47 (100)	37 (100)
Region, n (%)	France: 12 (12.6) USA: 83 (87.4)	France: 6 (8.3) USA: 66 (91.7)	France: 4 (8.5) USA: 43 (91.5)	France: 4 (10.8) USA: 33 (89.2)
ECOG PS, n (%)	0: 79 (83.2) 1: 14 (14.7) ≥2: 2 (2.1)	0: 62 (86.1) 1: 9 (12.5) ≥2: 1 (1.4)	0: 37 (78.7) 1: 10 (21.3) ≥2: 0	0: 30 (81.1) 1: 7 (18.9) ≥2: 0

	Combination immunotherapy		Ipilimumab	
	ITT population (n=95)	**BRAF mutation-negative population (n=72)**	**ITT population (n=47)**	**BRAF mutation-negative population (n=37)**
Metastasis stage, n (%)	M0: 8 (8.4) M1A: 15 (15.8) M1B: 27 (28.4) M1C: 44 (46.3)	M0: 6 (8.3) M1A: 9 (12.5) M1B: 22 (30.6) M1C: 34 (47.2)	M0: 5 (10.6) M1A: 8 (17.0) M1B: 12 (25.5) M1C: 21 (44.7)	M0: 5 (13.5) M1A: 7 (18.9) M1B: 8 (21.6) M1C: 16 (43.2)
Common metastasis site, n (%)	Lymph node: 43 (45.3) Lung: 57 (60.0) Liver: 24 (25.3)	Lymph node: 30 (41.7) Lung: 44 (61.1) Liver: 17 (23.6)	Lymph node: 25 (53.2) Lung: 27 (57.4) Liver: 18 (38.3)	Lymph node: 17 (45.9) Lung: 20 (54.1) Liver: 14 (37.8)
Elevated LDH, n (%)	24 (25.3)	15 (20.8)	11 (23.4)	7 (18.9)
History of brain metastases, yes n (%)	4 (4.2)	4 (5.6)	0	0
Disease duration, median years (range)	2.34 (0.1-47.4)	1.71 (0.1-23.5)	1.71 (0.1-20.4)	1.40 (0.1-20.4)
PD-L1-positive[b], n (%)	24 (25.3)	Not reported	11 (23.4)	Not reported
BRAF mutation-negative (wild-type), n (%)	72 (75.8)	72 (100)	37 (78.7)	37 (100)

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1; PS, performance status; SD, standard deviation.

[a] PD-L1 not quantifiable in 36 patients randomised to combination immunotherapy and 38 patients randomised to ipilimumab. Validated assay values reported (verified assay values reported in the CSR)

[b] PD-L1 not quantifiable in 15 patients randomised to combination immunotherapy and 9 patients randomised to ipilimumab.

Source: CheckMate 067 CSR[33]; CheckMate 069 CSR[34]; Larkin *et al*. 2015[31]; Postow *et al*. 2015[32]

The company reports that a lower proportion of $BRAF^+$ patients were included compared to the general population (Box 8).

Box 8 Proportion of $BRAF^+$ patients in randomised controlled trials

> Of note, in both trials, a lower proportion of patients had BRAF mutation-positive melanoma than is observed in the general population (~50%). This is likely to reflect current clinical practice where BRAF mutation positive patients with significant disease burden and highly symptomatic disease may be deemed less suitable for immunotherapy and instead offered targeted therapies as first-line treatment. This is reflected in the very similar demographics across BRAF mutation-positive and BRAF mutation-negative cohorts (see Appendix 5).

ERG's clinical expert opinion agree that in CheckMate 067 and 069, $BRAF^+$ patients are under-represented compared to clinical practice. The imbalance may be due to clinicians being reluctant to put $BRAF^+$ patients in clinical trials as they may respond better to BRAF inhibitors or to a combination of BRAF and MEK inhibitors. As discussed in Section 4.4.2, the company assumes the treatment efficacy of immunotherapies to be independent of BRAF mutation status.

In addition, the ERG's clinical experts note that patients in CheckMate 069 are different from those in CheckMate 067 in terms of performance status and elevated LDH levels. Patients in CheckMate 069 have a better performance status than patients in CheckMate 069 (approximately 80% of patients in CheckMate 69 have performance status 0 as opposed to 70% in CheckMate 67). The performance status of patients in both trials is better than what is seen in clinical practice (in clinical practice there are generally more patients with ECOG performance status of 2). Also only 5% of patients in CheckMate 069[32] have two times the upper limit of LDH compared to 11% in CheckMate 067[31]. Prognosis of patients in CheckMate 067 is thus poorer than those in CheckMate 069.

In summary, the ERG's clinical experts stated that the characteristics of the patient population enrolled in both CheckMate 067 and 069 are representative of patients with metastatic or unresectable melanoma in England and Wales, however, in clinical practice the performance status of patients will include patients with ECOG 2, which were excluded from both trials.

CheckMate 004 started in December 2009 and enrolled 150 patients of which 127 were treated and 23 did not receive treatment, because they did not meet eligibility criteria or withdrew consent. Primary analysis was undertaken in June 2014 when 72.4% of all patients had discontinued treatment. In cohort 8, 53.7% of patients enrolled discontinued, with the most common reason (24.4% of patients) being study drug toxicity (Table 16).

Table 16. Patient disposition summary in CheckMate 004 (reproduced from CS, Table 35, Section 4.11)

	Cohorts 1-3 (n=53)	**Cohorts 6&7 (n=33)**	**Cohort 8 (n=41)**	**All cohorts (n=127)**
Patients discontinuing, n (%)	42 (79.3)	28 (84.8)	22 (53.7)	92 (72.4)
Reason for discontinuation, n (%)				
Death	1 (1.9)	2 (6.1)	3 (7.3)	6 (4.7)
Study drug toxicity	18 (34.0)	3 (9.1)	10 (24.4)	31 (24.4)
Disease progression	15 (28.3)	20 (60.6)	8 (19.5)	43 (33.9)
AE unrelated to study drug	1 (1.9)	0	0	1 (0.8)
Maximum clinical benefit	4 (7.5)	1 (3.0)	0	5 (3.9)
Other	3 (5.7)	2 (6.1)	1 (2.4)	6 (4.7)

Abbreviations in table: AE, adverse event.
Notes: no patients enrolled in cohorts 4 or 5.
Source: CheckMate 004 CSR[59]

The company described patient characteristics of patients in CheckMate 004 and the ERG agrees with this description (Box 9).

Box 9 Patient characteristics in CheckMate 004 (CS, pg 105, Section 4.11)

In cohort 8 there were slightly more females than males enrolled but across cohorts, the majority of

patients were male and Caucasian with an average age over 55 years.

As observed in RCTs, a high percentage of patients had poor prognostic factors at baseline including M1c stage disease and elevated LDH. According to protocol, patients may have been treated with up to 3 prior systemic treatments for melanoma prior to enrolment. In cohort 8, 49% of all patients were treatment naïve with 27% of patients having received one prior treatment and 24% of patients having received 2 or 3 prior treatments.

There was some variation in patient characteristics across cohorts, representing the broad profile of advanced melanoma patients presenting in clinical practice. In cohort 8, no patients tested positive for PD-L1 expression at the 5% cut-off; 6/21 patients (28.6%) were PD-L1 positive using a 1% cut-off.

Table 17 outlines baseline characteristics of patients in CheckMate 004.

Table 17. Characteristics of participants in CheckMate 004 across concurrent and combination treatment groups (reproduced from CS, Table 36, Section 4.11)

	Cohorts 1-3 (n=53)	**Cohort 8 (n=41)**
Age, median years (range)	58 (22-79)	56 (22-80)
Age, mean years (SD)	56.6 (12.9)	55.2 (12.5)
Gender, male n (%)	32 (60)	18 (44)
Race, Caucasian n (%)	53 (100)	37 (90)
ECOG PS, n (%)	0: 44 (83) 1: 8 (15) Unknown: 1 (2)	0: 25 (61) 1: 11 (27) Unknown: 5 (12)
Metastasis stage, n (%)	M1c: 29 (55)	M1c: 21 (51)
Common metastasis site, n (%)	Lymph node: 28 (53) Lung: 27 (51) Liver: 16 (30)	Lymph node: 19 (46.3) Lung: 19 (46) Liver: 16 (39)
Elevated LDH, n (%)	20 (38)	16 (39)
PD-L1-positivea, n/N (%)	14/37 (38)	0/21 (0)
BRAF mutation-negative (wild-type), n (%)	39 (74)	27 (66)
Number of prior therapies, n (%)	0: 32 (60) 1: 15 (28) ≥2: 6 (11)	0: 20 (49) 1: 11 (27) ≥2: 10 (24)
Nature of prior therapy, n (%)	Immunotherapy: 10 (19) BRAF inhibitor: 2 (4)	Immunotherapy: 12 (29) BRAF inhibitor: 3 (7)

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death ligand-1; PS; performance status; SD, standard deviation.
Notes: a, PD-L1 not quantifiable in 16 patients in cohorts 1-3 and 20 patients in cohort 8.
Source: CheckMate 004 CSR[59]; Sznol *et al*. 2014[38]

4.2.3 Description and critique of statistical approach used

In CheckMate 067, the minimum follow-up of 22 months for OS analyses (planned 28 months per power calculation) had not been reached and therefore OS data were not available (Table 18). For PFS, a two-sided log-rank test stratified by PD-L1 status, BRAF status and M stage at screening was

conducted for comparing combination immunotherapy to ipilimumab. The company planned to include 915 patients in the trial, which meant that for the comparison of PFS at a follow-up of at least nine months the number of adverse events would give 83% power to detect an HR of 0.71 at a type I error rate of 0.005 (two-sided) for all comparisons.

Table 18 Summary of statistical analyses in the CheckMate 067 RCT (CS, pg 53-54, Table 12)

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Treatment with nivolumab monotherapy or nivolumab combined with ipilimumab will improve overall survival compared to ipilimumab monotherapy in patients with unresectable or metastatic melanoma.	OS analysis was targeted to occur after all subjects had 28 months follow-up per sample size and power considerations. However, the required minimum follow-up for analysis of OS was 22 months and as this has not been reached, results of this endpoint are not available at this time. PFS analysis was conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status and M stage at screening to compare each of the two experimental treatments to the control group. HRs and corresponding two-sided (1-adjusted α) % CIs were estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates were estimated using KM methodology. ORR analyses were conducted using a two-sided CMH test stratified by PD-L1 status, BRAF status and M stage at screening to compare each of the two experimental treatments to the control group. An associated OR and 95% CI were calculated. Additionally, ORRs and corresponding 95% exact CIs were calculated using the Clopper–Pearson method for each of the three treatment arms.	A sample of approximately 915 patients, randomly assigned in a 1:1:1 ratio to the three treatment groups was planned. For the comparison of PFS, it was estimated that the number of events projected to be observed at a follow-up of at least 9 months would give the study approximately 83% power to detect an average HR of 0.71 at a type I error rate of 0.005 (two-sided) for all comparisons. For each OS comparison, at least 460 events in the two respective treatment arms are required to provide at least 90% power to detect a HR of 0.72 with a type I error of 0.025 (two sided). The HR of 0.72 corresponds to a 39% increase in the median OS assuming a median OS of 14 months for ipilimumab and 19.4 months for each of the experimental treatment arms. The study was not designed for a formal statistical comparison between the nivolumab group and the combination immunotherapy group.	For patients without documentation of progression or death, PFS was censored on the date of their last evaluable tumour assessment. For patients who did not have any on study tumour assessments and did not die, PFS was censored on their date of randomisation.

Abbreviations in table: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; HR, hazard ratio; KM, Kaplan–Meier; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

Source: CheckMate 067 CSR[33], Larkin *et al*. 2015[31]

In CheckMate 069, ORR analysis for both the combination immunotherapy and ipilimumab arms was conducted using the Clopper-Pearson method (Table 19). For estimation of the unweighted difference in ORRs between the arms the Newcombe method was used. For estimation of the weighted difference in ORRs between the arms the Cochran–Mantel–Haenszel method of weighting adjusting for stratification factors was used. The company planned to include 100 $BRAF^-$ patients in the RCT who were assigned in a 2:1 ratio to the intervention and control arm. This meant that approximately 150 patients were to be included (100 $BRAF^-$ and 50 $BRAF^+$ patients), when assuming that 66% of patients were $BRAF^-$. A power of 87% was estimated to be reached with a two-sided alpha of 0.05 when assuming ORRs of 40% in the intervention and 10% in the control arm.

Table 19 Summary of statistical analyses in the CheckMate 069 RCT (CS, pg 53-54, Table 12)

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Treatment with nivolumab combined with ipilimumab will lead to clinical benefit, as demonstrated by an improved clinically meaningful ORR compared to ipilimumab monotherapy, including durable responses with substantial magnitude of tumour reduction.	ORRs and corresponding 95% exact CIs were calculated using the Clopper–Pearson method for each treatment arm. The unweighted difference in ORRs between the two treatment groups and corresponding exact 95% CI were estimated using the method of Newcombe. The weighted difference in ORRs between the two treatment groups along with corresponding two-sided 95% CI were estimated using the CMH method of weighting adjusting for stratification factors. Time to event distributions were estimated using KM techniques. When appropriate, the median along with 95% CI was estimated based on Brookmeyer and Crowley methodology. Rates at fixed timepoints were derived from the KM estimate along with their corresponding log-log transformed 95% CI. Minimum follow-up must be longer than the timepoint to generate rates at fixed timepoints. P-values other than those provided for the ORR primary analysis and the hierarchical analysis of key efficacy endpoints were for descriptive purposes only and not adjusted for multiplicity.	A sample of approximately 100 BRAF mutation-negative patients, randomly assigned in a 2:1 ratio to the two treatment groups was planned. Assuming 66% of subjects were observed to be BRAF mutation-negative, a total of approximately 150 subjects were to be randomised (100 BRAF mutation-negative and 50 BRAF mutation-positive patients). Given a two-sided alpha of 0.05, this number of BRAF mutation-negative patients provided approximately 87% power to show a statistically significant difference in the ORR between the combination group and the monotherapy group, assuming ORRs of 40% and 10%, respectively. For the comparison of PFS, it was estimated that the number of events projected to be observed at a follow-up of at least 9 months would give the study approximately 83% power to detect an average HR of 0.71 at a type I error rate of 0.005 (two-sided) for all comparisons.	For patients without documentation of progression or death, PFS was censored on the date of their last evaluable tumour assessment. For patients who did not have any on study tumour assessments and did not die, PFS was censored on their date of randomisation. For patients without documentation of death, OS was censored on the date the patient was last known to be alive. No adjustments have been made for use of subsequent nivolumab therapy on the ipilimumab arm of the study.

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Abbreviations in table: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; HR, hazard ratio; KM, Kaplan–Meier; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival. Source: CheckMate 069 CSR[34]; Postow *et al*. 2015[32]			

Subgroup analyses on clinical efficacy outcomes in the CheckMate 067 and CheckMate 069 RCTs were pre-planned for the following: age, gender, race, region, baseline ECOG performance status, M stage at study entry, history of brain metastases, smoking status, baseline LDH, and AJCC stage. Additional subgroup analyses in the CheckMate 067 RCT s were pre-planned for PD-L1 expression status and BRAF mutation status (Table 9).

For CheckMate 004, the company states, "Sample size could not be precisely determined as it depended on the observed toxicity but up to approximately 126 patients were planned, based on the study design for dose escalation and safety evaluation requirements.[38]" (CS, pg 104, Section 4.11). Descriptive statistics and ORR were used for summarising safety parameters. KM methodology was used to summarise time to event analyses (time to treatment response, duration of response, PFS and OS). The "all treated patients group", defined as all patients who received at least one dose of study drug, was used for the primary dataset. The "response-evaluable population", defined as all treated patients with at least one on-treatment tumour assessment, clinical progression or death (the response-evaluable population was the same as the all treated population), was used for response outcomes. Data imputation was undertaken using the conservative principle (CS, pg 104, Section 4.11).

Overall, the ERG considers the statistical approach used for the analyses of outcome data in CheckMate 067, CheckMate 069, and CheckMate 004 to be adequate.

4.2.4 Summary statement

In summary, the ERG considers the evidence provided by the company to inform one part of the decision problem: combination immunotherapy compared with ipilimumab, to be of high-quality. Two ongoing RCTs were included, CheckMate 067 and CheckMate 69, which evaluated the effectiveness of nivolumab plus ipilimumab (combination immunotherapy) in the treatment of advanced, unresectable melanoma. The phase III trial Checkmate 067 and phase II trial Checkmate 069 are well conducted, multicentre, double-blind RCTs. In addition, one non-RCT was included, CheckMate 004, that assessed the safety and efficacy of nivolumab and ipilimumab.

Baseline characteristics were mostly well balanced between the treatment arms in CheckMate 067 and CheckMate 069, but $BRAF^{+}$ patients were under-represented in these trials compared to UK clinical practice. Baseline characteristics for the subgroup of UK patients in CheckMate 067 were fairly balanced between the treatment arms. However, the ERG notes that in the UK subgroup a larger

proportion of patients had ECOG status 1, elevated LDH, and a smaller proportion was PD-L1positive compared to the full trial population.

CheckMate 004 comprised eight cohorts of which patients in cohort 8 (n=41) received combination immunotherapy dosing in line with the expected licence: nivolumab 1mg/kg plus ipilimumab 3mg/kg every three weeks for four doses followed by nivolumab 3mg/kg every two weeks.

Primary outcomes were OS and PFS in CheckMate 067 and ORR in patients with $BRAF^-$ tumours and tumour response in CheckMate 069. The primary objective of CheckMate 004 was the safety and tolerability of ipilimumab and nivolumab. Efficacy measures of CheckMate 004 included: tumour response; PFS; OS rate; and OS.

Overall, the ERG considers the choice of outcomes and statistical approach used for the analyses of outcome data in CheckMate 067, 069 and 004 to be adequate. However, the ERG notes that tumour assessments began at 12 weeks from first dose, which hindered an accurate assessment of time to response as any differences in time to response between combination immunotherapy and ipilimumab are likely to occur before this time point.

4.3 Clinical effectiveness results

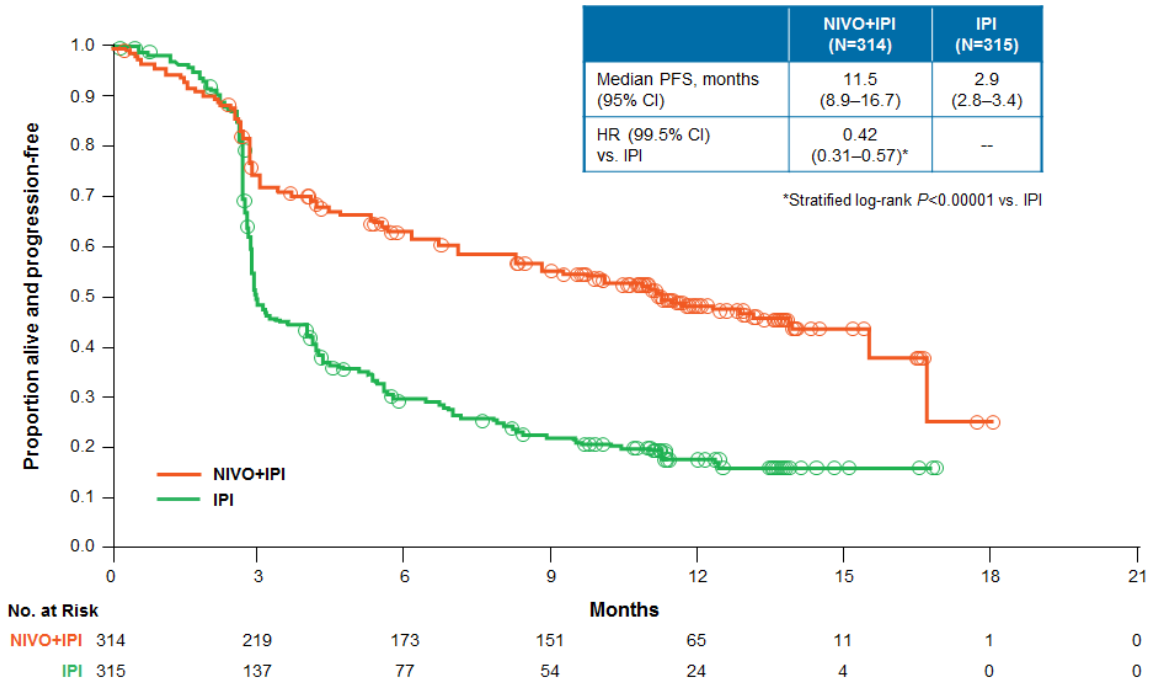
The company presents a summary of the outcome data from CheckMate 067 and 069 in CS Section 4.7 and CS Appendix 7. The primary efficacy analysis set in CheckMate 069 included the $BRAF^-$ trial population, however, throughout the following sections the results for the ITT population will be presented for both trials. Data presented in this section are based on a clinical database lock of 17th February 2015 for CheckMate 067 and clinical database lock of 30th January 2015 for CheckMate 069, unless otherwise stated.

4.3.1 PFS

Figure 5 and Figure 6 show KM curves for PFS in CheckMate 067 and 069, respectively. PFS was significantly longer for patients on combination immunotherapy compared to patients on ipilimumab in both trials (HR 0.42, 95% CI: 0.31 to 0.57, and HR 0.39, 95% CI: 0.25 to 0.63, respectively). In CheckMate 67, median PFS was 11.5 months (95% CI: 8.9 to 16.7) with combination treatment compared to 2.9 months (95% CI: 2.8 to 3.4) with ipilimumab. In CheckMate 069, median PFS was 3.0 months (95% CI: 2.8 to 5.1) with ipilimumab; for combination immunotherapy median PFS was not reached.

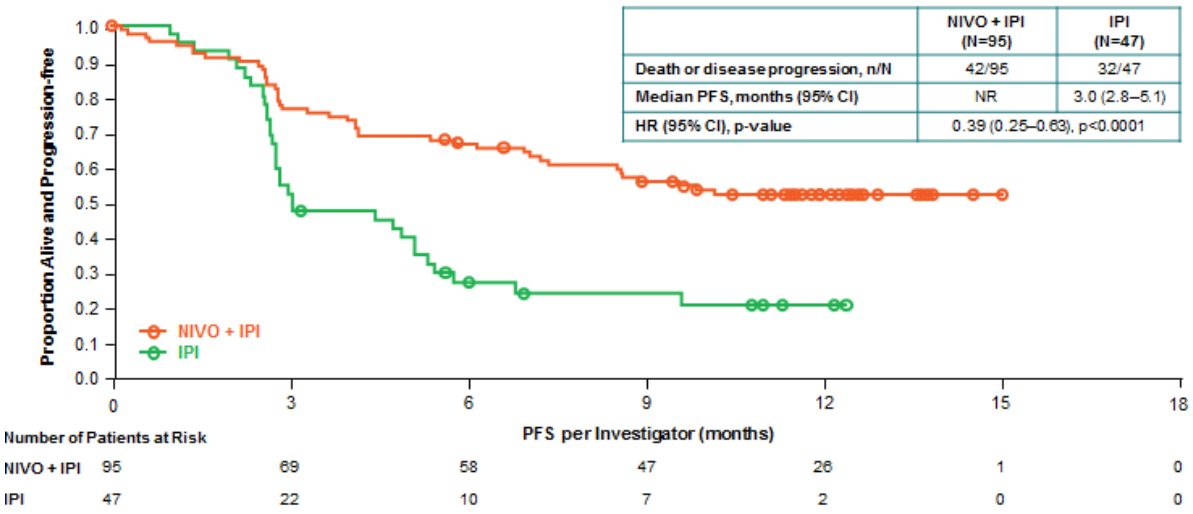
The ERG notes that the use of the RECIST criteria for progression is likely to lead to some false-positive progression assessments in CheckMate 067 and CheckMate 069. However, as patients in both trial arms are receiving immunotherapy, the proportion of patients with a false-positive progression assessment is likely to be similar between the trial arms.

Figure 5. KM curve for PFS in CheckMate 067, ITT analysis set (reproduced from CS Figure 10)



Abbreviations in figure: CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; ITT, intention-to-treat; KM, Kaplan-Meier; NIVO+IPI, nivolumab plus ipilimumab; PFS, progression-free survival.
Source: Larkin *et al*. 2015[31]

Figure 6. Kaplan-Meier curve for progression free survival in CheckMate 069, intention-to-treat analysis set (reproduced from CS Appendix 7, Figure 3)



Abbreviations in figure: CI, confidence interval; IPI, ipilimumab; ITT, intention-to-treat; KM, Kaplan–Meier; NIVO + IPI, nivolumab plus ipilimumab; PFS, progression-free survival.
Source: Hodi *et al*. 2015[56]

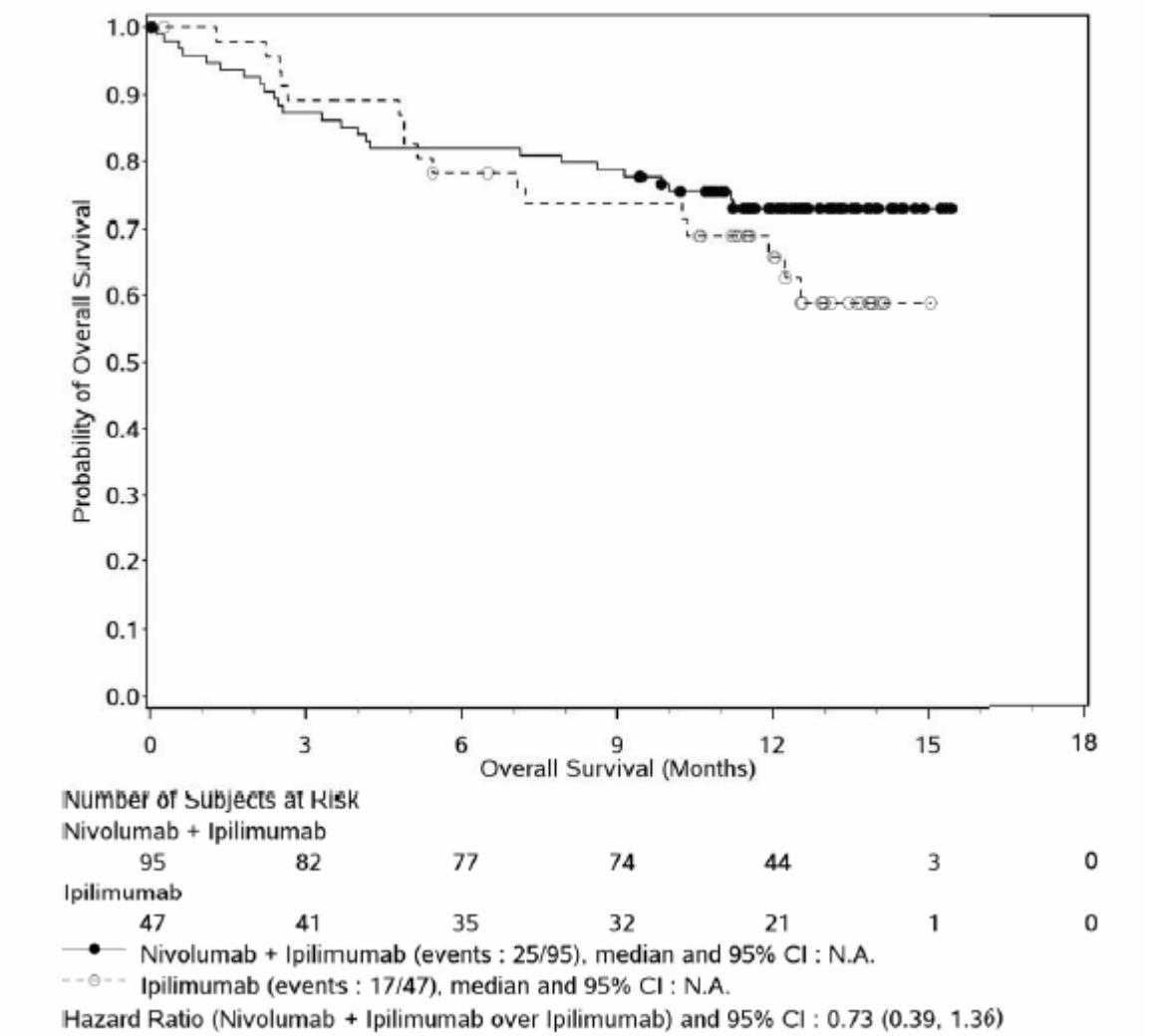
4.3.2 OS

In CheckMate 069 median OS was not reached in either arm at the most recently presented database lock (August 2015, Figure 7). The 75% OS (i.e. when a quarter of the patients have died) had been reached in both arms and shows an additional four months survival associated with combination

immunotherapy compared with ipilimumab (341 days versus 220 days, respectively), despite substantial crossover of patients from the ipilimumab arm to nivolumab monotherapy upon progression (56.5% at the time of analysis). However, the HR for OS for combination immunotherapy versus ipilimumab was not statistically significant in this interim analysis (HR 0.73, 95% CI: 0.39 to 1.36).

Survival rates at 6, 12 and 18 months in the combination immunotherapy arm (ITT population) were 82%, 73% and 69%, respectively. The equivalent survival rates in the ipilimumab arm were not provided in the CS; instead the company reports a comparison to 18-month OS rate of 35% for ipilimumab from a pooled analyses of trials.[4, 60] The ERG notes that the OS curve for ipilimumab in CheckMate 069 is markedly different from the OS curve for ipilimumab in trials included in the pooled analysis; the 12 month survival rate for patients on ipilimumab is around 65% in CheckMate 069 and around 50% in the pooled analysis by Schadendorf *et al*. (Figure 7 and Figure 8). The ERG notes that, the pooled analysis by Schadendorf *et al*. included may early phase studies, which were run at a time when PD-1 inhibitor was not available for patients on progression following treatment with ipilimumab. Hence, their results are not polluted by crossover from ipilimumab to subsequent nivolumab as in CheckMate 069. Also, in many of the included trials ipilimumab was given as second-line treatment compared to CheckMate 069, where patients were treatment naive.

Figure 7. Kaplan-Meier curve for overall survival in CheckMate 069, intention-to-treat analysis set (reproduced from CS Appendix 7, Figure 1)



Abbreviations in figure: CI, confidence interval; ITT, intention-to-treat; KM, Kaplan–Meier; N.A., not assessable; OS, overall survival.
Source: CheckMate 069 CSR[34]

Figure 8. Kaplan-Meier curve for overall survival from 12 studies of ipilimumab in metastatic melanoma[4]

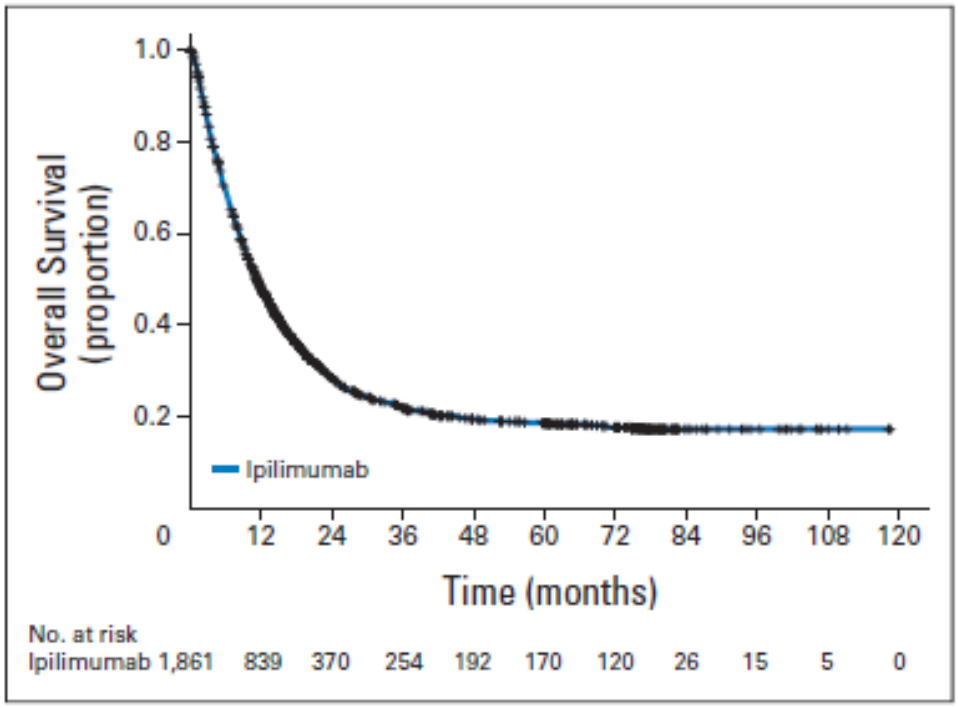


Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

No OS data were presented for CheckMate 067 in the CS, [redacted] Table 20 [redacted] Figure 9

[redacted]

Table 20 Interim OS analysis for CheckMate 067

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

Figure 9. Kaplan Meier curves[60]

[redacted]

4.3.3 Response analysis

The response analysis from CheckMate 067 is summarised in Table 21. In CheckMate 067 response to treatment was investigator-assessed. Both the proportion of patients with partial and complete response to treatment were higher in the combination immunotherapy arm than the ipilimumab arm; 57.6% of patients versus 19.0% with partial response and 11.5% versus 2.2% with complete response

for combination immunotherapy and ipilimumab, respectively. The response analysis from CheckMate 067 is summarised in Table 21. Time to treatment response (TTR) was similar between the treatment arms with a median of 2.8 months. The ERG notes that this coincides with the first tumour assessment taking place at 12 weeks (2.8 months) in both arms, and a large number of patients are seen to respond at or around the 12-week time-point.

Table 21. Summary of response in CheckMate 067 (reproduced from CS, pg 67, Table 15)

	Nivolumab plus ipilimumab (n=314)	**Ipilimumab (n=315)**
Objective response rate[a]		
Responders, n (%) (95% CI)	181 (57.6) (52.0 to 63.2)	60 (19.0) (14.9 to 23.8)
Best overall response CR, n (%) PR, n (%)	 36 (11.5) 145 (46.2)	 7 (2.2) 53 (16.8)
Unweighted ORR difference, %	38.4	
Estimated odds ratio (95% CI)	6.11 (3.59 to 10.38)	
p-value	<0.001	
Duration of response		
Median months (range)	Not reached	Not reached
Time to treatment response		
Median months (range)	2.8 (1.1 to 11.6)	2.8 (2.5 to 12.4)
Abbreviations in table: CI, confidence interval; CR, complete response; PR, partial response. Notes: [a], confirmed response (CR + PR) as per RECIST v1.1 criteria. Source: Larkin *et al*. 2015[31]		

Median duration of response (DOR) was not reached in either treatment arm. However, in a swimmer plot the company shows that response to treatment was often continued despite discontinuation of study drug in patients treated with combination immunotherapy (CS, pg 68, Figure 12). No data on this were presented for the ipilimumab arm. The ERG notes that the continued response after discontinuation of study drug highlights the uncertainty around the optimal length of maintenance nivolumab treatment. At the clarification stage, the company provided data on OS and PFS based on length of treatment. Table 22 depicts a consistent benefit for OS and PFS in patients receiving more than 4 doses. However, as the optimum number of doses for ipilimumab has been determined to be 4, it would be informative to see whether or not the same threshold applies to other immunotherapies.

Table 22. OS and PFS based on length of treatment (Clarification response A7)

Trial	**Treatment**	**OS**		**PFS**	
		≤ 4 doses	> 4 doses	≤ 4 doses	> 4 doses
		n/N (%)	n/N (%)	n/N (%)	n/N (%)
CheckMate 067 (17th Feb 2015 datacut)	Combination immunotherapy	N/A	N/A	102 / 167 (61.08)	49 / 147 (33.33)
	Ipilimumab	N/A	N/A	234 / 315 (74.29)	N/A

Trial	Treatment	OS		PFS	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 069 (30th Jan 2015 datacut)	Combination immunotherapy	22 / 57 (38.6)	3 / 38 (7.89)	34 / 57 (59.65)	8 / 38 (21.05)
	Ipilimumab	14 / 47 (29.78)	N/A	32 / 47 (68.09)	N/A
Abbreviations in table: PFS, progression-free survival; OS, overall survival.					

Patients in both treatment arms could be treated beyond progression (as defined by RECIST criteria) if they experienced clinical benefit and could tolerate the treatment. Suitability for treatment continuation was determined by the investigators. Of patients with a complete or partial response of progressive disease, 50 patients in the combination immunotherapy arm and 99 patients in the ipilimumab arm were treated beyond RECIST defined progression as per the study protocol. According to the company many of these patients developed or maintained a target lesion reduction of >30% compared to baseline after initial (RECIST defined) progression, however, no exact numbers or further details were presented in the CS.

The company also presents data on change in tumour burden, defined as percentage change from baseline in the sum of the longest diameters of the target tumour lesions. More patients in the combination immunotherapy arm experiencing a reduction in tumour size compared with patients in the ipilimumab arm. The median change in tumour burden was -51.9% (interquartile range: -75.8 to -10.2) in the combination therapy arm compared with +5.9% (interquartile range; -28.0 to +33.3) in the ipilimumab arm (response-evaluable analysis set).[31]

In the ITT population of CheckMate 069, investigator-assessed ORR was 59% in combination immunotherapy arm compared with 11% in the ipilimumab arm ($p<0.0001$). Both the partial and complete response rates were higher in the combination treatment arm compared to the ipilimumab arm in which there were no patients with a complete response at the latest database cut (Table 23). Time to objective response did not differ significantly between treatment arms with the majority of all responses observed at the time of the first scan. Median duration of response was not reached in either treatment arm, however, at the time of analysis (minimum follow-up of 11 months) 82% and 80% of responders continue to demonstrate response in the combination immunotherapy and ipilimumab arms, respectively.

The ORR among patients who discontinued study treatment due to side effects was 68% (95% CI: 52% to 81%) in the combination immunotherapy arm (30 of 44 patients), compared with 10% (95% CI: 0% to 45%) in the ipilimumab arm (1 of 10 patients). Similar to CheckMate 067, several patients

had continued response despite discontinuation of study treatment in both the combination and ipilimumab arm, as shown in a swimmer plot of all responders analysis set (CS, pg 71, Figure 15).

The number and proportion of patients who were treated beyond RECIST defined progression was not presented in the CS for CheckMate 069. The median change in tumour burden was -63.5% in the combination immunotherapy arm compared with +7.8% in the ipilimumab arm.[56]

Table 23. Summary of objective response in CheckMate 069, primary analysis set (adapted from CS, pg 71, Table 16)

	Nivolumab plus ipilimumab (n=95)	**Ipilimumab (n=47)**
Responders, n (%) (95% CI)	56 (59) (48 to 69)	5 (11) (4 to 23)
BOR CR, n (%) PR, n (%)	 21 (22) 35 (37)	 0 5 (11)
Estimated odds ratio (95% CI)	12.19 (4.41 to 33.68)	
p-value	<0.0001	
Abbreviations in table: BOR, best overall response; CR, complete remission; partial remission.		

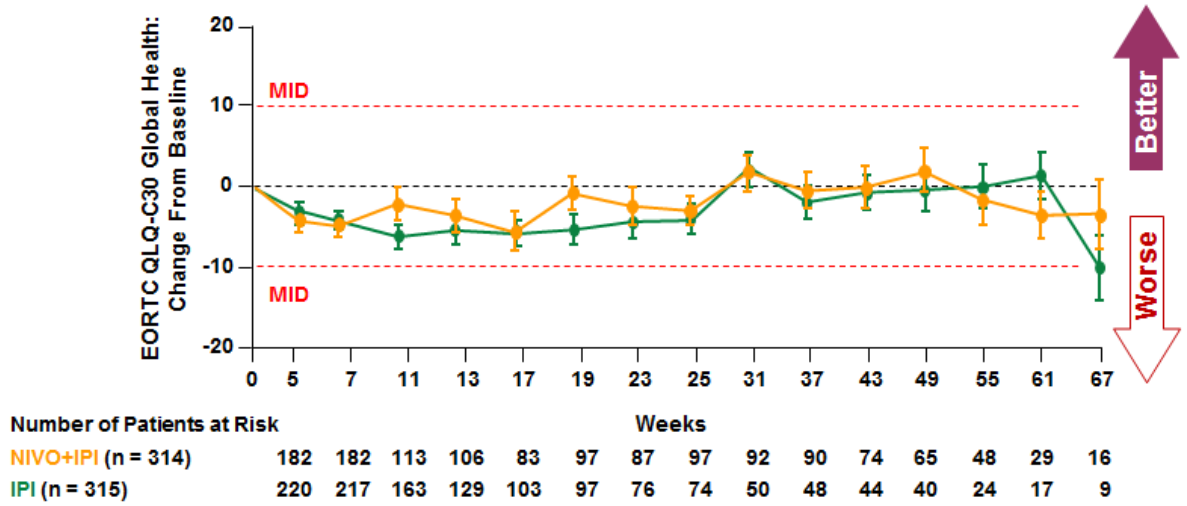
The ERG concludes that a proportion of patients appear to benefit from continued treatment with nivolumab beyond disease progression. However, for other patients, response to treatment appears to continue despite discontinuation of treatment, thus the optimal duration of treatment remains unknown.

4.3.4 HRQoL

HRQoL was assessed using EORTC QLQ-C30, which is specifically developed to assess the quality of life of cancer patients, and EuroQol-five dimension (EQ-5D), which is a standardised instrument for use as a measure of health outcome, which provides a single index value for health status (CS Appendix 8).

The HRQoL data from CheckMate 067 is presented in the CS for up to 67 weeks of follow-up. The proportion of patients with at least one baseline and post baseline EORTC QLQ-C30 assessment were 87.3% in the combination immunotherapy arm and 82.2% in the ipilimumab arm, with similar completion rates for EQ-5D.[54] Assessment of change from baseline in EORTC QLQ-C30 mean global health status scores shows no clinically meaningful changes (defined as a minimally important difference of ≥10 points) for either treatment arm at any time points up to week 67 (Figure 10). The company also presents EORTC QLQ-C30 global health status scores for patients who experienced a Grade 3-4 AE, with similar results (Figure not shown).

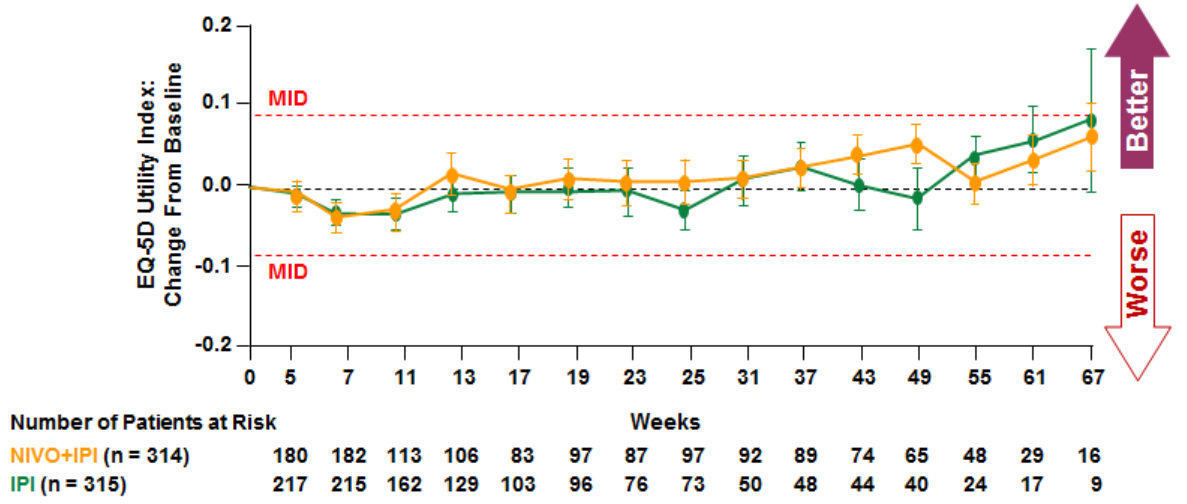
Figure 10. EORTC QLQ-C30 global health change from baseline in CheckMate 067, HRQL analysis set (reproduced from CS Figure 17)



Abbreviations in figure: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HRQL, health-related quality of life; IPI, ipilimumab; NIVO+IPI, nivolumab plus ipilimumab; MID, minimally important difference.
Source: Schadendorf *et al.* 2015[53]

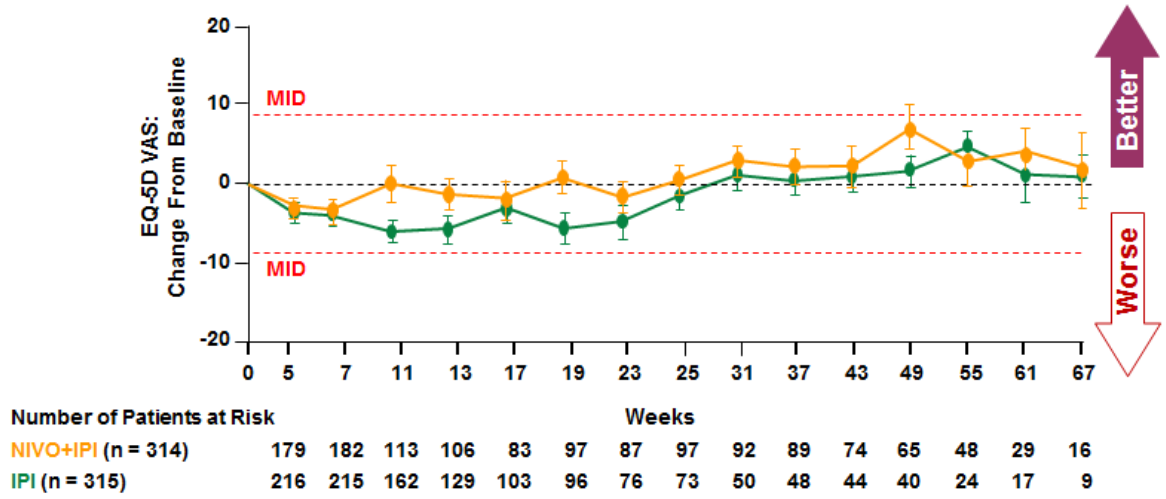
EQ-5D utility scores and EQ-5D VAS (visual analogue scale) showed no clinically meaningful changes (defined as a minimally important difference of ≥0.08 points for EQ-5D utility and ≥0.7 points for EQ-5D VAS) in either treatment arm, at any timepoint, up until week 67 (Figure 11 and Figure 12).

Figure 11. EQ-5D utility change from baseline in CheckMate 067, HRQL analysis set (reproduced from CS Figure 19)



Abbreviations in figure: EQ-5D, EuroQol-five dimension questionnaire; HRQL, health-related quality of life; IPI, ipilimumab; NIVO+IPI, nivolumab plus ipilimumab; MID, minimally important difference.
Source: Schadendorf *et al.* 2015[53]

Figure 12. EQ-5D VAS change from baseline in CheckMate 067, HRQL analysis set (reproduced from CS Figure 20)

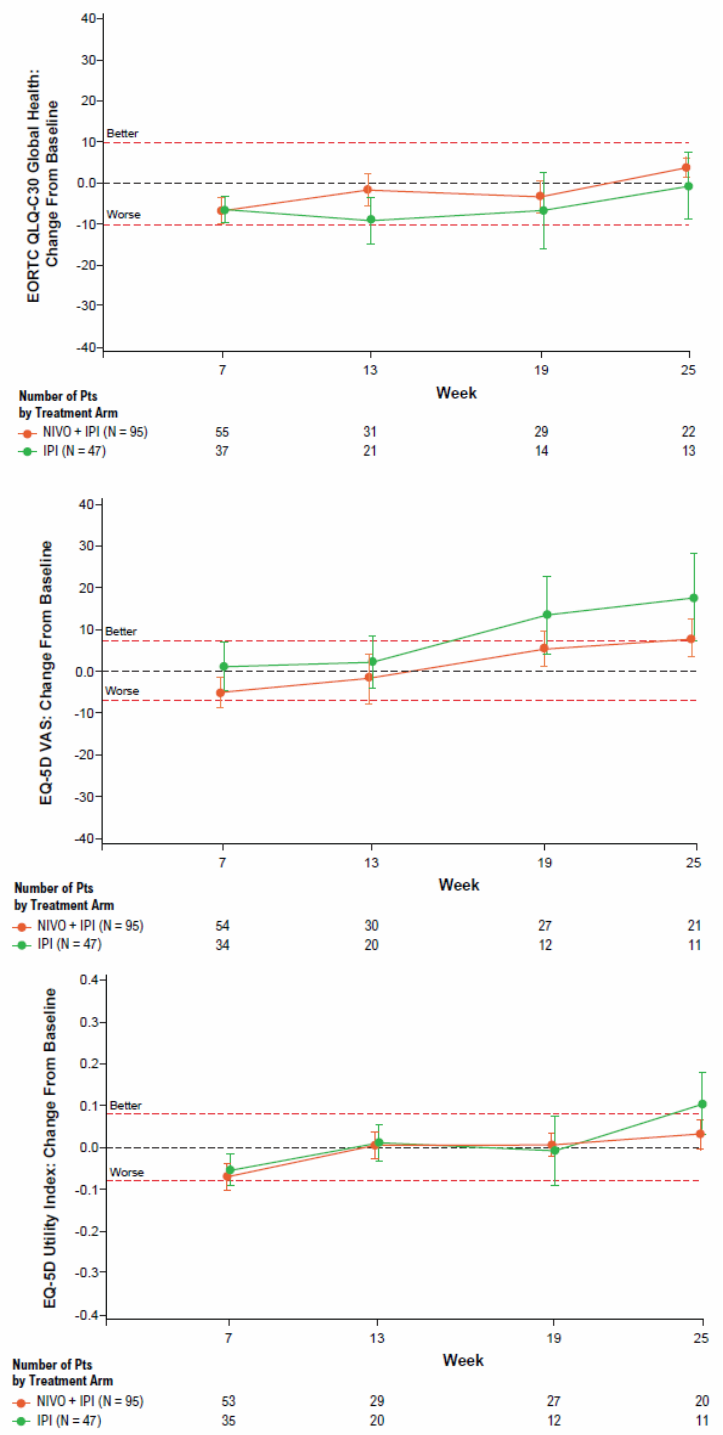


Abbreviations in figure: EQ-5D, EuroQol-five dimension questionnaire; HRQL, health-related quality of life; IPI, ipilimumab; NIVO+IPI, nivolumab plus ipilimumab; MID, minimally important difference; VAS, visual analogue scale.
Source: Schadendorf *et al*. 2015[53]

HRQoL data are presented for CheckMate 069 for a minimum follow-up of 25 weeks. At baseline around 65% of patients in the combination immunotherapy arm and 77% in the ipilimumab arm completed EQ-5D and EORTC QLQ-C30 questionnaires.[55] The completion rates stayed relatively stable throughout the study. HRQoL seemed to deteriorate at the assessment at seven weeks, but return towards baseline by week 13 in both treatment arms, for EORTC QLQ-C30, EQ-5D VAS, and EQ-5D utility score.

According to the CS longitudinal mixed-effects modelling (controlling for baseline HRQoL) demonstrated statistically significant improvements in dyspnoea and emotional functioning subscales of the EORTC QLQ-C30 with combination immunotherapy (Figure 13). With ipilimumab alone, there were statistically significant improvements in emotional functioning and statistically significant deteriorations in fatigue, global health and physical functioning (no p values reported). However, no clinically meaningful changes were observed in either treatment arm and no significant findings were observed between treatment arms at any timepoint. No numerical data for these outcomes are presented in the CS.

Figure 13. HRQL change from baseline in CheckMate 069, HRQL analysis set (reproduced from CS Figure 21)

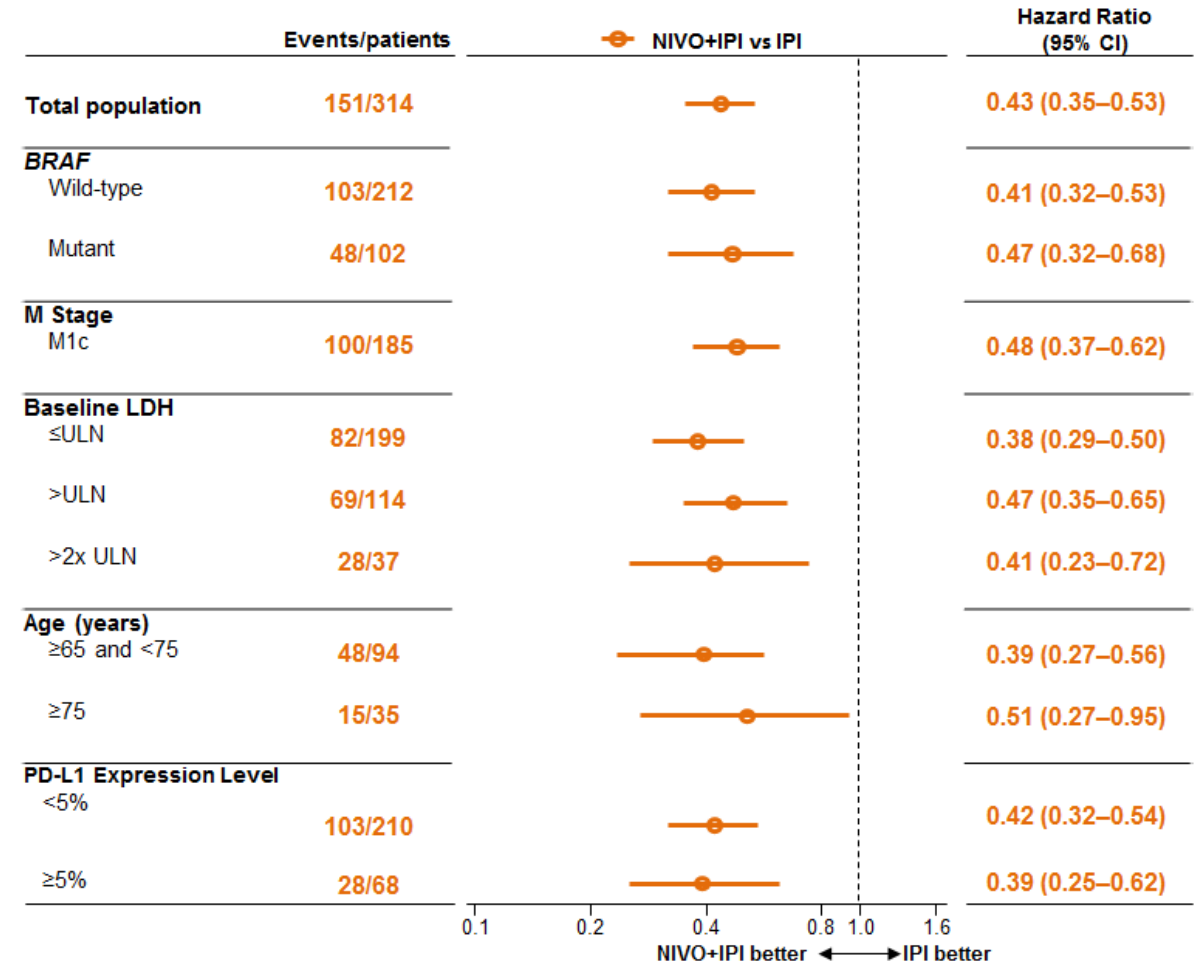


Abbreviations in figure: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol-five dimension questionnaire; IPI, ipilimumab; NIVO, nivolumab; VAS, visual analogue scale.
Source: Abernethy *et al*. 2015[55]

4.3.5 Subgroup analysis

Pre-specified subgroups in CheckMate 067 included age, gender, race, region, baseline ECOG PS, PD-L1 expression status, BRAF mutation status, M stage at study entry, history of brain metastases, smoking status, baseline LDH and AJCC stage. Of these subgroups, data on PFS and ORR are reported in the CS only for: age, PD-L1 expression status, BRAF mutation status, M stage at study entry and baseline LDH. The subgroup analyses showed consistently longer PFS and higher ORR with combination immunotherapy than with ipilimumab treatment alone (Figure 14).

Figure 14. Forest plot of treatment effect on PFS in pre-defined subgroups of CheckMate 067, ITT analysis set (reproduced from CS Figure 22)



Abbreviations in figure: CI, confidence interval; ITT, intention-to-treat; LDH, lactate dehydrogenase; M, metastatic; NIVO+IPI, nivolumab plus ipilimumab; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.
Source: Larkin *et al*. 2015[31]

[redacted]

Table 24 [redacted]

[redacted] Table 24 [redacted]

[redacted]

Table 24. Summary of progression free survival and objective response rate in CheckMate 067 UK population subgroup and ITT population.

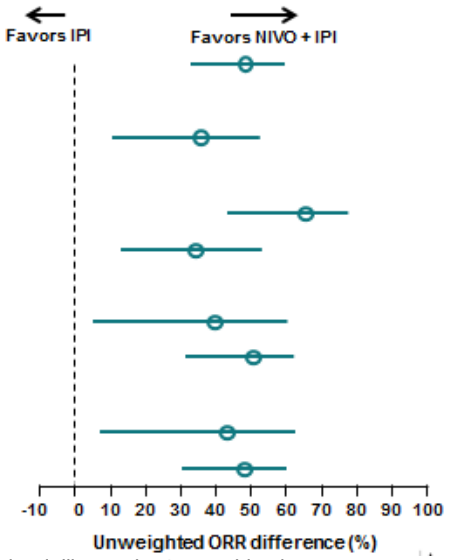
PFS	**ITT population**			[redacted]	
Treatment	n/N (%)	Median months (95% CI)		[redacted]	[redacted]
Combination immunotherapy	151 / 314 (48.1%)	11.5 (8.9-16.7)		[redacted]	[redacted]
Ipilimumab	234 / 315 (74.3%)	2.9 (2.8-3.4)		[redacted]	[redacted]
ORR	**ITT population**			[redacted]	
Treatment	Responders n/N (%)	CR n/N (%)	PR n/N (%)	[redacted]	[redacted]
Combination immunotherapy	181/314 (57.6)	36/314 (11.5)	145/314 (46.2)	[redacted]	[redacted]
Ipilimumab	60/315 (19.0)	7/315 (2.2)	53/315 (16.8)	[redacted]	[redacted]

Abbreviations in table: ITT, intention-to-treat; ORR, objective response rate; PFS, progression-free survival.

In CheckMate 069 the same subgroups as in CheckMate 067 were pre-planned for BRAF- and $BRAF^{+}$ patients. However, subgroup analyses of the ITT population were presented in the CS, which show consistently higher ORR for combination immunotherapy compared to ipilimumab alone (Figure 15).

Figure 15. Forest plot of treatment effect on ORR in pre-defined subgroups of CheckMate 069, ITT analysis set (reproduced from CS, pg 78, Figure 23)

	N	ORR, % (n/N)	
		NIVO + IPI	IPI
Overall	142	59 (56/95)	11 (5/47)
M Stage at study entry			
M1c	65	59 (26/44)	24 (5/21)
Age category I			
<65 years	68	65 (31/48)	0 (0/20)
≥65 years	74	53 (25/47)	19 (5/27)
PD-L1 status[a]			
≥5% expression	35	58 (14/24)	18 (2/11)
<5% non-expression	83	55 (31/56)	4 (1/27)
BRAF status			
MT	32	55 (12/22)	10 (1/10)
WT	110	60 (44/73)	11 (4/37)



Abbreviations in figure: IPI, ipilimumab; M, metastatic; NIVO+IPI, nivolumab plus ipilimumab; ORR, objective response rate; PD-L1, programmed death-ligand 1.
Source: Hodi *et al*. 2015[56]

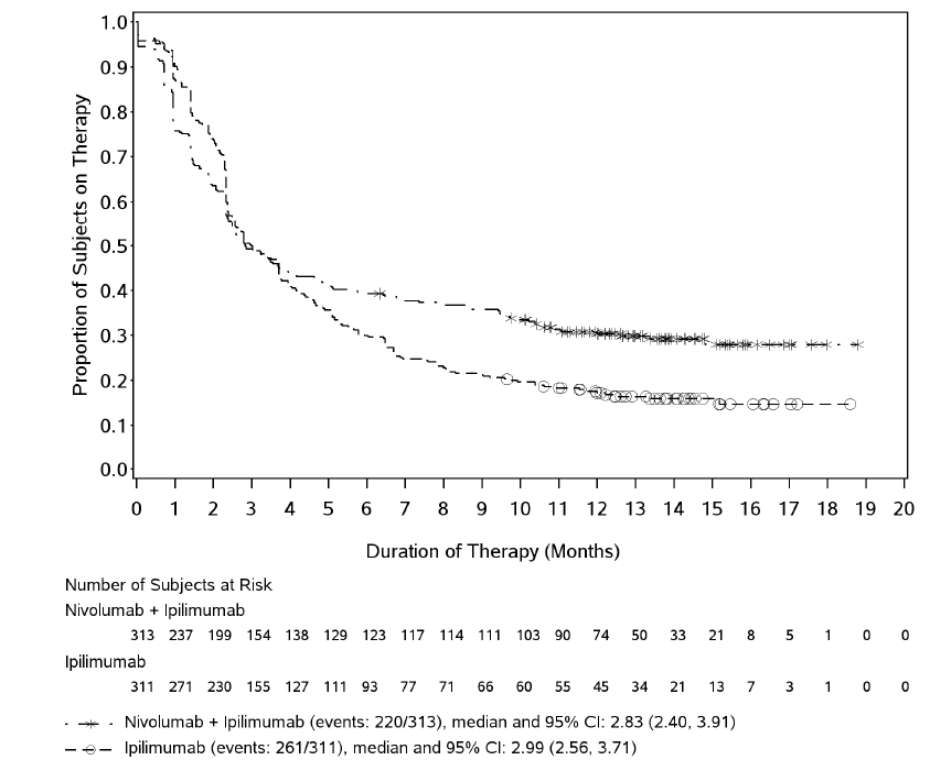
4.3.6 Adverse effects

The company presents safety data from CheckMate 067, CheckMate 069 and CheckMate 004 with the following reason: "Apart from those studies presented in Sections 4.2 and 4.11, no other studies investigate the Regimen [combination immunotherapy]; safety data are therefore only presented from CheckMate 067, CheckMate 069 and CheckMate 004" (CS, pg 112, Section 4.12).

Treatment exposure

In CheckMate 067, 313 of 314 patients randomised to the combination immunotherapy group received at least one study treatment dose (CS, pg 112, Section 4.12). Patients received a median of four doses of both nivolumab and ipilimumab: 147/313 (47%) patients received more than four nivolumab doses and 179/313 (57.2%) patients received all four ipilimumab doses (CS, pg 112, Section 4.12). Median duration of study treatment was 2.8 months (95% CI: 2.4 to 3.9; Figure 16). A total of 311 of 315 patients randomised to ipilimumab received at least one treatment dose (CS, pg 112, Section 4.12). Patients received a median of four doses of ipilimumab and median duration of study treatment was 3.0 months (95% CI: 2.6 to 3.7; CS, pg 112, Section 4.12).

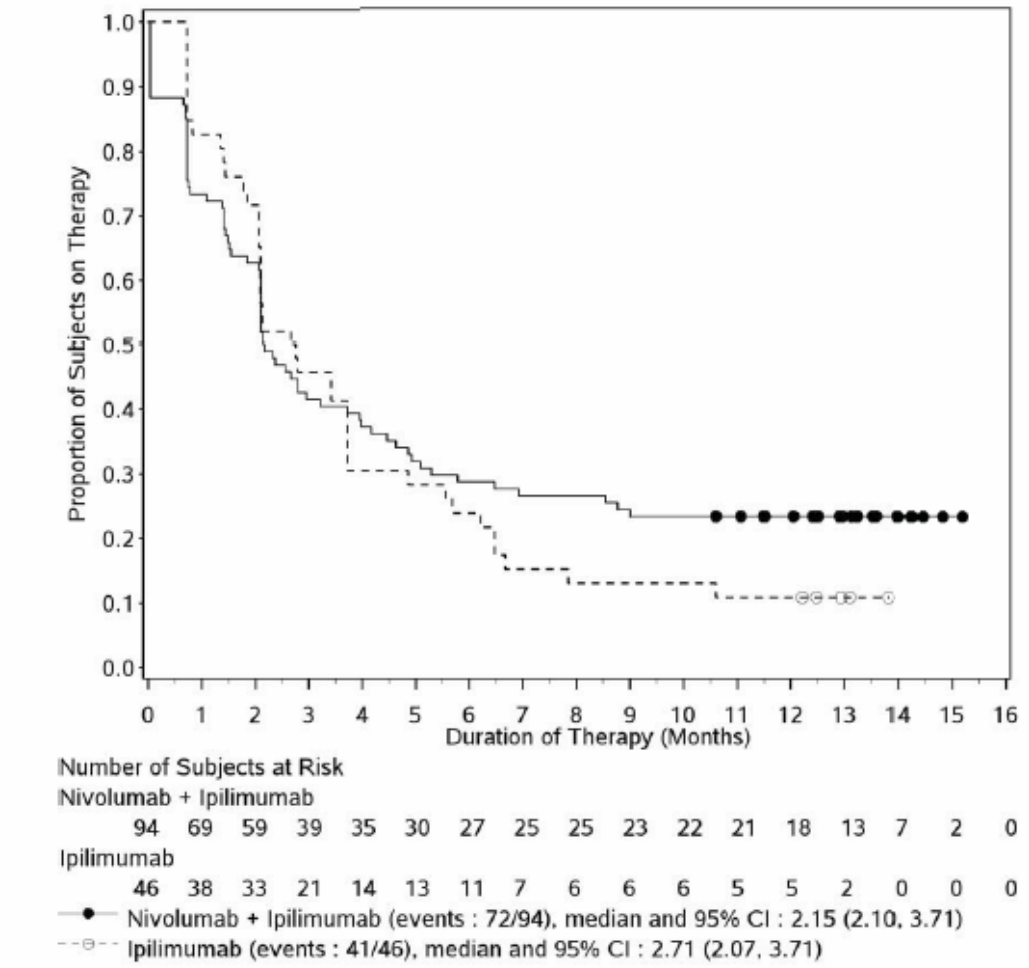
Figure 16. Kaplan-Meier curve for time-on-treatment in CheckMate 067, safety analysis set (reproduced from CS, pg 112, Figure 40)



Abbreviations in figure: CI, confidence interval.
Notes: symbols represent censored observations.
Source: CheckMate 067 CSR[33]

In CheckMate 069, 94 out of 95 patients randomised to combination immunotherapy received at least one dose of study treatment. Patients received a median of four nivolumab and ipilimumab doses: 38/94 (40.4%) patients received more than four nivolumab doses and 54/94 (57.4%) of patients received all four ipilimumab doses. Median duration of study therapy was 2.2 months (95% CI: 2.1 to 3.7 patients). A total of 46 out of 47 patients randomised to ipilimumab received at least one dose of study treatment. Patients received a median of four doses and 32/46 (69.6%) of patients received all four ipilimumab doses. Median duration of study therapy was 2.7 months (95% CI: 2.1 to 3.7; Figure 17).

Figure 17. Kaplan-Meier curve for time-on-treatment in CheckMate 069, safety analysis set (reproduced from CS, pg 113, Figure 41)



Abbreviations in figure: CI, confidence interval.
Notes: symbols represent censored observations; excludes exposure data collected in crossover patients.
Source: CheckMate 069 CSR[34]

In CheckMate 004 cohort 1-3, median duration of treatment was 23.9 weeks for nivolumab and 13.0 weeks for ipilimumab.[59] In 41 patients in cohort 8, median duration of treatment was 28.0 weeks for nivolumab and 11.9 weeks for ipilimumab (CS, pg 113-114, Section 4.12).

Safety profile

The company provides an overview of the safety profile of combination immunotherapy (Box 10).

Box 10. Safety profile of combination immunotherapy (CS, pg 144, Section 4.12)

> In general, the safety profile of the Regimen [combination immunotherapy] was consistent with the mechanisms of action of nivolumab and ipilimumab monotherapy. No new safety signals were identified and AEs were manageable with established treatment guidelines suggesting this combination regimen can be well tolerated under controlled settings.

In CheckMate 067, almost all patients in both the combination immunotherapy arm and ipilimumab arm experienced at least one any grade AE (Table 25). The rates of grade 3-4 AEs were considerably higher in the combination immunotherapy arm compared to the ipilimumab arm for: all AE (68.7% versus 55.6%, respectively), treatment-related adverse events (TRAE; 55.0% versus 27.3%, respectively), serious adverse event (SAE; 50.8% versus 38.3%, respectively), and treatment-related serious adverse event (TRSAE; 35.8% versus 16.4%, respectively, Table 25). Discontinuation due to AE or TRAE was also considerably higher in the combination immunotherapy arm compared to the ipilimumab arm (33.5% versus 19.9% and 29.4% versus 13.2%, respectively). In the ipilimumab arm one death was reported by the investigators as being due to study drug toxicity (cardiac arrest). In the combination immunotherapy therapy arm no deaths were considered to be related to treatment (Table 25).

Table 25. Summary of safety data from CheckMate 067, safety analysis set (reproduced from CS, pg 114, Table 39)

	Nivolumab plus ipilimumab (n=313)		**Ipilimumab (n=311)**	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All AEs, n (%)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
TRAEs, n (%)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
All SAEs, n (%)	217 (69.3)	159 (50.8)	162 (52.1)	119 (38.3)
TRSAEs, n (%)	150 (47.9)	112 (35.8)	69 (22.2)	51 (16.4)
DC due to AEs, n (%)	135 (43.1)	105 (33.5)	70 (22.5)	62 (19.9)
DC due to TRAEs, n (%)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)
Deaths relating to study drug, n	0		1	

Abbreviations in table: AE, adverse event; DC, discontinuation; SAE, serious adverse event; TRAE, treatment related adverse event; TRSAE, treatment related serious adverse event.
Source: Larkin *et al*. 2015[31]; CheckMate 067 CSR [33]

In CheckMate 067, the company reports that the most common TRAEs in the combination immunotherapy and ipilimumab arms were diarrhoea (44.1% and 33.1%, respectively), fatigue (35.1% and 28.0%, respectively) and pruritus (33.2% and 35.4%, respectively). Discontinuation of the study drug was most commonly caused by treatment-related diarrhoea and colitis.

In the combination immunotherapy arm the most frequent TRSAEs with a frequency ≥2% were: diarrhoea (9.3%), colitis (9.3%), pyrexia (3.8%), increased transaminases (2.6%), nausea (2.2%) and hypophysitis (2.2%). In the ipilimumab arm these TRSAEs were: colitis (9.0%), diarrhoea (7.1%) and hypophysitis (2.6%).

The company reports, "In both treatment groups, a similar incidence was observed for SAEs (all causality and treatment related) reported within 100 days of last dose compared to those reported

within 30 days of last dose." (CS, pg 115, Section 4.12). Also the company provides an overview of AEs with a potential immunological cause: select AEs (Box 11 and Table 26).

Box 11. Select AEs (CS, pg 115, Section 4.12)

Select AEs, defined as AEs with a potential immunological cause, were analysed according to organ category (skin, gastrointestinal, endocrine, pulmonary, hepatic, and renal) as in previous studies. The most frequent Select AEs occurred in the skin, gastrointestinal, endocrine and hepatic organ categories and were observed more frequently in the Regimen [combination immunotherapy] group.

Median time to onset of Select AEs did not exceed 12.1 weeks across organ categories (irrespective of Grade). Resolution rates for Select AEs were greater than 70% in the Regimen [combination immunotherapy] group for all organ categories with the exception of the endocrine category where events were not considered resolved in approximately 50% of patients at the time of analysis (February 2015). Aside from the endocrine Select AE category, median time to resolution of Select AEs was <10 weeks in the Regimen [combination immunotherapy] group.

Immune modulatory agents to manage AEs were used in 83.4% of patients in the Regimen [combination immunotherapy] group and 55.9% of patients in the ipilimumab group; secondary immunosuppressive agents were used in 6.1% and 5.1% of patients, respectively. Aside from the endocrine Select AE category, median time to resolution of Select AEs in patients who received immune modulating medication (IMM) did not exceed 9 weeks in the Regimen [combination immunotherapy] group. Select AEs in patients who received IMM were resolved in between 75 and 100% of patients in the Regimen [combination immunotherapy] group with the exception of Select AEs in the endocrine category; similar trends were observed in Grade 3-4 Select AEs analyses (data not shown).

In CheckMate 067, there were a higher proportion of all and grade 3-4 select AEs in the combination immunotherapy arm compared to the ipilimumab arm for the categories: endocrine, gastrointestinal, hepatic, pulmonary, renal and skin (Table 26). However, in these categories of select AEs, the proportion of patient with resolution of events was higher or approximately similar in the combination immunotherapy arm compared to the ipilimumab arm. Time to resolution was not reached in the endocrine category and was similar between the combination immunotherapy arm and the ipilimumab arm for the gastrointestinal, renal and hypersensitivity/infusion reactions categories. Time to resolution was shorter in the combination immunotherapy arm compared to the ipilimumab arm for the skin category, but longer for the hepatic and pulmonary categories (Table 26).

Table 26. Select AE data from CheckMate 067, safety analysis set (reproduced from CS, pg 115-117, Table 40)

	Nivolumab plus ipilimumab (n=313)	**Ipilimumab (n=311)**

	All causality	Drug related	All causality	Drug related
Endocrine category				
All AEs, n (%)	105 (33.5)	94 (30.0)	38 (12.2)	34 (10.9)
Grade 3-4 AEs, n (%)	19 (6.1)	15 (4.8)	7 (2.3)	7 (2.3)
Resolution of event, n (%)[a]	53 (50.5)	51 (54.3)	15 (40.5)	13 (38.2)
Time to resolution, median weeks[a]	Not reached	Not reached	Not reached	Not reached
Resolution of event after treatment with IMM, n/N (%)[a]	14/37 (37.8)	14/34 (41.2)	4/15 (26.7)	4/14 (28.6)
Time to resolution with IMM, median weeks[a]	Not reached	Not reached	Not reached	Not reached
Gastrointestinal category				
All AEs, n (%)	171 (54.6)	145 (46.3)	150 (48.2)	114 (36.7)
Grade 3-4 AEs, n (%)	50 (16.0)	46 (14.7)	40 (12.9)	36 (11.6)
Resolution of event, n (%)[a]	162 (95.3)	138 (95.8)	134 (90.5)	102 (90.3)
Time to resolution, median weeks[a]	2.4	2.7	2.4	2.9
Resolution of event after treatment with IMM, n/N (%)[a]	61/65 (93.8)	62/66 (93.9)	43/49 (87.8)	44/50 (88.0)
Time to resolution with IMM, median weeks[a]	4.7	4.5	5.3	4.9
Hepatic category				
All AEs, n (%)	105 (33.5)	95 (30.4)	34 (10.9)	22 (7.1)
Grade 3-4 AEs, n (%)	62 (19.8)	60 (19.2)	14 (4.5)	5 (1.6)
Resolution of event, n (%)[a]	92 (87.6)	88 (92.6)	26 (76.5)	21 (95.5)
Time to resolution, median weeks[a]	5.3	5.0	4.3	4.2
Resolution of event after treatment with IMM, n/N (%)[a]	42/44 (95.5)	43/45 (95.6)	5/6 (83.3)	3/3 (100)
Time to resolution with IMM, median weeks[a]	5.7	5.9	8.1	4.1
Pulmonary category				
All AEs, n (%)	23 (7.3)	22 (7.0)	10 (3.2)	6 (1.9)
Grade 3-4 AEs, n (%)	4 (1.3)	3 (1.0)	2 (0.6)	1 (0.3)
Resolution of event, n (%)[a]	20 (87.0)	20 (90.9)	9 (90.0)	5 (83.3)
Time to resolution, median weeks[a]	7.0	6.7	4.6	6.3
Resolution of event after treatment with IMM, n/N (%)[a]	16/17 (94.1)	16/17 (94.1)	4/5 (80.0)	2/3 (66.7)
Time to resolution with IMM, median weeks[a]	6.1	6.1	6.0	6.1
Renal category				
All AEs, n (%)	32 (10.2)	17 (5.4)	14 (4.5)	8 (2.6)
Grade 3-4 AEs, n (%)	11 (3.5)	6 (1.9)	4 (1.3)	1 (0.3)
Resolution of event, n (%)[a]	26 (81.3)	15 (88.2)	14 (100)	8 (100)
Time to resolution, median weeks[a]	2.1	1.9	2.5	2.5
Resolution of event after treatment with IMM, n/N (%)[a]	3/3 (100)	3/3 (100)	4/4 (100)	3/3 (100)
Time to resolution with IMM, median weeks[a]	1.7	1.7	4.7	4.6
Skin category				
All AEs, n (%)	201 (64.2)	185 (59.1)	194 (62.4)	168 (54.0)
Grade 3-4 AEs, n (%)	19 (6.1)	18 (5.8)	12 (3.9)	9 (2.9)

	Nivolumab plus ipilimumab (n=313)		Ipilimumab (n=311)	
	All causality	**Drug related**	**All causality**	**Drug related**
Resolution of event, n (%)[a]	143 (71.5)	135 (73.0)	139 (71.6)	123 (73.2)
Time to resolution, median weeks[a]	9.9	9.4	12.1	11.0
Resolution of event after treatment with IMM, n/N (%)[a]	58/77 (75.3)	55/73 (75.3)	42/59 (71.2)	41/55 (74.5)
Time to resolution with IMM, median weeks[a]	9.0	8.6	12.9	12.4
Hypersensitivity/infusion reactions category				
All AEs, n (%)	14 (4.5)	13 (4.2)	9 (2.9)	8 (2.6)
Grade 3-4 AEs, n (%)	0	0	1 (0.3)	1 (0.3)
Resolution of event, n (%)[a]	12 (85.7)	11 (84.6)	9 (100)	8 (100)
Time to resolution, median weeks[a]	0.3	0.3	0.1	0.1
Resolution of event after treatment with IMM, n/N (%)[a]	1/1 (100)	1/1 (100)	2/2 (100)	1/1 (100)
Time to resolution with IMM, median weeks[a]	0.1	0.1	0.2	0.3

Abbreviations in table: AE, adverse event; IMM, immune modulating medication.
Notes: [a] any grade events.
Source: Larkin *et al*. 2015[31]; CheckMate 067 CSR[33]

In CheckMate 069, the proportion of patients with any grade TRAEs was similar between the combination immunotherapy arm (91.5%) and ipilimumab arm (93.5%, Table 27). The proportion of grade 3-4 TRAEs was higher in the combination immunotherapy group (54.3%) compared to the ipilimumab group (23.9%). Also the proportion of discontinuation due to any grade and grade 3-4 TRAEs was higher in the combination immunotherapy group (46.8% and 38.3%, respectively) compared to the ipilimumab group (17.4% and 13.0%, respectively).

Table 27. Summary of safety data from CheckMate 069, safety analysis set (reproduced from CS, pg 118, Table 41)

	Nivolumab plus ipilimumab (n=94)		Ipilimumab (n=46)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
TRAEs, n (%) Age <65 years, n/N (%) Age ≥65 years, n/N (%) M1c disease, n/N (%)	86 (91.5) 43/48 (89.6) 43/46 (93.5) 39/44 (88.6)	51 (54.3) 26/48 (54.2) 24/46 (52.2) 26/44 (59.1)	43 (93.5) 19/19 (100) 24/27 (88.9) 18/20 (90.0)	11 (23.9) 5/19 (26.3) 4/27 (14.8) 4/20 (20.0)
DC due to TRAEs, n (%)	44 (46.8)	36 (38.3)	8 (17.4)	6 (13.0)
Deaths relating to study drug, n (%)	3		0	

Abbreviations in table: AE, adverse event; DC, discontinuation; M1c, metastases stage 1c; TRAE, treatment-related adverse event.
Source: Hodi *et al*. 2015[56]; Postow *et al*. 2015[30

In CheckMate 069, the company reports three deaths related to study treatment in the combination immunotherapy arm caused by: ventricular arrhythmia 29 days after last study treatment, pneumonitis

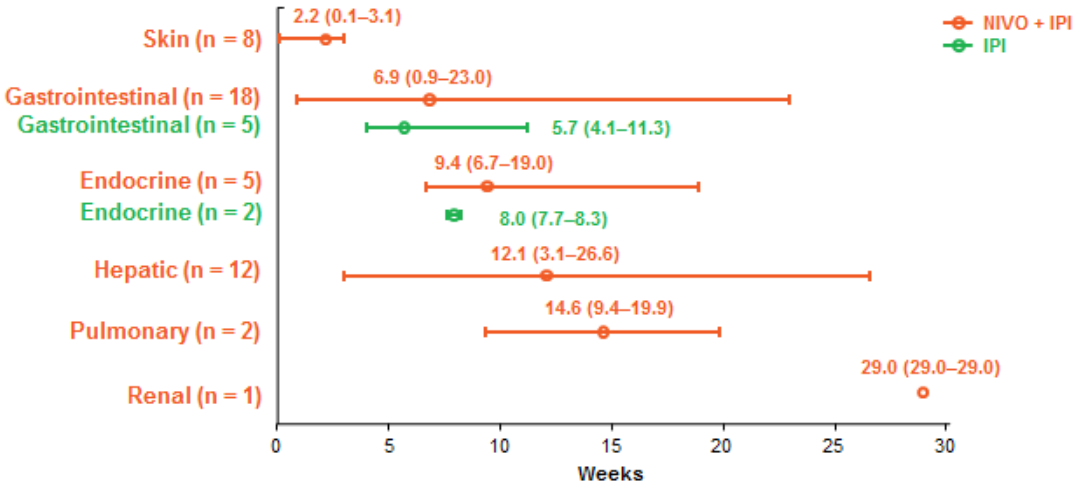
69 days after last study treatment, and pneumonia and hypercalcaemia 86 days after last study treatment (Box 12). No further information is provided on the causal mechanism of these deaths in the CS.

Box 12. Deaths related to combination immunotherapy (CS, pg 117, Section 4.12)

> Three deaths in the Regimen [combination immunotherapy] group were reported by the investigators as being related to study drug. One patient with a history of cardiac disease died from ventricular arrhythmia 29 days after the last dose of study treatment; the second died suddenly 69 days after the last dose of study treatment while clinically improving from pneumonitis and having an iatrogenic pneumothorax; the third patient died suddenly 86 days after the last dose of study treatment, 3 days after the resolution of Grade 3 pneumonia and Grade 4 hypercalcaemia. There were no deaths in the ipilimumab monotherapy group.

The company states, "The most common TRAEs in the Regimen [combination immunotherapy] group and the ipilimumab group were diarrhoea (44.7% and 37.0%), rash (41.5% and 26.1%), fatigue (39% and 43%) and pruritus (35.1% and 28.3%). The most common Grade 3-4 TRAEs with the Regimen [combination immunotherapy] were colitis (17.0%), diarrhoea (10.6%) and elevated alanine aminotransferase (10.6%)." (CS, pg 118, Section 4.12). Figure 18 presents the time of onset of grade 3-4 select AEs. The company reports, "Most Select AEs occurred during the concurrent period of treatment with the Regimen, as presented in (Figure 18)." (CS, pg 118, Section 4.12). The ERG notes that the time of onset for grade 3-4 select AEs appeared to have a fairly large range for several of the categories (Figure 18). It is unclear to the ERG whether patients were on treatment during the time of onset of grade 3-4 select AEs in Figure 18, and notes that the large spread in time to onset of grade 3-4 select adverse events may lead to a need for prolonged monitoring after treatment has started and after treatment has stopped.

Figure 18: Time to onset of grade 3-4 select AEs in CheckMate 069, safety analysis set (reproduced from CS, pg 118, Figure 42)



Abbreviations in figure: AE, adverse event; IPI, ipilimumab; NIVO + IPI, nivolumab plus ipilimumab
Source: Hodi *et al*. 2015[56]

In CheckMate 069, there were a higher proportion of all and grade 3-4 select AEs in the combination immunotherapy arm compared to the ipilimumab arm for all categories (Table 28). The proportion of patients with resolution of events was higher in the ipilimumab arm compared to the combination immunotherapy arm for the endocrine, pulmonary and skin category and lower for the gastrointestinal category. Time to resolution was not reached in the endocrine category and similar between the combination immunotherapy and the ipilimumab arm for the gastrointestinal, category. Time to resolution was longer in the combination immunotherapy arm compared to the ipilimumab arm for the pulmonary and skin category.

Table 28. Select AE data from CheckMate 069, safety analysis set (reproduced from CS, pg 119, Table 42)

	Nivolumab plus ipilimumab (n=94)		**Ipilimumab (n=46)**	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
Endocrine category				
Events, n (%)	32 (34.0)	5 (5.3)	8 (17.4)	2 (4.3)
Resolution of event after treatment with IMM, n/N (%)	2/14 (14.3)	1/4 (25.0)	1/3(33.3)	1/2 (50.0)
Time to resolution, median weeks	Not reached	Not reached	Not reached	Not reached
Gastrointestinal category				
Events, n (%)	48 (51.1)	20 (21.3)	17 (37.0)	5 (10.9)
Resolution of event after treatment with IMM, n/N (%)	26/28 (92.9)	15/17 (88.2)	7/9 (77.8)	4/5 (80.0)
Time to resolution, median weeks	4.7	4.3	5.0	3.6
Hepatic category				
Events, n (%)	26 (27.7)	14 (14.9)	2 (4.3)	0

	Nivolumab plus ipilimumab (n=94)		Ipilimumab (n=46)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
Resolution of event after treatment with IMM, n/N (%)	11/13 (84.6)	10/12 (83.3)	-	-
Time to resolution, median weeks	14.1	8.3	-	-
Pulmonary category				
Events, n (%)	11 (11.7)	3 (3.2)	2 (4.3)	1 (2.2)
Resolution of event after treatment with IMM, n/N (%)	6/8 (75.0)	2/3 (66.7)	2/2 (100)	1/1 (100)
Time to resolution, median weeks	6.1	9.0	3.2	3.6
Renal category				
Events, n (%)	3 (3.2)	1 (1.1)	1 (2.2)	0
Resolution of event after treatment with IMM, n/N (%))	2/2 (100)	1/1 (100)	-	-
Time to resolution, median weeks	0.4	0.6	-	-
Skin category				
All AEs, n (%)	67 (71.3)	9 (9.6)	26 (56.5)	0
Resolution of event after treatment with IMM, n/N (%)	24/35 (68.6)	8/9 (88.9)	11/13 (84.6)	-
Time to resolution, median weeks	18.6	6.1	8.6	-

Abbreviations in table: AE, adverse event; IMM, immune modulating medication.
Source: Postow *et al*. 2015[32]

More patients in the ipilimumab arm (52.2%) had no grade 2-4 select AEs across organs compared to the combination immunotherapy arm (21.3%, Table 29). More patients in the combination therapy arm had two organ categories (23.4%) involved compared to the ipilimumab arm (6.5%). In the combination immunotherapy arm, eight patients had three or more organ categories involved versus no patients in the ipilimumab group.

Table 29. Grade 2-4 Select AEs across organ categories in CheckMate 069, safety analysis set (reproduced from CS, pg 120, Table 43)

Number of organ categories	Nivolumab plus ipilimumab (n=94)	Ipilimumab (n=46)
0, n (%)	20 (21.3)	24 (52.2)
1, n (%)	44 (46.8)	19 (41.3)
2, n (%)	22 (23.4)	3 (6.5)
3, n (%)	7 (7.4)	0
>3, n (%)	1 (1.1)	0

Abbreviations in table: AE, adverse event.
Source: Hodi *et al*. 2015[56]

The company only presents limited information on AEs in CheckMate 004 (Box 13). In cohort 8 in which the recommended dose of combination immunotherapy was used the company implies that TRAEs were consistent with those seen with use of nivolumab and ipilimumab.

Box 13. AEs in CheckMate 004 (CS, pg 120, Section 4.12)

As anticipated a priori, there were fewer Grade 3-4 AEs, SAEs (all causality and treatment related), Grade 3-4 SAEs and AEs leading to discontinuation in the lowest dose cohort of CheckMate 004 (cohort 1) compared with the higher dose escalation cohorts. This is because the higher dose escalation cohort (3mg/kg nivolumab plus 3mg/kg ipilimumab) exceeded the maximum tolerated dose (MTD).

The safety profile observed in cohort 8 was similar to that observed in RCTs; most patients experienced a TRAE but the nature of events was consistent with the mechanisms of action of nivolumab and ipilimumab.

Overall, the safety profile of combination immunotherapy in CheckMate 067 and 069 appeared to be similar. However, while no deaths due to study drug toxicity were reported in the combination immunotherapy in CheckMate 067, three deaths related to combination immunotherapy were reported in CheckMate 069. Given the limited information provided on CheckMate 004 in the CS, the ERG is unable to comment further on its safety profile compared to the other trials.

In CheckMate 067 and 069, most patients experienced a TRAE and the proportions of patients with any grade TRAEs were similar in the combination immunotherapy arm (99.7% versus 91.5%, respectively) and ipilimumab arm (99.0% versus 93.5%, respectively). Also the proportion of grade 3-4 AEs were similar in CheckMate 067 and 069 and higher in the combination immunotherapy arm (55.0% versus 54.3%, respectively) compared to the ipilimumab arm (27.3% versus 23.9% respectively). Additionally, the proportions of discontinuation due to any grade and grade 3-4 AEs were similar in both trials; the proportion of discontinuation due to any grade AEs was higher in the combination immunotherapy arm in CheckMate 067 and 069 (36.4% and 46.8%, respectively) compared to the ipilimumab arm (14.8% versus 17.4%, respectively) as well as the proportion of discontinuation due to grade 3-4 AEs in the combination immunotherapy arm (29.4% and 38.3%, respectively) versus the ipilimumab arm (13.0% versus 13.2%, respectively).

The proportions of the most common TRAEs, diarrhoea, fatigue, and pruritus, were similar in the combination immunotherapy and ipilimumab arms in CheckMate 067 and 069. In both trials, there were a higher proportion of all and grade 3-4 select AEs in the combination immunotherapy arm compared to the ipilimumab arm for the endocrine, gastrointestinal, hepatic, pulmonary, renal and skin categories.

4.3.7 Meta-analysis

At the clarification stage the company supplied the results of a meta-analysis of CheckMate 067 and CheckMate 069 for PFS and ORR (Table 30 and Table 31). The results of the meta-analyses are in

line with the individual trial results. For PFS, the meta-analysis of CheckMate 067 and CheckMate 069 showed a statistically significantly longer PFS in the combination immunotherapy arm compared to the ipilimumab arm (HR 0.41, 95% CI: 0.34 to 0.50). There was little heterogeneity in the analysis, which decreased the uncertainty around the HR compared to the individual trials. For ORR, responders, CR and PR all showed statistically significant differences between the treatment arms, favouring combination immunotherapy. There was some heterogeneity between the trials for CR and responders, due to the low number of events in the ipilimumab arm in CheckMate 069.

Table 30. Direct Meta-Analyses of CheckMate 067 and 069 for PFS (reproduced from Clarification response A12)

Outcome	**Trial**	**Combination immunotherapy**		**Ipilimumab**		**In-trial HR (95% CI)**	**Pooled HR (95% CI) [p-value]**	**Hetero-geneity p-value**
		n	N	n	N			
PFS	CheckMate 067 (17th Feb 2015 datacut)	151	314	234	315	0.42 (0.31, 0.57)[a]	0.41 (0.34, 0.50) [<0.001]	0.775
	CheckMate 069 (30th Jan 2015 datacut)	42	95	32	47	0.39 (0.25, 0.63)		
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.42 (0.35, 0.50) [<0.001]	0.772
	CheckMate 069 (30th Jan 2015 datacut)	42	95	32	47	0.39 (0.25, 0.63)		

Notes: [a] 99.5% CI

Table 31. Meta-Analyses of CheckMate 067 and 069 for Responders, complete response and partial response (reproduced from Clarification response A12)

Outcome	**Trial**	**Combination immunotherapy**		**Ipilimumab**		**In-trial OR (95% CI)**	**Pooled OR (95% CI) [p-value]**	**Heterog eneity p-value**
		n	N	n	N			
Responders	CheckMate 067 (17th Feb 2015 datacut)	181	314	60	315	5.78 (4.04, 8.29)	6.40 (4.57, 8.96) [<0.001]	0.179
	CheckMate 069 (30th Jan 2015 datacut)	56	95	5	47	12.06 (4.38, 33.23)		
CR	CheckMate 067 (17th Feb 2015 datacut)	36	314	7	315	5.70 (2.50, 13.01)	7.94 (3.53, 17.89) [<0.001]	0.244
	CheckMate 069 (30th Jan 2015 datacut)	21	95	0	47	27.42 (1.62, 463.38)		
PR	CheckMate 067 (17th Feb 2015 datacut)	145	314	53	315	4.24 (2.93, 6.14)	4.33 (3.06, 6.12) [<0.001]	0.793
	CheckMate	35	95	5	47	4.90		

Outcome	Trial	Combination immunotherapy		Ipilimumab		In-trial OR (95% CI)	Pooled OR (95% CI) [p-value]	Heterogeneity p-value
		n	N	n	N			
	069 (30th Jan 2015 datacut)					(1.77, 13.54)		
Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.40 (4.57, 8.96) [<0.001]	0.179
	CheckMate 069 (30th Jan 2015 datacut)	56	95	5	47	12.06 (4.38, 33.23)		
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.32 (3.70, 18.70) [<0.001]	0.263
	CheckMate 069 (30th Jan 2015 datacut)	21	95	0	47	27.42 (1.62, 483.38)		
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.23 (2.99, 5.99) [<0.001]	0.758
	CheckMate 069 (30th Jan 2015 datacut)	35	95	5	47	4.90 (1.77, 13.54)		

Abbreviations in table: CI, confidence interval; CR, complete response; OR, odds ratio; PR, partial response.

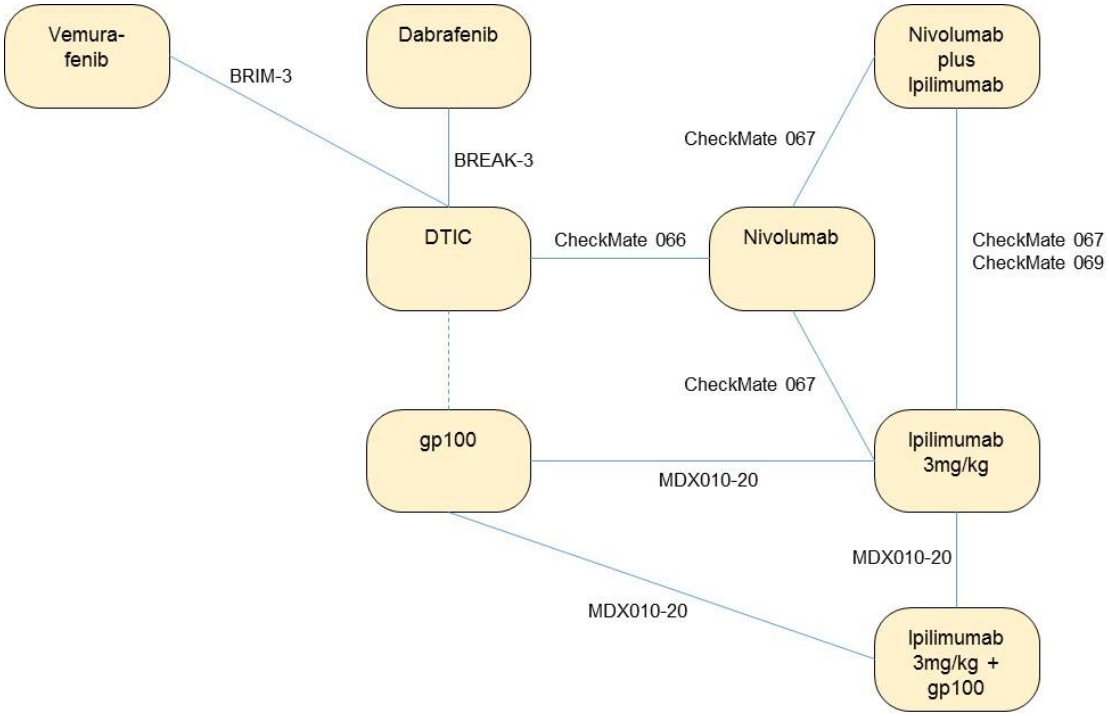
4.4 Critique of trials identified and included in the indirect comparison and/or network meta-analysis

The company did not identify any head-to-head trials of combination immunotherapy versus either of the BRAF inhibitors, vemurafenib and dabrafenib. The company, therefore, explored the possibility of conducting an indirect comparison. The company presented methods for performed indirect comparisons in CS Section 4.10.

The company identified trials relevant for the indirect comparison from the list of included trials from the systematic search (Table 4). The company formed a network of trials for the relevant comparisons, which report PFS and/or OS (Figure 19). CheckMate 066, which was not identified in the systematic search, was also included in the network.

The ERG is concerned that the company used the same inclusion criteria to inform both the direct and indirect evidence, which were limited to the intervention and comparator in the scope (with the exception of pembrolizumab, which was excluded). Tailoring the inclusion criteria for the indirect comparison by, e.g. including nivolumab monotherapy as an intervention, would have identified CheckMate 066, and potentially other relevant trials, that could link the network, or inform an indirect comparison using covariate adjusted data as presented by the company (Section 4.4.1 and Section 4.4.2).

Figure 19. Network diagram (reproduced from CS, pg 81, Figure 24)



Abbreviations in figure: DTIC, dacarbazine; gp-100, gp-100 melanoma peptide vaccine.
Notes: The dotted line between DTIC and gp-100 does not indicate a trial, but rather indicates that if DTIC and gp-100 are considered equivalent, it allows for MDX010-20 to be linked within this network of treatments.

However, a network meta-analysis (NMA), combining combination immunotherapy with ipilimumab and the BRAF inhibitors was not considered appropriate for several reasons including (CS, pg 84, Section 4.10):

- Non-proportional hazards between BRAF inhibitors, immunotherapies and chemotherapy due to their different mechanisms of action.
- High levels of crossover from chemotherapy to BRAF inhibitor therapy in relevant BRAF inhibitor trials[2, 27], and subsequent use of ipilimumab in several relevant trials. [2, 27, 36] Appendix 9.4).
- Differences between the trial designs and populations in terms of BRAF mutation status, line of therapy, prognostic characteristics of patients within the trials in the proposed network. (Appendix 9.2 and 9.3) However, the company also stated that BRAF mutation status and line of therapy are not expected to influence treatment effects (discussed in Section 4.4.2).

The non-proportional hazards and differences between these trials and trial populations have been highlighted in previous NICE appraisals of nivolumab monotherapy[61] and ipilimumab monotherapy.[62]

The ERG agrees with the company that the proportional hazards assumption is unlikely to hold for the entirety of the survival curves for the BRAF inhibitors versus dacarbazine[2, 27]and for ipilimumab versus gp100.[26] However, an alternative approach could have been to segment the survival curves into different sections within which the HRs are different but the proportional hazards assumptions holds. The company could then have used a piecewise constant model.[63] For CheckMate 066 (nivolumab versus dacarbazine) the proportional hazards assumption is unlikely to hold even when using this approach. However, this trial could have been excluded from the network as combination immunotherapy can be linked to vemurafenib and dabrafenib via MDX010-20 (ipilimumab versus gp100), if dacarbazine and gp100 can be assumed to have equivalent efficacy, as indicated in the proposed network.

The differences between the trials in terms of crossover and subsequent therapies may have a substantial impact on the comparability of the trials in the network.[64] However, the company could have used an appropriate method to adjust for switching[64] or used the ITT method as more complicated methods advocated by the DSU for dealing with treatment switching are only substantially more reliable than using the ITT results when switching affects more than 60% of patients.[65]

There were also differences in patient baseline characteristics for key prognostic factors (Appendix 9.2); e.g. patients in MDX010-20 seems to have been worse than patients in the other trials in terms of worse ECOG, M-stage and brain metastases. Also, patients in BRIM-3 had a substantially higher LDH than patients in the other included trials. The ERG does not consider that the impact of the differences in these prognostic indicators on the relative treatment effect would have been so profound as to make the results from an NMA unsuitable for decision making. Therefore the ERG preferred approach would be an NMA. However, due to time constraints the ERG was unable to explore the impact of this alternative approach.

As a result of the reasons stated above, no NMA was presented in the CS. Instead two indirect comparisons were created, one for combination immunotherapy versus ipilimumab and one for combination immunotherapy versus BRAF inhibitor, using an approach whereby selected trial arms (rather than indirect comparison via a common comparator) were compared using a covariate-adjusted model. An indirect comparison of combination immunotherapy versus ipilimumab was needed because of the immaturity of the survival data for CheckMate 067 and CheckMate 069; PFS data from CheckMate 067 were supported by data on long-term predications of ipilimumab and nivolumab monotherapy, assuming equivalent efficacy of long term survival (assumption discussed in Section 4.4.1 below).

The two indirect comparisons are described and appraised separately below, including identification and selection of trial evidence, and statistical procedures used (methods, assumptions, covariate selection). Sections 5.4 and 5.5 of this report describe and critique the statistical procedures used to fit and extrapolate parametric survival curves from the trials to inform the comparisons made within the economic model.

4.4.1 Indirect comparison of combination immunotherapy and ipilimumab

Evidence base

For the comparison of combination immunotherapy versus ipilimumab, OS data from CheckMate 067 and CheckMate 069 were not used because they were immature. In addition, for CheckMate 069 the OS results were potentially confounded by substantial crossover from the ipilimumab arm to nivolumab monotherapy (56.5%, Appendix 9.4). Instead the company used PFS data from CheckMate 067 (combination immunotherapy and ipilimumab arm) and data from CheckMate 066 (nivolumab arm) and MDX010-20 (ipilimumab and ipilimumab+gp100 arms) as a proxy for OS, assuming similar post-progression survival efficacy for ipilimumab, nivolumab and combination immunotherapy (assumption discussed later in this Section).

Among the trials included in the review (Table 4), five studies investigated ipilimumab monotherapy 3mg/kg (Table 32). The reason for the company's decision to use data from MDX010-20 as the basis for the long term survival data of combination immunotherapy and ipilimumab is not clearly stated in the CS. However, the ERG notes that of the five ipilimumab trials, MDX010-20 had the most mature OS data with a median follow-up for survival of 27.8 months in the ipilimumab monotherapy arm. MDX010-20 also had the largest sample size as a result of combining the ipilimumab arm and the ipilimumab plus dacarbazine arm (based on the company's assumption of equal efficacy of ipilimumab and ipilimumab plus chemotherapy [dacarbazine and gp100], this is discussed later in this Section).

Table 32 Included trials with an ipilimumab 3mg/kg monotherapy arm (adapted from CS, pg 42, Table 9)

Study	Ipilimumab treatment schedule	N randomised	median follow up	Other
CA184-004[40]	Q3W *4 + Q12W	Ipilimumab N = 40	8.9 months	Phase II
CA184-022[41]	Q3W *4 + Q12W	Ipilimumab N = 72	8.7 months	Phase II
MDX010-08[42]	Q3W *4	Ipilimumap N = 40	16.4 months	Phase II
		Ipilimumab + dacarbazine N = 36	20.9 months	

MDX010-20	Q3W *4	Ipilimumab + gp100 N = 403	21.0 months	Phase III
		Ipilimumab N = 137	27.8 months	
Keynote 006	Q3W *4	Ipilimumab N = 278	Minimum follow up 9 months	Phase III
Abbreviations used in table:Q3W, every three weeks; Q12W, every 12 weeks				

As mentioned previously, the ERG notes that nivolumab monotherapy trials were not included in the systematic review, and the reason for using data from the nivolumab trial CheckMate 066 was not clearly described in the CS. CheckMate 066 includes up to two year data for OS, however, the ERG notes that at the latest data cut off used the median OS had still not been reached, i.e. similar to CheckMate 067 and CheckMate 069 the data would be considered immature. Also, at this data cut off point over a quarter of the patients in the nivolumab arm had crossed over to receive subsequent ipilimumab, which potentially confounds the data available for analysis (27.7%, Appendix 9.4).

It is also unclear why the company used data from both CheckMate 066 and MDX010-20 rather than choosing one trial (e.g. the trial with the most mature data set and largest trial population), as the company's assumption of equal efficacy was for all three treatments for post progression survival.

Methods

The IPD from CheckMate 067, CheckMate 066 and MDX010-20 were adjusted for the covariates listed in Table 33. Baseline characteristics for the listed covariates for the three trials are presented in Table 34. The selection of prognostic factors used as covariates was based on a meta-analysis of phase II trials by Korn *et al*. 2014[(19)], identifying variables affecting OS and PFS in patients with advanced melanoma. According to the company the covariates used are also consistent with those used in NICE technology assessment 319 (TA319)[(62)] on ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma, and they were validated by an advisory board to the company of UK clinicians.

The ERG notes that in the Korn meta-analysis statistically significant prognostic factors for OS were limited to performance status, presence of visceral disease, gender and brain metastases; for PFS performance status, gender, and age were statistically significant prognostic factors. However for PFS there was residual between-trial variation after adjusting for these factors.[(19)] LDH was not assessed in this study because of limited data. The ERG also notes that there are discrepancies in the codification of several of the prognostic factors in the Korn *et al.* study compared to the company's analysis. This is explored in detail in Section 5.5.5.1. Additionally, the company ignored several variables considered in the Korn *et al.* study: exclusion of patients with liver metastases, exclusion of patients

with visceral metastases, previous treatment for metastatic disease, and the year during which accrual was completed.

Based on clinical expert advice, the ERG agrees that the prognostic factors listed in Table 33, are the most relevant, however, the ERG notes that the specific codification of the prognostic factors were not justified in the CS.

Analyses of data informing PFS were based solely on data from CheckMate 067 and therefore a trial effect was not required. For long-term survival, post progression (post progression survival, PPS), a trial effect was included to account for differences between CheckMate 066 and MDX010-20, but a treatment effect was not included as the treatment effect of ipilimumab and nivolumab was assumed to be equivalent.

Table 33. Prognostic factors included within the covariate-adjusted parametric survival models (reproduced from CS Table 20)

Covariate	**Levels**
Treatment (only included for TTP and PrePS)	2 levels: nivolumab plus ipilimumab and ipilimumab
Trial (only included for PPS)	2 levels: MDX010-20 and CheckMate 066
Baseline ECOG	2 levels: 0 and ≥1
LDH	2 levels: >ULN and ≤ULN
M stage	2 levels: M1c and 'M0 or M1a or M1b'
History of brain metastases	2 levels: yes and no
Age group	2 levels: <65 and ≥65
Gender	2 levels: male and female
Subsequent ipilimumab (only included for PPS)	2 levels: yes and no
Abbreviations in table: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; PrePS, pre-progression survival; PPS, post-progression survival; TTP, time to progression; ULN, upper limit of normal range. Notes: The underlined covariate levels indicate which were used as reference categories in the survival models.	

Table 34. Baseline characteristics CheckMate 067, CheckMate 066, and MDX010-20

	CheckMate 067	**CheckMate 066**	**MDX010-20**

Characteristic	Ipilimumab (n=315)	Nivolumab plus ipilimumab (n=314)	Nivolumab (n=210) n/N (%)	Ipilimumab (n=137) n/N (%)
ECOG = 0	71.1%	73.3% (unknown=0.3%)	148/210 (70.5)	72/137 (52.6)
LDH (>ULN)	36.5% (1.9% not reported)	36.3% (0.3% not reported)	79/210 (37.6)	53/137 (38.7)
M stage = M1c	58.1%	57.6%	128/210 (61.0)	100/137 (73.0)
History of brain metastases	4.8%	3.5%	7/210 (3.3)	15/137 (10.9)
Age (under 65)	57.8% Median=62 years	58.9% Median=61 years	106/210 (50.5)	95/137 (69.3)
Gender (males)	64.1%	65.6%	121/210 (57.6)	81/137 (59.1)
Abbreviations in table: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; NR, not reported; ULN, upper limit of normal range.				

For the "indirect" comparison the company makes the following assumptions:

- Post-progression survival (PPS) efficacy is equivalent for ipilimumab, nivolumab and combination immunotherapy. This assumption was needed as OS data from both CheckMate 067 and 069, available at the time of submission, were immature and in CheckMate 069 also potentially confounded by crossover. Therefore, data for nivolumab and ipilimumab monotherapy were used to inform PPS, and therefore also OS. The company states that the assumption of equal post-progression survival is conservative. The ERG notes that no rational or references were provided to support the assumption. [redacted].

- BRAF mutation status does not affect the treatment effect of immunotherapies. BRAF status was therefore not included as an outcome or treatment effect modifying factor in the analyses even though CheckMate included around 70% $BRAF^-$ patients, CheckMate 066 included only $BRAF^-$ patients, and MDX010-20 did not report the BRAF mutation status of patients. To support this assumption the company references several sources:

- "The effect of BRAF status on PFS was investigated for the Regimen [combination immunotherapy] using Cox proportional hazards regression analyses in CheckMate 067. As would be expected based upon previously published information[62] and the fact that the mechanism of action of both nivolumab and ipilimumab is independent of BRAF status, BRAF status had neither a substantial nor significant impact on outcomes. BRAF status had neither a substantial nor significant impact on outcomes. Controlling for other prognostic factors (ECOG, M-stage, LDH, brain metastases, age group and gender) BRAF status was not seen to be a treatment effect modifier; i.e. treatment by BRAF status interaction was not statistically significant (p-value=0.49)." (CS, pg 81, Section 4.10) This statement was not referenced and hence the ERG has not been able to verify it.

- "In a separate model, including BRAF status as a covariate but not an interaction with treatment, and again controlling for the other prognostic factors, BRAF status was not seen to be an independently prognostic factor; i.e. the BRAF status covariate was not statistically significant (p-value=0.26)." (CS, pg 81, Section 4.10) This statement was not referenced either and hence the ERG has not been able to verify it.

- "The lack of effect of BRAF status on PFS for the Regimen [combination immunotherapy] is also demonstrated by Larkin *et al*. (2015), which presents similar median PFS estimates in both the BRAF mutation positive (11.7 months) and negative (11.2 months) patients.[52]" (CS, pg 82, Section 4.10) The ERG was not able to identify the numbers above in the linked reference. However, the ERG notes that the reference is a conference presentation of CheckMate 067 showing the results of pre-planned subgroups, as described in this report (Figure 14), which were similar for $BRAF^+$ (HR 0.41, 95% CI: 0.32 to 0.53) and $BRAF^-$ (HR 0.47, 95% CI: 0.32 to 0.68) patients for PFS when comparing combination immunotherapy to ipilimumab.

- In the phase II trial CA184-004, comparing ipilimumab 10 mg/kg and 3 mg/kg, ipilimumab demonstrated similar efficacy in $BRAF^+$ (34 patients) and $BRAF^-$ (35 patients) patients for best overall response (BOR).[66]

The ERG agrees with the company that because the mechanism of action of both nivolumab and ipilimumab is independent of BRAF status, it is reasonable to assume that treatment effect of these immunotherapies, whether administered as a combination or as monotherapies, will not be impacted by BRAF status. The BRAF status subgroup analysis of PFS from CheckMate 067 (combination immunotherapy versus ipilimumab), and the retrospective

analysis of the impact of BRAF status on BOR in CA184-004 (ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg) supports this assumption.

- Line of treatment is not independently prognostic and does not independently impact treatment effectiveness. This assumption was needed as MDX010-20 enrolled previously treated patients whereas the other trials in the indirect comparisons, CheckMate 067 and CheckMate 066, enrolled treatment naive patients. To support the assumption the company reference several sources:

    - A pooled analysis of long-term survival data from 12 phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma showed a median OS of 13.5 months (95% CI: 11.9 to 15.4) for treatment-naive patients and 10.7 months (95% CI: 9.6 to 11.4) for patients previously treated with ipilimumab, with 3-year survival rates of 26% (95% CI: 21% to 30%) and 20% (95% CI: 18% to 23%), respectively.[(4)] While the ERG agrees that the results are not statistically significantly different from one another, it considers the differences in the median OS (2.8 months) and 3-year survival rates (6%) to be substantial.

    - A meta-analysis, sponsored by the company, of five phase II and III ipilimumab trials (all included in the meta-analysis mentioned above) showed no statistically significant difference between the subgroups of patients with or without prior systemic anticancer therapy for OS (previously treated n=438, previously untreated n=569; HR 1.21, 95% CI: 0.862 to 1.71).[(67)]

    - A meta-analysis by Korn *et al*. 2008, which informed the choice of covariates in the indirect analysis, of 42 phase II trials in metastatic stage IV melanoma showed that previous treatment was not a prognostic factor for OS.[(19)] Although it is specified that the meta-analysis includes any treatment, the ERG notes that it only included trials up until 2005 and hence trials assessing more resent therapies, like the immunotherapies nivolumab and/or ipilimumab, were not included.

    - One small non-randomised retrospective study (54 patients) showed that BRAF mutation status and prior ipilimumab therapy were not associated with OR or OS.[(68)]

    - In TA319, Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma, this assumption was considered plausible by the committee in the context of MDX010-20 (previously treated patients with advanced melanoma) and its applicability to first-line therapy with ipilimumab.[(62)]

The ERG does not consider the evidence presented by the company to definitively demonstrate no impact of line of therapy on treatment effect. [redacted] If previous treatments do affect the efficacy of immunotherapies, the impact may be an underestimation of PPS for combination immunotherapy and ipilimumab, as both are based on data from MDX010-20, which only enrolled previously treated patients.[53] However, the ERG notes that the company's arguments for the assumption around line of therapy is based on OS data, and may not hold for PPS.

- Ipilimumab plus gp100 and ipilimumab monotherapy were assumed to have equal efficacy in MDX010-20. This assumption was required to maximise the data used by including data from both these trial arms in MDX010-20 to estimate PPS of combination immunotherapy and ipilimumab. In MDX010-20 there was no marked difference in OS or PFS for ipilimumab plus gp100 and ipilimumab monotherapy.[26] In the previous NICE appraisal for ipilimumab in previously treated patients (NICE TA268) the committee agreed that gp100 was likely to be an acceptable proxy for best supportive care.[69] The ERG's clinical experts agree that this is a reasonable assumption.

The company states that, "using this approach [covariate-adjusted model], and in particular [using] PPS rather than OS, allows increased validity and robustness of survival extrapolations for long-term estimation of treatment effects when data are relatively immature (i.e. they do not reach the median survival point)" (CS, pg 85, Section 4.10). The ERG acknowledges the uncertainty introduced if extrapolating OS and PFS long-term from very immature data, and notes that with this approach the company could use data from MDX010-20, with a follow-up of up to 56 months (4.7 years) for OS, compared to the available data for the direct comparison from CheckMate 069 with a follow up of up to 18 months for OS. [redacted]

There are several issues with the covariate-adjusted model approach, which may affect the validity of and increase the uncertainty around the results:

- The intrinsic advantage of using data derived from RCT is lost.
- It is unclear if all relevant prognostic factors have been adjusted for and if the adjustments were sufficient.
- The covariate adjusted model approach was not validated in the CS.

Loss of randomisation. The intrinsic advantage of randomisation is the minimisation of several types of bias, as all factors other than the effect of the intervention and comparator are considered balanced in the treatment arms as a result of the randomisation process.[70] In the company approach, only observed prognostic covariates could be adjusted for. Any unobserved prognostic covariates could not have been accounted for. This isn't a problem when using a method that preserves randomisation since the randomisation should provide balanced groups within each trial. As is discussed below, it is unclear if the covariate adjustments made in the company approach can capture and adequately adjust for all differences between the trials, which would be minimised in a direct RCT and would have been retained in an NMA.

The prognostic factors adjusted for in the analyses had been validated by expert clinicians, however, as Korn *et al*. show, not all of them were statistically significant for OS and/or PFS, and for PFS there was residual between-trial variation after adjusting for some of these factors. There are also discrepancies in definitions of visceral disease and brain metastases between the Korn meta-analysis and the equivalent prognostic factor listed by the company. The ERG notes that these factors may all influence the validity of the approach, however, it is not clear how much, and it what direction they may influence the results.

Validation of covariate adjustment approach. At the clarification stage, the company was asked to examine the validity of their approach by comparing the relative treatment effect estimates using the covariate adjusted "indirect" comparison approach with relative treatment effect of nivolumab versus ipilimumab obtained in an adjusted indirect comparison using dacarbazine/gp100 as a common comparator. Instead the company provided more details around the methodology employed in the covariate adjusted approach, and provided a comparison of the results from their model with unadjusted, partially adjusted (study and treatment), and fully adjusted (all covariates) results, and results from CheckMate 067. The methods, as described by the company, are presented in Box 14.

Box 14. Methods for the adjusted indirect comparison (Clarification response A4)

Cox proportional hazards models were fitted to PFS, OS, and post-progression survival (PPS) patient level data for the indirect comparison of nivolumab with ipilimumab, using the studies CheckMate 066 and MDX010-20. Each outcome was analysed in a model that included variables for study (to form the bridge for the indirect comparison and account for variance not captured by the differences in

other prognostic factors) and treatment. The study variable also captures all other variables not already accounted. Each outcome was then analysed in a model with additional covariates included (ECOG (0 vs >0), M-stage (M1c vs other), age (under 65 vs 65 and older), gender (male vs female), history of brain metastases (yes vs no), and elevated LDH (yes vs no)).

The ERG notes that it is unclear what differences would not be captured by prognostic factors, and more importantly what the "other variables not already accounted for" refers to, i.e. what differences would be captured in the study covariate.

The indirect treatment effect estimates (hazard ratios) for nivolumab versus ipilimumab for the models adjusted for study and treatment, and adjusted for all covariates are presented in Table 35. The residual deviance and likelihood ratio tests between the models with and without covariates are presented in Table 36.

[redacted]

Table 35. Indirect comparisons using patient level data for nivolumab versus ipilimumab

Outcome	Hazard ratio (95% CI) for Cox model with covariates for study and treatment	Hazard ratio (95% CI) for Cox model with covariates for study, treatment, ECOG, M-stage, age group, gender, brain metastases and elevated LDH
OS	0.607 (0.402, 0.916)	0.596 (0.395, 0.901)
PFS	0.536 (0.391, 0.735)	0.544 (0.396, 0.746)
PPS	0.991 (0.606, 1.618)	0.900 (0.550, 1.473)

Table 36. Likelihood ratio test and residual deviance for selected models

	Residual deviance	Likelihood ratio test

Outcome	No covariates	A: covariates for study and treatment (degrees of freedom)	B: covariates for study, treatment, ECOG, M-stage, age group, gender, brain metastases, and elevated LDH (degrees of freedom)	Difference between A and B (degrees of freedom) [p-value]
OS	8246.949	8172.320 (3)	7972.887 (9)	199.4 (6) [<0.001]
PFS	10923.548	10841.179 (3)	10781.197 (9)	60.0 (6) [<0.001]
PPS	5547.061	5532.682 (3)	5440.375 (9)	92.3 (6) [<0.001]

The ERG notes that there are only modest differences in the treatment effect with any of the models assessed by the company but agrees that the fully covariate adjusted model appears to have the lowest residual deviance.

4.4.2 Indirect comparison of combination immunotherapy and BRAF inhibitors

Evidence base

For the comparison of combination immunotherapy to BRAF inhibitors in $BRAF^{+}$ patients, the company used the same data for combination immunotherapy as in the comparison versus ipilimumab, i.e. PFS were based on IPD from CheckMate 067 and PPS was based on IPD from CheckMate 066 and MDX010-20. For the BRAF inhibitors the company used aggregate data from BRIM-3 (vemurafenib arm). The company based the comparison with BRAF inhibitors on only one BRAF inhibitor trial assuming equal efficacy of vemurafenib and dabrafenib, to avoid having to make two comparisons, one for each BRAF inhibitor. This assumption was accepted by the Appraisal Committee in a previous NICE Technology Appraisal (TA321).[71] However, the ERG notes that the indirect comparison of dabrafenib and vemurafenib in TA321 was not considered robust by the ERG who appraised the CS, and therefore the ERG was unable to comment on the clinical effectiveness of dabrafenib compared with vemurafenib. However, the Appraisal Committee concluded that there was no clear evidence that dabrafenib and vemurafenib differed in clinical effectiveness and that it would not be unreasonable to assume that they have a similar effect.

The company describes the choice of trial as between BRIM-3 and BREAK-3, the two BRAF inhibitor trials in the proposed network (Figure 19). The company justifies the choice of using BRIM-3 as the trial on which to base the indirect comparison, "the trial was substantially larger than BREAK-3 (n=337 received BRAF inhibitors versus n=187), and the patient characteristics were thought to be more reflective of patients receiving BRAF inhibitors in UK clinical practice, i.e. higher LDH levels." and, "BRIM-3 was selected as it was the source with the largest sample size, the longest length of follow-up, and it was the basis for the original NICE recommendation for vemurafenib." (CS, pg 97, Section 4.10).

The ERG notes that although LDH levels in BRIM-3 may be more reflective of patients seen in UK clinical practice, they differ quite substantially to the LDH levels in CheckMate 067,CheckMate 066 and MDX010-20 (Table 34and Table 38); the basis of the immunotherapy combination effectiveness. The ERG is concerned that no reasons were given in the CS for the exclusion of the other six BRAF inhibitor trials identified in the systematic search (Table 37). Of the seven included BRAF inhibitor trials, BRF113220 and Grippo *et al.* 2014 are phase I trials with small sample sizes. However, in addition to BRIM-3 there are four other phase III trials (BREAK-3, COMBI-d, COMBI-v and coBRIM) with relatively large sample sizes and median follow up of 10 to 20 months. The baseline characteristics appeared to be relatively similar between these five trials, apart from the higher LDH levels in BRIM-3 (Table 38). Limited time precluded the ERG from investigating the impact of trial selection on the subsequent analyses.

Table 37. Included trials with a BRAF inhibitor monotherapy arm (adapted from CS, pg 42, Table 9)

Study	**Design**	**N randomised to BRAF inhibitor**	**Outcome**	**Median length of follow up for which the most recent Kaplan Meier curve is reported**
Studies investigating dabrafenib 150 mg monotherapy				
BREAK-3	Phase III	187	OS	16.9 months[72]
			PFS	4.9 months[2]
COMBI-d	Phase III	212	OS	20 months[73]
			PFS	
BRF113220	Phase I	54	OS	Median overall survival not reached at time of analysis[45]
			PFS	14.1 months[45]
Studies investigating vemurafenib 960 mg monotherapy				
BRIM-3	Phase III	337	OS	13.4 months[74]
			PFS	9.5 months[3]
COMBI-v	Phase III	352	OS	10 months[46]
			PFS	
coBRIM	Phase III	248	OS	~14 months[47]
			PFS	
Grippo *et al.* 2014	Phase I	16	OS	15 days, no KM data reported[48]
			PFS	
Abbreviations in table: OS, overall survival; PFS, progression-free survival.				

Table 38. Baseline characteristics of BRAF inhibitor (dabrafenib or vemurafenib) monotherapy arm (adapted from CS, pg 97, Table 29)

Characteristic	**Dabrafenib trials**			**Vemurafenib trials**			
	BREAK-3	**Combi-d**	**BRF113220**	**BRIM-3**	**Combi-V**	**coBRIM**	**Grippo *et al.* 2014**

Patients randomized to BRAF inhibitor (n)	187	212	54	337	352	248	16
ECOG = 0 (%)	66%	71%	63%	68%	70%	67%	50%
LDH (>upper limit of the normal range) (%)	36% (<1% unknown)	33%	50%	58%	32%	43%	31%
M stage = M1c (%)	66%	67%	69%	66%	59%	62%	56%
History of brain metastases (%)	NR	NR	7%	NR	NR	1%	NR
Age (up to 65) Median, years (range), unless stated otherwise	78.6%* 53 (22 to 93)	NR 56.5 (22–86)	NR 50 (18 to 82)	100%* 56 (21 to 86)**	NR 54 (18–88)	NR 55 (25 to 85)	NR Mean=50.5 (SD=11.9)
Gender (% males)	60%	54%	54%	59%	51%	56%	50%

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; NR, not reported; ULN, upper limit of normal range.
*reported in CS, Table 29, Section 4.10
**reported in Chapman 2011[27] and Hauschild 2013[75]

Methods

Data for combination immunotherapy were based on PLD from CheckMate 067 for PFS and PLD from CheckMate 066 and MDX010-20 for PPS. Data for vemurafenib were based on published Kaplan-Meier (KM) curves from BRIM-3 (vemurafenib arm). The method used is described in Box 15 below.

Box 15 Method for indirect comparison of combination immunotherapy and BRAF inhibitors

Using the published KM curves for OS and PFS for vemurafenib, KM data were estimated using digitisation software.

Using the estimated KM data, pseudo patient level data were created for vemurafenib using the Guyot 2012 method.[76]

Parametric survival curves for OS and PFS were fitted separately to the single arm pseudo patient level data – these curves were then used directly in the economic model.

To compare OS and PFS between vemurafenib and the Regimen [combination immunotherapy], the Regimen [combination immunotherapy] estimates of OS and PFS (as constructed within the economic model from TTP, PrePS and PPS) were re-estimated, adjusted for the observed patient characteristics in the BRIM-3 trial. This approach estimates the efficacy of the Regimen [combination

immunotherapy] in the BRAF mutation-positive patient population, keeping the efficacy observed for vemurafenib within BRIM-3 unaltered.

Similar to the indirect comparison of combination immunotherapy and ipilimumab, the company assumes that BRAF mutation status does not affect the treatment effect of immunotherapies, and that line of treatment is not independently prognostic and does not independently impact treatment effectiveness. These assumption were necessary as 100% of patients in BRIM-3 were $BRAF^{+}$, around 30% of patients in CheckMate 067 were $BRAF^{+}$, CheckMate 066 included only $BRAF^{-}$ patients and MDX010-20 did not report the BRAF mutation status of patients, and BRIM-3, CheckMate 067 and CheckMate 066 all enrolled treatment naive patients, whereas MDX010-20 enrolled previously treated patients. The rationales for these assumptions for the comparison of combination immunotherapy and BRAF inhibitors are the same as discussed previously (Section 4.4.1).

The ERG notes that it is not specified which patient characteristics were adjusted for and how; though it seems reasonable to assume that they were the same as the covariates used in the combination immunotherapy versus ipilimumab comparison (ECOG, LDH, M stage, brain metastases, age and gender). However, there is no mention in the CS of adjusting for potential trial differences or subsequent ipilimumab therapy as was done in the analysis of PPS for CheckMate 066 and MDX010-20. Also, no adjustments have been made for pseudo progression, which would be expected to affect PFS in the comparison of combination immunotherapy and BRAF inhibitors. However, according to the ERG clinical experts, the impact of pseudo progression is expected to be low.

The ERG notes, the same limitations for the comparison of combination immunotherapy and BRAF inhibitors as for combination immunotherapy versus ipilimumab (Section 4.4.1): advantage of using data derived from RCTs is lost, it is unclear if all relevant prognostic factors have been adjusted for and if the adjustments were sufficient, and no validation of the covariate adjusted approach was provided in the CS. In addition, the selection of study data was inadequately described and unclear, no reliable long-term survival data were available for either of the BRAF inhibitors, and if the efficacy of the BRAF inhibitors is not equivalent, no estimate of combination immunotherapy versus dabrafenib is available.

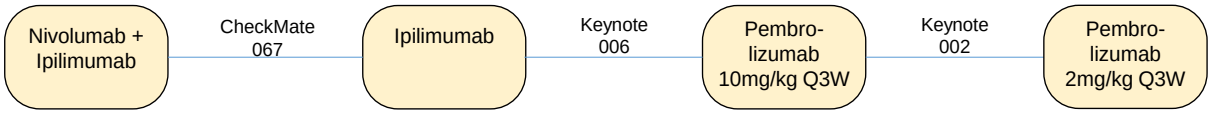
4.4.3 Indirect comparison of combination immunotherapy and pembrolizumab

Evidence base

At the clarification stage the company performed an adjusted indirect comparison to enable a comparison of combination immunotherapy and pembrolizumab by including the trials: CheckMate 067, Keynote 006 (pembrolizumab 10m/kg Q3W versus ipilimumab) and Keynote 002

(pembrolizumab 10m/kg Q3W versus pembrolizumab 2m/kg Q3W). The network diagram for the comparison is illustrated in Figure 20.

Figure 20. Network of evidence for combination immunotherapy and pembrolizumab (reproduced from Clarification response Figure 1)



Abbreviations in figure: q3w, every 3 weeks.

CheckMate 069 was not considered appropriate by the company for inclusion in the OS analysis due to substantial crossover to nivolumab in the ipilimumab arm. However, the company did present scenario analysis demonstrating the impact of either using the CheckMate 069 hazard ratio versus ipilimumab for PFS or the meta-analysis hazard ratio combining CheckMate 069 and CheckMate 067. Keynote 002 was included in the network to allow comparison of combination immunotherapy to the licensed dose of pembrolizumab. The company justification to include Keynote 002 is presented in Box 16. The ERG agrees with the company's inclusion of Keynote 002.

Box 16. Company justification to include Keynote 002 in adjusted indirect comparison (Clarification response A2)

It is noted that within previous NICE appraisals (TA319) that there has been reluctance to accept equivalence of doses of treatments within melanoma where available evidence indicates that there may be a difference in effectiveness[62] Available evidence for pembrolizumab from KeyNote 002 indicates that the 2mg/kg Q3W licensed dose has a lower effectiveness in terms of both OS and PFS than the 10mg/kg Q3W dose included in the KeyNote 006 trial.[77] Whilst this difference is not statistically significant, the KeyNote 002 trial was not powered to provide a significant result between the two treatment arms and, similar to NICE's conclusions relating to the doses of ipilimumab, we believe that the observed difference in the effectiveness between the doses should not be ignored.

Methods

[redacted]

Results

[redacted]

[redacted]

Table 39. Input data for indirect comparisons

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]Figure 21.Network meta-analysis results for overall survival

[redacted]

[redacted]

Figure 22. Network meta-analysis results for progression free survival

4.4.4 Summary of indirect comparisons

The company did not identify any head-to-head trials of combination immunotherapy versus BRAF inhibitors, necessitating an indirect comparison. An adjusted indirect comparison/network meta-analysis to compare combination immunotherapy to ipilimumab and BRAF inhibitors was not deemed appropriate by the company, due to clinical and methodological heterogeneity. Also, the OS data for combination immunotherapy from CheckMate 067 and CheckMate 069 are still immature. Therefore, the company designed covariate-adjusted survival models to produce comparative efficacy estimates for combination immunotherapy and relevant comparators and to extrapolate survival data that were used in the economic model. Combination immunotherapy compared to ipilimumab was estimated using patient level data (PLD) from CheckMate 067(combination immunotherapy and ipilimumab arm) for PFS, and PLD from CheckMate 066 (nivolumab arm) and MDX010-20 (ipilimumab arms) as proxy for OS. Combination immunotherapy compared to BRAF inhibitors was similarly estimated using PLD from CheckMate 067, CheckMate 066 and MDX010-20, together with aggregate/summary ('pseudo' patient-level) data from BRIM-3 (vemurafenib) to form an indirect comparison. All PLD were adjusted for key prognostic factors (ECOG, LDH, M stage, history of brain metastases, age, gender), and for additional covariates including trial differences, treatment, and subsequent ipilimumab therapy.

On request, the company also performed an adjusted indirect comparison of combination immunotherapy and pembrolizumab using CheckMate 067, Keynote 006 and Keynote 002. The ERG emphasise that this is an exploratory analysis as the comparability of the included trials has not been fully assessed.

The ERG considers there to be more appropriate methods, than the covariate-adjusted indirect comparison used by the company, to deal with immature survival data and when an adjusted indirect comparison is deemed inappropriate. The company approach requires many assumptions, most

importantly breaking randomisation, and the possibility of validating it is limited. Additionally, the selection of study data was inadequately described and unclear.

4.5 Conclusions of the clinical effectiveness section

4.5.1 Clinical results

- The direct evidence of the efficacy and safety of combination immunotherapy is derived from CheckMate 069 and CheckMate 067; two good quality, double blind, phase II and III randomised controlled trials.

- CheckMate 067 and CheckMate 069 assessed the effects of combination immunotherapy versus ipilimumab in patients with previously untreated, unresectable Stage III or Stage IV melanoma.

- Nivolumab and ipilimumab combination immunotherapy does not currently have a European marketing authorisation for the treatment of advanced melanoma. At the time of writing no CHMP opinion has been published.

- In both CheckMate 067 and CheckMate 069 combination immunotherapy was associated with a statistically significant improvement in PFS (HR 0.42, 95% CI: 0.31 to 0.57 and HR 0.39, 95% CI: 0.25 to 0.63, respectively).

- OS data were immature for both CheckMate 067 and CheckMate 069, with median survival not reached in either intervention or comparator arm in either trial. No OS data was presented for CheckMate 067 in the CS. An interim analysis of CheckMate 069 showed no statistically significant difference in OS for combination immunotherapy versus ipilimumab (HR 0.73, 95% CI: 0.39 to 1.36).

- [redacted]

- Combination immunotherapy was associated with a statistically significant ORR compared to ipilimumab in both CheckMate 067 (OR 6.11, 95% CI: 3.59 to 10.38) and CheckMate 069 (OR 12.19, 95% CI: 4.41 to 33.68)

- In both CheckMate 067 and CheckMate 069 time to response did not differ significantly between treatment arms, with the majority of all responses observed at the time of the first scan at 12 weeks.

- Data from CheckMate 067 and 069 indicate that a substantial proportion of patient experience continued clinical response after discontinuation of treatment with combination immunotherapy.

- A substantial proportion of patients in both CheckMate 067 and 069 were treated beyond RECIST defined progression because they showed continued clinical benefit and could tolerate the treatment.

- There were no clinically meaningful differences in HRQoL between combination immunotherapy and ipilimumab in either trial.

- The rates of grade 3-4 AE were considerably higher among patients treated with combination immunotherapy compared to ipilimumab. The most common treatment-related serious adverse effects associated with combination immunotherapy were diarrhoea, colitis, pyrexia, increased transaminases, nausea and hypophysitis.

- The company used a covariate-adjusted approach to produce comparative efficacy estimates for combination immunotherapy, ipilimumab and BRAF inhibitors to extrapolate survival data that were used in the economic model.

    - Combination immunotherapy compared to ipilimumab was estimated using participant level data (PLD) from CheckMate 067 for PFS, and PLD from CheckMate 066 and MDX010-20 as proxy for OS (due to the immaturity of OS data from CheckMate 067 and 069).

    - Combination immunotherapy compared to BRAF inhibitors was similarly estimated using PLD from CheckMate 067, CheckMate 066 and MDX010-20, together with aggregate data from BRIM-3 (vemurafenib) to form an indirect comparison.

- [redacted]

4.5.2 Clinical issues

- There is a lack of data in the CS to support the company claim that the response kinetics is similar for combination immunotherapy and BRAF inhibitors, and therefore the use of combination immunotherapy as first line therapy for all patients, including patients deemed to be at high risk.

- The company excluded pembrolizumab as a comparator and hence no evidence for the comparison of combination immunotherapy and pembrolizumab was searched for or presented in the CS.

- The choice of trials to inform the indirect comparisons of combination immunotherapy versus ipilimumab and BRAF inhibitors was not clear in the CS, and may have substantial impacts on the results from the economic model. However, it was not possible for the ERG to estimate the size or direction of the impact.

- The evidence presented by the company, in support of some of the assumptions does not definitively demonstrate their validity (i.e. the effect of line of treatment, equal PPS for immunotherapies, and the equivalence of BRAF inhibitor efficacy). The assumption of no effect of previous treatments is likely to give a conservative estimate of OS for combination immunotherapy and ipilimumab in the company approach. However, it has not been shown that this holds for PPS. Also, if the efficacy of the BRAF inhibitors is not equivalent, no estimate of combination immunotherapy versus dabrafenib is available.

- It is unclear if all relevant covariates were captured and adjusted for in the indirect comparisons. It is also unclear if the adjustments of the included covariates were sufficient, and what was captured in the trial covariate.

- By using the covariate adjusted data approach, the intrinsic advantages of randomisation is lost. In the CS, the company did not present any validation of the approach to show if it would give similar results to data from randomised trials. Hence, it is not possible for the ERG to comment on the validity of the results.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company for nivolumab in combination with ipilimumab (hereafter referred to as combination immunotherapy) for patients with advanced (unresectable or metastatic) melanoma.

The company provided a written submission of the economic evidence along with an electronic version of the Microsoft Excel® based economic model. According to the NICE Final Scope, the target population of the analysis was adults with advanced (unresectable or metastatic) melanoma.[(1)] The population was partitioned into two groups based on the BRAF V600 gene mutation status, as the current treatment pathway (Section 2.2) is different for these two subpopulations:

- BRAF V600 mutation-positive patients, hereafter referred to as the $BRAF^+$ subpopulation. These patients are eligible for first-line treatment with immunotherapy (e.g. ipilimumab) or BRAF inhibitors (dabrafenib or vemurafenib);

- BRAF V600 mutation-negative patients, hereafter referred to as the $BRAF^-$ subpopulation. These patients are eligible for first-line treatment with immunotherapy (e.g. ipilimumab).

The electronic model included both subpopulations, which were presented separately throughout the CS when needed. Table 40 summarises the location of the key economic information within the company's submission (CS).

Table 40. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	5.1
Model structure	5.2.2
Technology	5.2.3
Clinical parameters and variables	4.10, 5.3.1, 5.3.2, 5.3.3
Measurement and valuation of health effects and adverse events	5.3.6, 5.4
Resource identification, valuation and measurement	5.3.4, 5.3.5, 5.5
Sensitivity analysis	5.8
Results	5.7
Validation	5.9
Subgroup analysis	Not performed
Strengths and weaknesses of economic evaluation	Not reported separately
Abbreviations used in table: CS, company's submission.	

5.2 Summary of the company's key results

The company presented the results of two analyses:

- The comparison of combination immunotherapy to ipilimumab monotherapy in $BRAF^-$ patients, summarised in Table 41 and Table 42 respectively using list prices and patients access scheme (PAS) prices;

- Combination immunotherapy compared to ipilimumab monotherapy, vemurafenib and dabrafenib in $BRAF^+$ patients. The results of the company's analysis are reported in Table 43 Table 44 for the list price and PAS scenarios, respectively.

Table 41. Base case results for BRAF^{-} patients (CS, pg 182, Table 71)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
Ipilimumab	[redacted]	3.77	2.90				
Combination immunotherapy	[redacted]	6.55	5.09	£22,826	2.79	2.19	£10,433
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 42. Base case results using PAS prices for BRAF^{-} patients (CS, pg 183, Table 73)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

Table 43. Base case results for BRAF^{+} patients (CS, pg 182, Table 72)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)

Dabrafenib	[redacted]	2.24	1.74						
Vemurafenib	[redacted]	2.24	1.74	£19,070	0.00	0.00	Same QALYs	Dominated	Excluded due to dominance
Ipilimumab	[redacted]	3.38	2.59	£25,161	1.13	0.85	£29,597	Extendedly dominated	Excluded due to dominance
Combination immunotherapy	[redacted]	6.26	4.85	£35,085	4.02	3.11	£11,284		£11,284
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Note: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.									

Table 44. Base case results PAS prices for BRAF^{+} patients (CS, pg 183, Table 74)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

5.3 ERG comment on company's review of cost-effectiveness evidence

The company provided an overview of the cost-effectiveness search in Section 5.1 of the main submission, and details of search terms were reported in Appendix 10. The search strategy and terms the company used to identify cost-effectiveness studies were reasonable and in line with SIGN guidelines.[78]

The company carried the first systematic review in November 2014, and updated the search in October 2015. The search aimed to identify any full economic evaluation comparing nivolumab and ipilimumab to any comparator for the treatment of adults with advanced (unresectable or metastatic) melanoma.

The following databases were searched:

- Medline;
- Embase;
- EconLit;
- NHS Economic Evaluation Database (EED);
- Cochrane Database of Systematic Reviews (CDSR);
- HTA Database of Abstracts of Reviews of Effects (DARE);
- Cumulative Index to Nursing & Allied Health Literature (CINAHL).

The company also reported hand-searching lists of references in the cost-effectiveness studies identified for additional publications of relevance to the research question. The inclusion and exclusion criteria applied, with rationale are presented in Table 45.

No studies were identified in both the original search carried out in November 2014 and in the search update performed in October 2015. Only one study was reviewed in full in the two searches before being excluded with reason "Wrong study type".[79]

Table 45. Eligibility criteria for cost-effectiveness search (CS, pg 126, Table 46)

Inclusion criteria		
Category	**Inclusion criteria**	**Rationale**
Study type	Full economic evaluation (including cost-consequence, cost-minimisations, cost-effectiveness, cost-utility and cost-benefit evaluations) that compares nivolumab to any comparator(s)	The aim of the review was to identify relevant economic evaluations.

Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population.
Interventions	The intervention of interest is nivolumab or nivolumab in combination with ipilimumab	This is the relevant intervention.
Comparators	No restriction to comparators	To allow all relevant papers to be identified.
Outcomes	Incremental costs and QALYs; any other measure of effectiveness reported together with costs	The aim of the review was to identify relevant economic evaluations, which reported costs.
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed, and the study's data and results must be extractable	Only studies that provided extractable data and results were usable.
Exclusion criteria		
Category	**Exclusion criteria**	**Rationale**
Publication year	Studies before 1970	The earliest melanoma trial was published in 1972.
Language	Non-English language literature	Time and resource required for translation and relevance for UK setting.
Publication type	Letters, editorials and review studies	Primary study articles are required.
Abbreviations in table: QALY, quality-adjusted life year; UK, United Kingdom.		

The ERG considers the approach taken by the company to identify published cost-effectiveness studies to be reasonable, and that it is unlikely that the company missed any studies. Due to time constraints, the ERG was unable to replicate and validate the company's search and appraisal of identified abstracts.

5.4 Overview of company's economic evaluation

5.4.1 Model structure

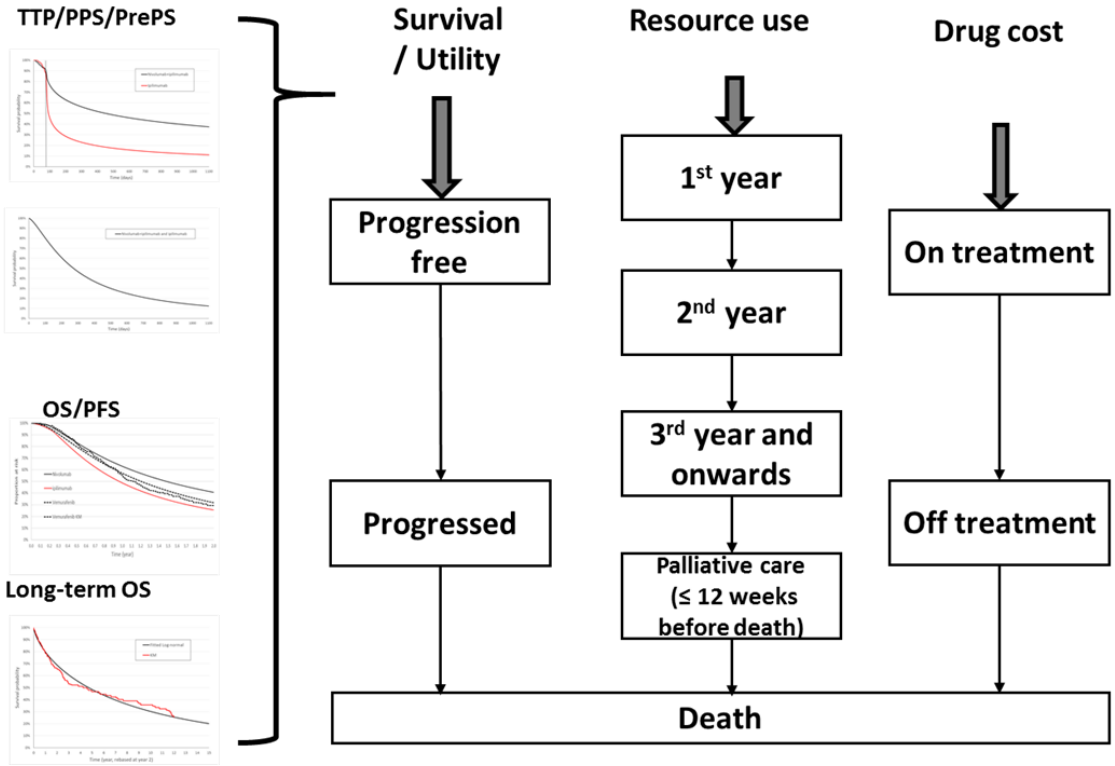
In this Section, the ERG presents the model developed by the company. A detailed discussion and critique of the modelling approaches and model structures is included in Section 5.5.2.

The company developed a *de novo* model developed in Microsoft Excel® to assess the comparative cost-effectiveness profile of combination immunotherapy (i.e. nivolumab and ipilimumab, referred to as "the Regimen" in the CS) in adults with advanced (unresectable or metastatic) melanoma. Two subpopulations were identified based on the BRAF status and analysed separately. For ease of reporting, the ERG will refer to "the model" when there are no differences between the approaches used in the two subpopulation. Any difference between the two will be made clear throughout the report.

The comparators considered in the analyses were: combination immunotherapy and ipilimumab in the $BRAF^-$ subpopulation; combination immunotherapy, ipilimumab, vemurafenib and dabrafenib in the $BRAF^+$ subpopulation. The company used the same model structure but different approaches to model the transitions between health states for the immunotherapies (i.e. combination immunotherapy and ipilimumab) and the BRAF inhibitors (i.e. vemurafenib and dabrafenib). The immunotherapies were modelled using a semi-Markov approach, with survival curves used to determine the transition probabilities between health states, used to estimate the proportions of patients in each model health state. On the other hand the BRAF inhibitors were modelled using a partitioned survival (or area under the curve, AUC) approach, where the survival curves determined directly the proportion of patients in each health state at any time, and the transitions among health states were implicit.

The model was composed of three health states: progression-free survival (PFS), post-progression survival (PPS) and death. The model diagram is presented in Figure 23. All patients were assumed to be alive and progression-free when they enter the model, i.e. in the PFS health state. From the PFS health state patients could progress and move to the PPS health state. Death was possible from both the PFS and PPS health states.

Figure 23. Structure of economic model (CS, pg 169, Figure 44)



Abbreviations in figure: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival, TTP, time-to-progression.

The modelling approach was based on the data analysis strategy. The company reported a lack of long-term data, determining the need of robust extrapolations of the outcomes. The justification for the approach used for immunotherapies is reported in Box 17.

Box 17. Company's justification for the modelling approach used for immunotherapies (CS, pg 85, Section 4.10)

Mature OS data is not available for the Regimen [combination immunotherapy], and therefore OS data from CheckMate 066 and MDX010-20 has been used as a proxy assuming equal efficacy between ipilimumab, nivolumab and the Regimen [combination immunotherapy]. This assumption is unlikely to hold for OS, but when adopting a Markov state-transition approach, as used in the nivolumab monotherapy submission, only post-progression survival (PPS) relies on OS data, and the assumption of equal efficacy is considered conservative for PPS. Additionally, using this approach, and in particular PPS rather than OS, allows increased validity and robustness of survival extrapolations for long-term estimation of treatment effects when data are relatively immature (i.e. the do not reach the median survival point). As a result, the economic model has been designed to adopt a Markov-based state-transition approach using time to progression (TTP), pre-progression survival (PrePS), and PPS for modelling survival.
Abbreviations in box: OS, overall survival; PPS, post-progression survival; PrePS, pre-progression survival; TTP, time to progression.

The AUC approach used for the BRAF inhibitors is justified by the company as reported in Box 18.

Box 18. Company's justification for the modelling approach used for BRAF inhibitors (CS, pg 130, Section 5.2.2)

Patient level data were not available for the BRAF inhibitor comparisons. For BRAF mutation-positive patients only, survival with dabrafenib and vemurafenib was therefore modelled based upon parametric curves fitted on trial-based empirical OS and PFS using digitised data, which were used to derive the proportions of patients in the progression-free, progressed and death states in each Markov cycle using the area under the curve method […]. This method was used as data were not available for TTP, PPS and PrePS.
Abbreviations in box: OS, overall survival; PPS, post-progression survival; PrePS, pre-progression survival; TTP, time to progression.

A different model structure was used to estimate resource use and costs, based on time on treatment, time since treatment initiation and time to death, as showed in Figure 23. Treatment-related costs (i.e. pharmacological and administration costs) were based on time on treatment. Other cost categories were modelled based on the assumption that resource use varies according to time from treatment initiation and time to death.

Health effects were estimated according to health state and treatment received, using EQ-5D data collected in the phase III CheckMate 067 trial. The effect of treatment-related adverse events

(TRAEs) on patients' HRQoL was accounted for by including a treatment-specific average utility decrement.[80]

A life time horizon of 40 years was adopted, and time was discretised into weekly cycles. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects were discounted at annual rate of 3.5%, in line with the NICE Reference Case.[81]

5.4.2 Treatment effectiveness

Treatment effectiveness was implemented using the same methodology in the two subpopulations. Treatments were assumed to influence the transition of patients between the PFS and PPS (i.e. disease progression), and the PFS and death health states (i.e. pre-progression mortality). The rates of transition from the PPS to death health state, i.e. post-progression mortality, was assumed by the company to be independent on treatment (or treatments) received and time since first-line treatment initiation.

For the immunotherapies, the data selected and used by the company in the base case model are described in Box 19. Treatment effectiveness is described separately based on the different components parts of the company's model:

- Time to progression (TTP), regulating the transitions from the PFS to the PPS health state;
- Pre-progression survival (PrePS), i.e. the determinant of mortality of patients in the PFS health state;
- Post-progression survival (PPS), used to determine mortality in the PPS health state.

Box 19. Company's immunotherapy data use strategy (CS, pg 85, Section 4.10)

TTP and PrePS are used to inform the long-term extrapolation of PFS. TTP, PrePS and PPS are used to inform the long-term extrapolation of OS. Participant level data (PLD) from CheckMate 067 has been used to estimate PrePS and TTP, and PLD from MDX010-20 and CheckMate 066 has been used to estimate PPS.
Abbreviations in box: OS, overall survival; PLD, participant-level data; PPS, post-progression survival; PrePS, pre-progression survival; TTP, time to progression.

The company reported that, as mature OS data were not available for the combination immunotherapy, the OS data from CheckMate 066 and MDX010-20 trials were used to model PPS, while the survival in the pre-progression state (PrePS) was mainly based on data from the CheckMate 067 trial. It is stated in the CS that, "using this approach, and in particular PPS rather than OS, allows increased validity and robustness of survival extrapolations for long-term estimation of treatment

effects when data are relatively immature" (CS, pg 85, Section 4.10). The company stated that, "the assumption of equal efficacy is considered conservative for PPS" (CS, pg 85, Section 4.10).

Treatment efficacy was modelled using a different approach for vemurafenib and dabrafenib in the $BRAF^{+}$ subpopulation, by using an AUC approach modelling directly PFS and OS.

An additional aspect of treatment effectiveness considered was tolerability, measured by the impact of adverse effects on patients' HRQoL. This impact is mostly caused by the detrimental effects of treatment-related adverse events (TRAEs), which can cause early therapy discontinuation and potentially loss of treatment benefit. These effects were modelled as HRQoL decrements based on treatment-specific effects observed in RCTs, and are discussed in detail in Section 5.5.7.

In this Section the ERG looks at the data and the chosen efficacy modelling approach in the company's economic model. Sections 5.4.2.1 to 5.4.2.6 focus on the efficacy of combination immunotherapy and ipilimumab. Sections 5.4.2.7 and 5.4.2.8 describe the approach taken by the company to include the indirect comparison with BRAF inhibitors. The integration of the evidence sources and their implementation in the economic model is presented in Section 5.4.2.9.

5.4.2.1 Immunotherapy data analysis strategy

According to Section 4.10 and Appendix 9 of the CS, the company fitted parametric survival curves to TTP, PrePS and PPS separately. The *flexsurv* library in the *R* statistical software[82, 83] was used, and the following parametric distributions were investigated:

- Exponential;
- Weibull;
- Log-normal;
- Log-logistic;
- Gamma;
- Gompertz.

In Appendix 9 of the CS the company also reported the Akaike Information Criterion (AIC) and Bayesian Information criterion (BIC) measures for generalised gamma parametric models; however, the resulting parameter coefficients were not reported. The ERG notes that the AIC and BIC associated to the generalised gamma models reported by the company were never the lowest compared to the other tested models. Results from the generalised F model, easily available in the

software package reported to have been used by the company (i.e. *flexsurv*), were not reported and it is unclear whether it was tested.

The company conducted an indirect treatment comparison for all outcomes, described in detail in Section 4.4.1. The prognostic factors selected in the models and used to adjust the parametric models were based upon a meta-analysis of phase II trials in metastatic stage IV melanoma by Korn *et al.*[19] These factors were:

- Eastern Cooperative Oncology Group (ECOG) performance status: 0 or >:0;
- Lactate dehydrogenase (LDH) levels: equal or lower than or greater than the upper limit of normal range (ULN);
- M stage: M1c; or M0, M1a or M1b;
- Presence of brain metastases;
- Age group: less than or equal or more than 65 years of age;
- Gender: male or female.

According to Section 4.10 of the CS the list, "was validated with UK clinicians during an advisory board conducted for use in the appraisal for nivolumab monotherapy in March 2015" (CS, pg 85, Section 4.10). All prognostic covariates were, "included within the model regardless of their statistical significance" (CS, pg 86, Section 4.10). The effects of these covariates were estimated in the survival models, and were assumed to be transferable among the studies. The effects were then applied to the survival models based on the better-fitting curve among the tested ones, obtaining the adjusted outcomes.

The company applied the extrapolations obtained from the survival analysis of mortality data only for the first 3 years in the base case economic model, as reported in Box 20.

Box 20. Justification for using survival models based on trial data for the first 3 years of the model only (CS, pg 131, Section 5.2.2)

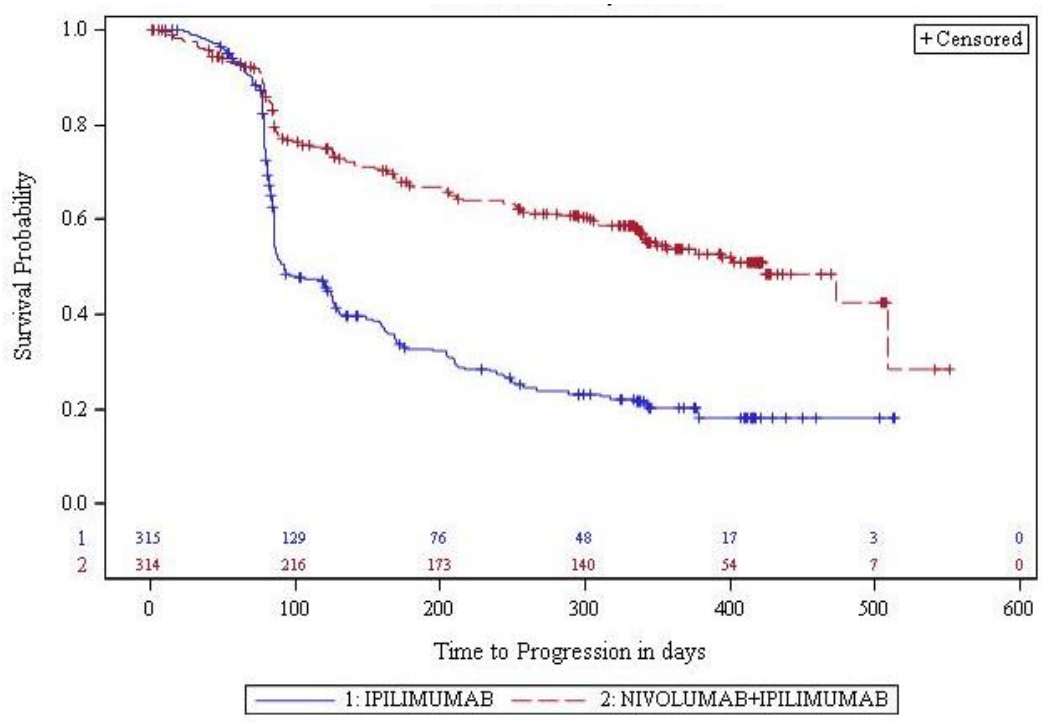
> The survival methods outlined [~~above~~] are applied within the first 3 years of the model for all treatments in the base case. The 3-year cut-off was chosen because: a) the maximum follow-up period for the CheckMate 067 trial is around 18 months, and therefore, long-term extrapolation of TTP and PrePS and subsequently OS (which is estimated conditional on progression in the state-transition model) for the [combination immunotherapy] and ipilimumab are subject to greater uncertainty; b) recent published long-term pooled ipilimumab study showed a plateau in the OS beginning around Year 3 and this is assumed for immunotherapies including the [combination

immunotherapy] and ipilimumab from Year 3 onwards. Given the uncertainty and methodological difficulty of extrapolating trial-based parametric curves beyond the trial follow-up period, alternative sources for long-term survival are used for the extrapolation of long-term OS for all treatment arms. These include the use of melanoma registry data (from Year 3 onwards for BRAF inhibitors in the base case), long-term ipilimumab OS data (from Year 3 onwards for the [combination immunotherapy] and ipilimumab in the base case), and general UK population mortality as background mortality.
Abbreviations in box: OS, overall survival; PPS, post-progression survival; PrePS, pre-progression survival; TTP, time to progression.

5.4.2.2 Time to progression data analysis, immunotherapies

The company reports the TTP data analysis strategy and the statistical analyses carried out in Section 4.10 of the CS. The company used data from the phase III CheckMate 067 trial for the comparison between combination immunotherapy and ipilimumab.[31] The first tumour assessment in the trial was scheduled to occur at 12 weeks (84 days) from treatment initiation, which led to a relatively high proportion of patients progressing at or shortly after 3 months, as shown in Figure 24. The company stated that, "in reality, some of these patients will have progressed at a time earlier than 3 months, but this information cannot be captured" (CS, pg 87, Section 4.10).

Figure 24. Kaplan Meier curves for time to progression, CheckMate 067 (CS, pg 88, Figure 25)



The company reported that, "this unrealistic clustering […] makes it difficult to fit meaningful parametric survival curves to these data near to the start of the curves" (CS, pg 87, Section 4.10). To

circumvent this problem, the company proposed two separate analyses, before and after day 84. At 84 days, 16% and 33% of patients progressed in the combination immunotherapy and ipilimumab arms, respectively.[31] The number of progression events before and after the 84 days cut-off point selected by the company are reported in Table 46.

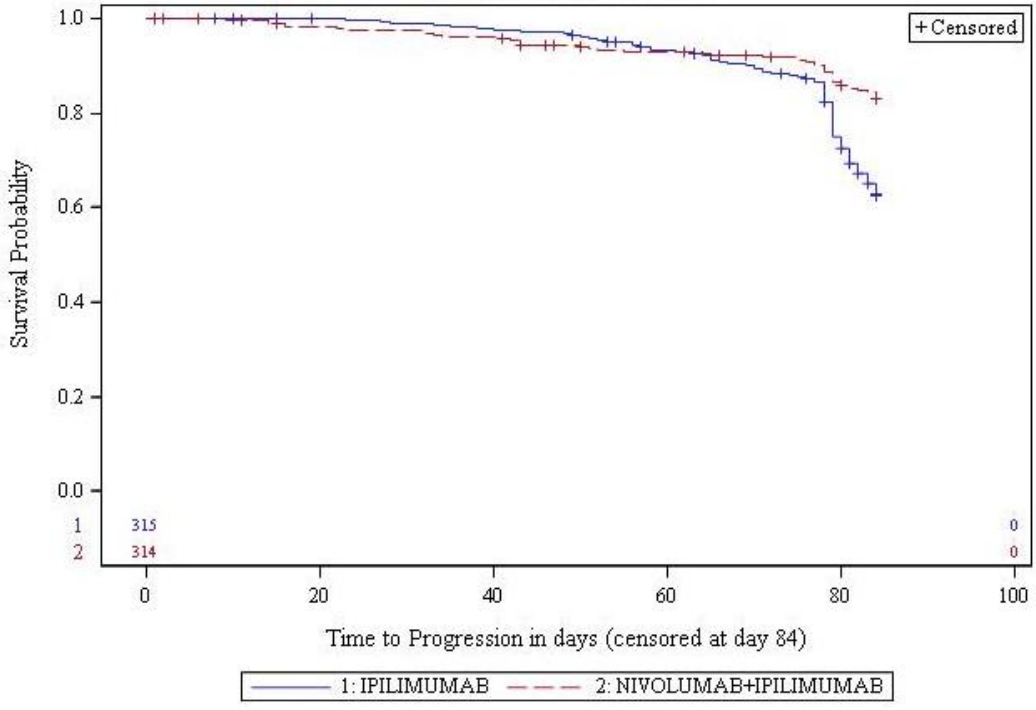
Table 46. Events by trial and treatment for TTP before and after day 84 (CS, pg 89, Table 22)

Study	Treatment group	TTP ≤84 days Events n/N (%)	TTP >84 days Events n/N (%)
Full population			
CheckMate 067	Nivolumab plus ipilimumab	50 / 314 (15.9%)	79 / 238 (33.2%)
	Ipilimumab	105 / 315 (33.3%)	107 / 169 (63.3%)
Population of patients with complete covariate information			
CheckMate 067	Nivolumab plus ipilimumab	50 / 313 (16.0%)	79 / 238 (33.2%)
	Ipilimumab	105 / 309 (34.0%)	106 / 167 (63.5%)
Abbreviations in table: TTP, time to progression.			

TTP: pre-day 84 analysis

The company based the pre-84 days TTP efficacy for combination immunotherapy and ipilimumab on the analysis of the outcomes observed in the phase III CheckMate 067 trial, shown in Figure 25.

Figure 25. Kaplan Meier curves for TTP pre-84 days from CheckMate 067 (CS, pg 88, Figure 26)



The company fitted a Cox proportional hazards model to the pre-84 days TTP to estimate the effect of the covariates listed in Section 5.4.2.1. The company stated that, "This method assumes proportionality of the effects of the prognostic factors […] Proportionality of treatment effects (which clearly does not hold for TTP pre-84 days based on the KM data) is not assumed given that the observed by-treatment KM data (rather than fitted parametric curves) are used in the economic model" (CS, pg 89, Section 4.10). The resulting parameter coefficients are shown in Table 47.

Table 47. Cox proportional hazards model: TTP pre-84 days (CS, pg 90, Table 23)

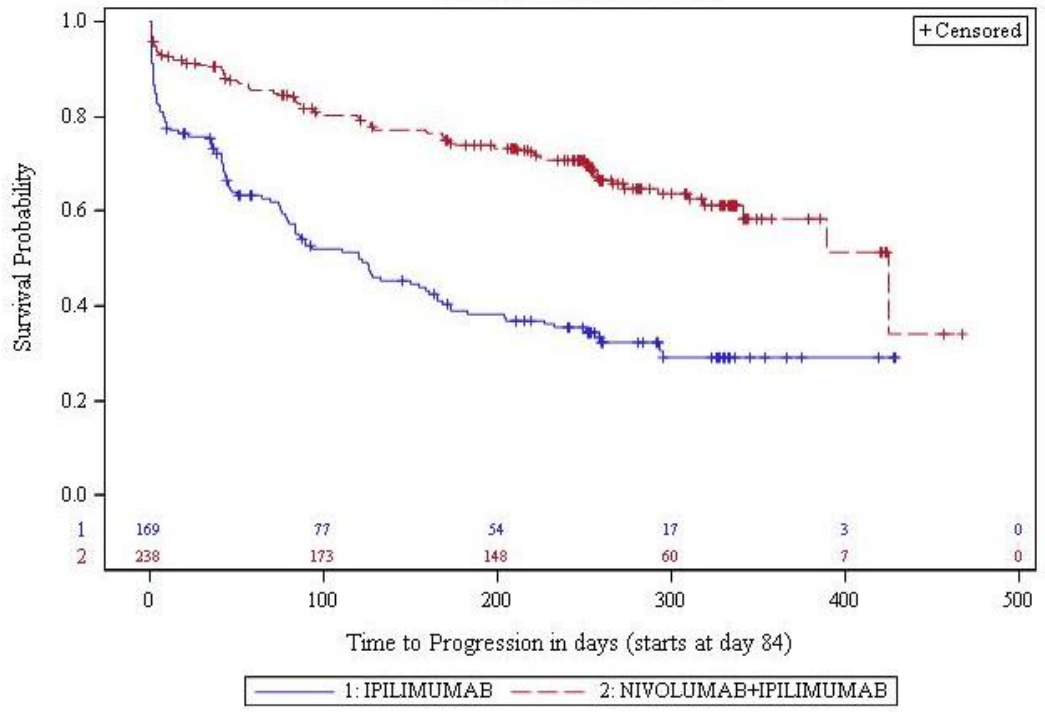
Model parameter	Parameter estimate	Standard error	P-value	Hazard ratio
Treatment (ipilimumab vs nivolumab plus ipilimumab)	0.89648	0.17306	<0.0001	2.451
Sex (male vs female)	-0.10989	0.16633	0.5088	0.896
Age group (under 65 vs 65 and over)	-0.03545	0.16317	0.828	0.965
ECOG (ECOG=0 vs ECOG ≥1)	-0.20108	0.1772	0.2565	0.818
Elevated LDH (>ULN vs ≤ULN)	0.83486	0.16578	<0.0001	2.304
History of brain metastases (yes vs no)	-0.62663	0.51079	0.2199	0.534
M stage (M1c vs M0 or M1a or M1b)	0.40334	0.17891	0.0242	1.497

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; ULN, upper limit of normal (range); TTP, time to progression.

TTP: post-day 84 analysis

The company fitted survival parametric functions based on the CheckMate 067 TTP data from day 84 onwards. The post-84 days Kaplan Meier curves are shown in Figure 26.

Figure 26. Kaplan Meier curves for time to progression measured from day 84 (CS, pg 89, Section 4.10)



The company tested the fit of the aforementioned parametric survival models to the post-day 84 TTP data from the CheckMate 067 trial. The model with the lowest AIC and BIC was the lognormal model. The company stated that, "[the] long-term extrapolations for log-normal were judged to be clinically plausible and in line with long-term data available for ipilimumab; therefore, log-normal was selected as the best-fitting/most appropriate model selected for use in the economic model base case" (CS, pg 90, Section 4.10). The model fit statistics are reported in Table 48.

Table 48. Model fit estimates for TTP post 84 days (CS, pg 92, Table 24)

Model	AIC	BIC
Log-normal	**2432.75**	**2468.79**
Generalised Gamma	2433.45	2473.49
Weibull	2433.87	2469.91
Log-logistic	2433.94	2469.98
Gompertz	2488.42	2524.46
Exponential	2521.43	2553.46
Abbreviations in table: AIC, Akaike information criteria; BIC, Bayesian information criteria; TTP, time to progression.		

The log-normal model coefficients are reported in Table 49. The company reported that, "Although many of the covariates individually had modest effects on the outcome and were not statistically significant, [the company] felt it important to retain these in the model to fully adjust for prognostic

factors and to allow more flexibility within the economic model for different patient populations" (CS, pg 90, Section 4.10).

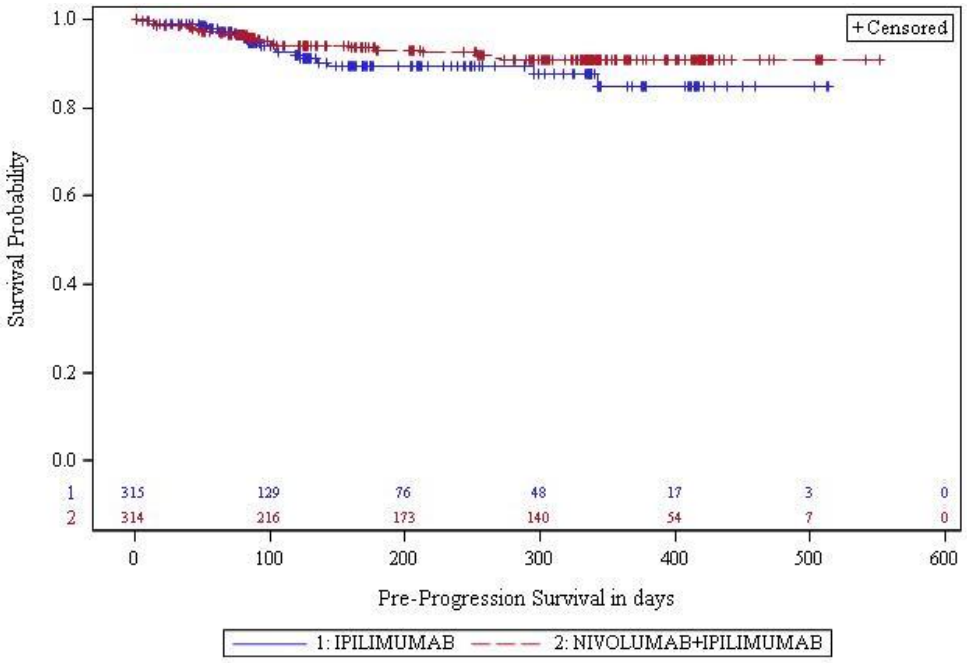
Table 49. Log-normal model parameter estimates for TTP post 84 days (CS, pg 92, Table 25)

Model Parameter	Estimate	Lower 95% CL	Upper 95% CL
Sdlog	0.973	0.862	1.084
Meanlog (intercept)	5.291	4.338	6.245
Treatment: nivolumab plus ipilimumab vs ipilimumab	2.110	1.498	2.723
ECOG: 0 vs ≥1	-0.034	-0.752	0.683
M stage: M1c vs 'M0 or M1a or M1b'	-0.597	-1.217	0.023
Aged under 65: Yes vs No	-0.453	-1.063	0.157
Sex: male vs female	0.012	-0.620	0.644
History of brain metastases: Yes vs No	1.666	-0.105	3.437
High LDH: Yes vs No	-0.634	-1.311	0.042
Abbreviations in table: CL, confidence limit; ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; TTP, time to progression; ULN, upper limit of normal range			

5.4.2.3 Pre-progression survival data analysis, immunotherapies

Pre-progression survival (PrePS) determines the transition of patients between the PFS and death health states. The company based the PrePS for combination immunotherapy and ipilimumab on the CheckMate 067 trial, shown in Figure 27.

Figure 27. Kaplan Meier curves for pre-progression survival, CheckMate 067 (CS, pg 96, Figure 31)



The company reported that, as none of the tested parametric curves provided an acceptable visual fit to the data, the Kaplan Meier curves were used directly in the model. These were supplemented by a long-term extrapolation informed by melanoma registry data, long-term OS based on pooled ipilimumab trials, and general population mortality. For the adjustment of the KM data, the company estimated the effects of treatment and the six identified prognostic factors by using a Cox proportional hazards model. The model results are shown in Table 50. Among the tested parameters, only the effects of elevated LDH resulted significantly different from zero in the full model.

Table 50. Cox proportional hazards model, PrePS (CS, pg 96, Table 28)

Model parameter	Parameter estimate	Standard error	P-value	Hazard ratio
Treatment (ipilimumab vs nivolumab plus ipilimumab)	0.36131	0.31353	0.2492	1.435
Sex (male vs female)	-0.29357	0.31254	0.3476	0.746
Age group (under 65 vs 65 and over)	-0.50544	0.30668	0.0993	0.603
ECOG (ECOG=0 vs ECOG ≥1)	-0.73449	0.31234	0.0187	0.480
Elevated LDH (>ULN vs ≤ULN)	1.41064	0.33771	<.0001	4.099
History of brain metastases (yes vs no)	-0.00987	0.61527	0.9872	0.990
M stage (M1c vs M0 or M1a or M1b)	0.88523	0.39194	0.0239	2.424
Abbreviations in table: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; PrePS, pre-progression survival; ULN, upper limit of normal (range).				

5.4.2.4 Long-term pre-progression survival, immunotherapies

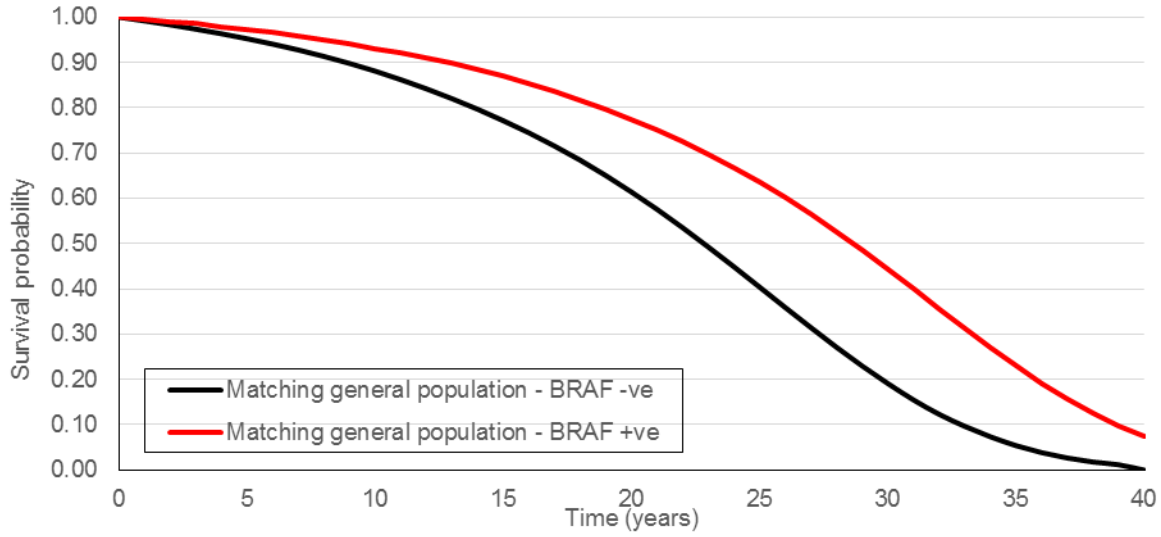
Long-term pre-progression survival was set equal to the English life tables based on data for the years 2012-2014, even though the reference reported in Section 5.3.2, page 145 of the CS, referred to the years 2011-2013. The mortality rates were correctly translated into cycle probabilities. The gender split and average age at beginning of the model for the two subpopulations are reported in Table 51. The gender split was assumed to remain constant over time and not to be influenced by the different mortality rates.

Table 51. Baseline patients' characteristics influencing general population mortality

Subpopulation	Proportion of male patients	Age at baseline	Source
BRAF- patients	66%	62	Checkmate 067[80]
BRAF+ patients	59%	56	BRIM-3[2]

The survival curves, dependent on the gender split and average age parameters in Table 51, are showed in Figure 28.

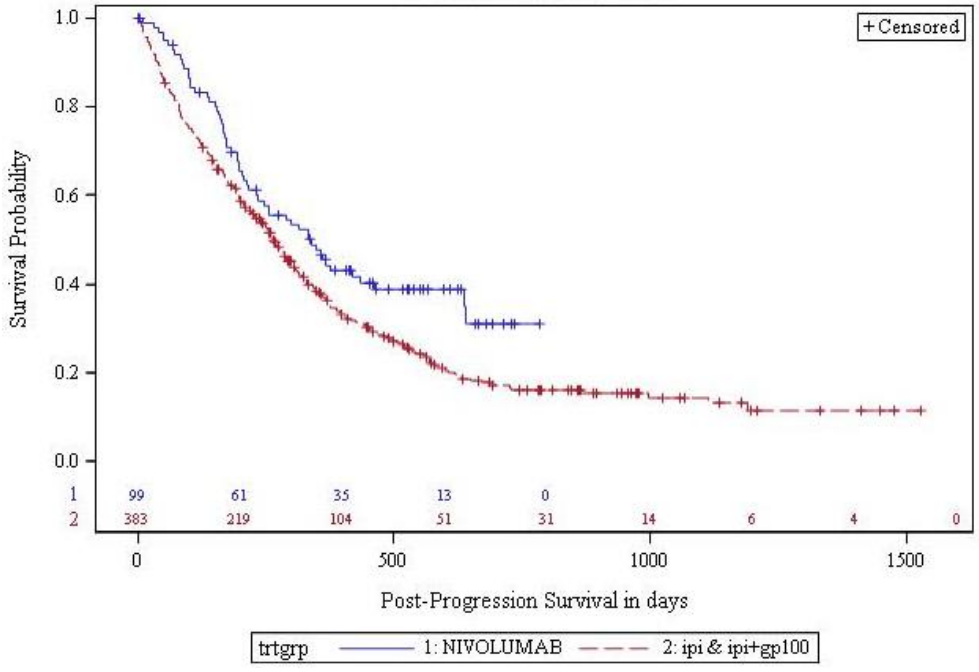
Figure 28. General population mortality based on the baseline subpopulation characteristics



5.4.2.5 Post-progression survival data analysis, immunotherapies

The company pooled together data from the nivolumab arm of the CheckMate 066 trial, and ipilimumab and ipilimumab plus gp100 arms of the MDX010-20 trial to produce a parametric survival estimate of PPS. The Kaplan Meier curves are shown in Figure 29.

Figure 29. Kaplan Meier curves for PPS, CheckMate 066 and MDX010-20 (CS, pg 93, Section 4.10)



The parametric models included the six covariates identified based on the Korn *et al.* study (CS, pg 84, Section 4.10) and listed in Section 5.4.2.1, as well as two additional parameters: an effect attributed to the study and to subsequent ipilimumab therapy. The company's justification is reported in Box 21.

Box 21. Company's justification for inclusion of effects of study and subsequent ipilimumab in the PPS parametric models (CS, pg 93, Section 4.10)

In CheckMate 066, patients were permitted to receive ipilimumab upon progression, hence the inclusion of subsequent ipilimumab (yes/no) as a covariate for PPS. As described, the nivolumab and ipilimumab data from CheckMate 066 and MDX010-020, respectively, are used as proxy to estimate PPS conservatively assuming equal efficacy between nivolumab, ipilimumab and [combination immunotherapy]. Using this assumption, the effect of treatment is not included in the PPS covariate adjusted models. However, the effect of study is included to adjust for unmeasured differences between the studies.
Abbreviations in box: PPS, post-progression survival.

According to the analysis of the AIC and BIC statistics reported by the company, the generalised gamma, log-logistic and log-normal models were the best fitting models among the tested ones. The measures of relative fit are shown in Table 52.

Table 52. Model fit estimates for PPS (CS, pg 93, Table 26)

Model	AIC	BIC
Log-logistic	**4906.00**	**4947.76**
Log-normal	4908.50	4950.26
Generalised Gamma	4909.10	4955.04
Gompertz	4923.98	4965.74
Exponential	4928.89	4966.47
Weibull	4930.78	4972.54
Abbreviations in table: AIC, Akaike information criteria; BIC, Bayesian information criteria; PPS, post-progression survival.		

The log-logistic model was selected as the best-fitting/most appropriate model in the economic model base case, "given the slight superiority in AIC/BIC and validation of the expected survival for ipilimumab" (CS, pg 95, Section 4.10). The model parameter estimates for the log-logistic model are reported in Table 53.

Table 53. Log-logistic model parameter estimates for PPS (CS, pg 95, Section 4.10)

Model parameter	Estimate	Lower 95% CL	Upper 95% CL	p-value
Scale[a]	0.7152	0.6553	0.7805	
Intercept	5.7804	5.2737	6.2871	<.0001

Model parameter	Estimate	Lower 95% CL	Upper 95% CL	p-value
Study: MDX010-20 vs CheckMate 066	-0.1867	-0.6193	0.2458	0.3975
ECOG: 0 vs ≥1	0.3339	0.0839	0.5838	0.0089
M stage: M1c vs 'M0 or M1a or M1b'	-0.2313	-0.5020	0.0394	0.0940
Aged under 65: Yes vs No	0.1858	-0.0741	0.4456	0.1612
Sex: male vs female	-0.0272	-0.2618	0.2074	0.8203
History of brain metastases: Yes vs No	-0.0581	-0.4610	0.3447	0.7773
High LDH: Yes vs No	-0.9328	-1.1984	-0.6672	<.0001
Subsequent ipilimumab: Yes vs No	0.5646	0.0310	1.0982	0.0381

Abbreviations in table: CL, confidence limit; ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; PPS, post-progression survival; ULN, upper limit of normal range.
Notes: [a] care should be taken as different statistical packages have different model parameterisations and use different terminology for parameters; the estimates reported here are taken from the SAS software parameterisation.

The company noted that, "after adjustment for prognostic factors, the effect of trial (which is fully confounded with any treatment effect) was not significant, adding support to the assumption of equal PPS between nivolumab and ipilimumab" (CS, pg 95, Section 4.10).

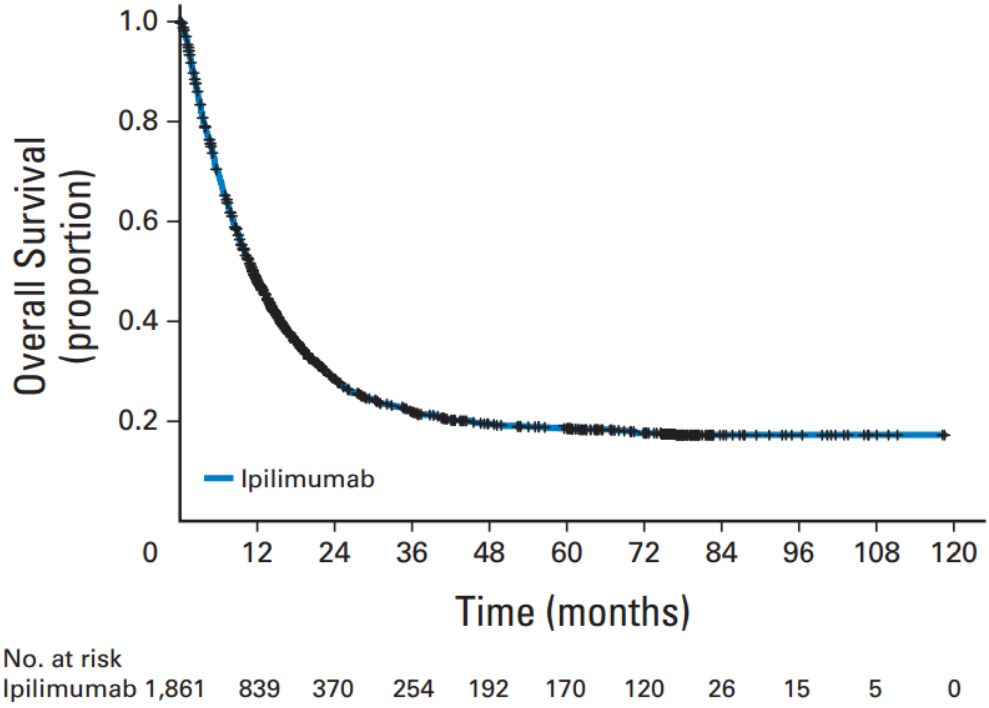
5.4.2.6 Long-term post-progression survival, immunotherapies

The company went beyond the available trial data to model long-term survival, "to avoid extrapolating long-term OS from fitted parametric curves based on short follow-up data" (CS, pg 145, Section 5.3.2). The company used an analysis of pooled ipilimumab data reported by Schadendorf *et al.* to model long-term survival.[4] The authors pooled OS data for 1,861 patients from 12 studies assessing the efficacy of ipilimumab (median follow-up time approximately 11 months), calculating survival rates using the Kaplan Meier estimator.[4]

The company extracted the data from the pooled Kaplan Meier curve in the publication using digitisation software. Pseudo-PLD were simulated using the method reported by Guyot *et al.*[76]. Parametric survival models were then fitted to the simulated data. The company reported the analysis in Appendix 9, Section 9.3 of the CS.

While the company did not state clearly which figure was used as the source of OS data, the ERG it was likely to be Figure 1 in the Schadendorf *et al.* publication, shown in Figure 30.[4]

Figure 30. Pooled ipilimumab overall survival data (Schadendorf *et al.*, Figure 1)[4]



The company reported that, "The pooled ipilimumab data were rebased at 3 years, after which time the OS estimates are seen to plateau. This curve is then applied to both ipilimumab and nivolumab plus ipilimumab OS estimates within the economic model for long-term predictions of OS" (Appendix 9 of the CS, pg 90, Section 9.3).

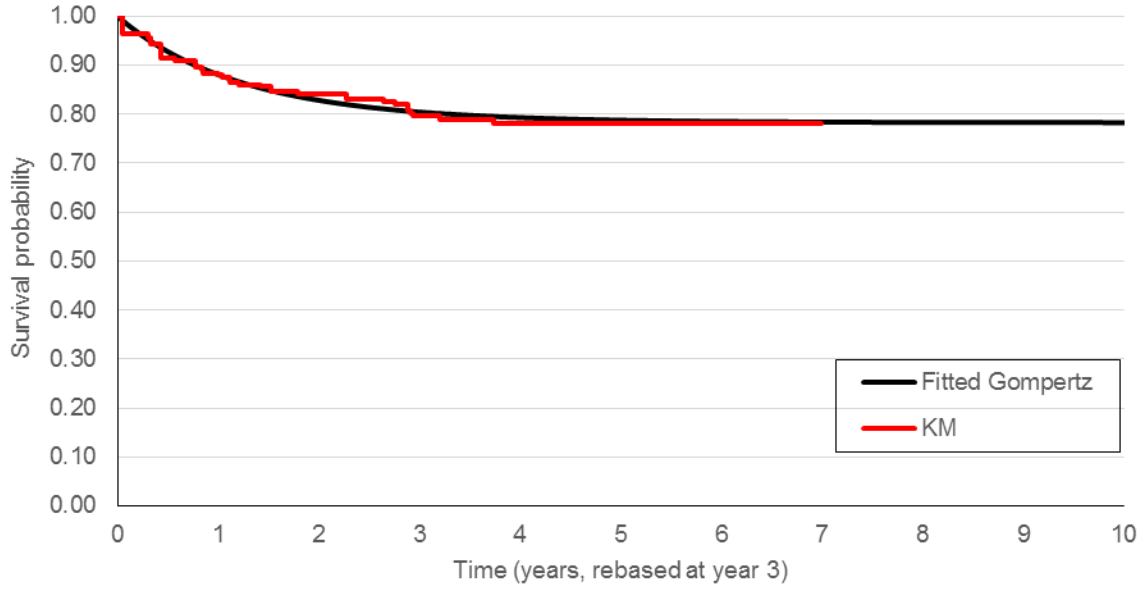
The relative goodness of fit measures resulting from the parametric survival analysis are reported in Table 54. The analyses were carried out using the R library *flexsurv*.[82]

Table 54. Model fit estimates for pooled ipilimumab data, rebased at 3 years (Appendix 9 of the CS, pg 90, Table 18)

Model	AIC	BIC
Exponential	935.67	939.20
Generalised Gamma	892.43	903.04
Gompertz	**888.42**	**895.50**
Log-logistic	899.94	907.02
Log-normal	895.83	902.91
Weibull	901.51	908.59
Abbreviations in table: AIC, Akaike information criterion; BIC, Bayesian information criterion.		

The Gompertz model provided the best fit to the data among the parametric models tested by the company. The model fit to the pseudo-PLD is shown in Figure 31.

Figure 31. Gompertz model fit to the pseudo-PLD



In Appendix 9 of the CS, the company reported using a Gompertz model with shape and rate parameters equal to -0.002 and -7.621, respectively.

5.4.2.7 Analysis of the efficacy of BRAF inhibitors

The company conducted an indirect comparison between combination therapy, ipilimumab, vemurafenib and dabrafenib. This was to inform the comparison between these treatment strategies in the economic model for the $BRAF^{+}$ subpopulation. The indirect comparison carried out by the company is described in detail in Section 4.4.2.

Under the assumption of equal efficacy between vemurafenib and dabrafenib, the company based the efficacy of the BRAF inhibitors on the BRIM-3 trial, which assessed the efficacy of vemurafenib compared to dacarbazine in 675 advanced melanoma patients. [3] The trial results were extracted from the papers by digitising the Kaplan Meier OS and PFS data from the Hauschild *et al.* 2013 and the McArthur *et al.* 2014 publications, respectively.[2, 3] The company reported that the two publications were selected as, "the most up to date information on OS and PFS for vemurafenib at the time of submission" (CS, pg 99, Section 4.10). Pseudo patient-level data (PLD) were simulated using the algorithm developed and reported by Guyot *et al.* 2012.[76] Figure 32 and Figure 33 show the OS and PFS curves used to extract the data, respectively.

Figure 32. Overall survival Kaplan Meier plot for BRIM-3: vemurafenib versus DTIC, censored at crossover (CS, pg 99, Figure 32)

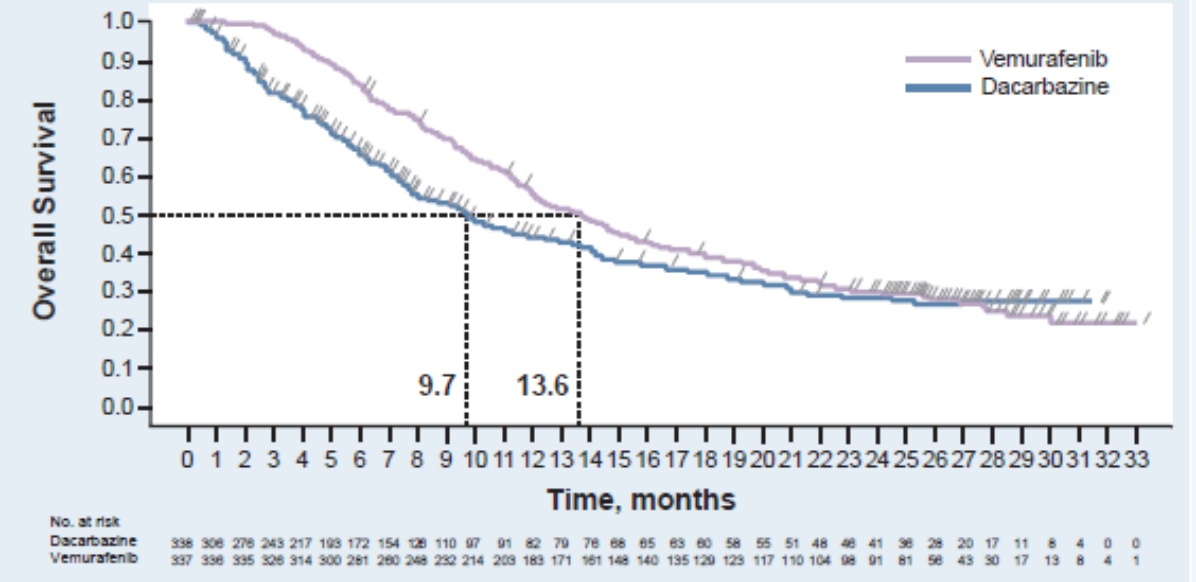
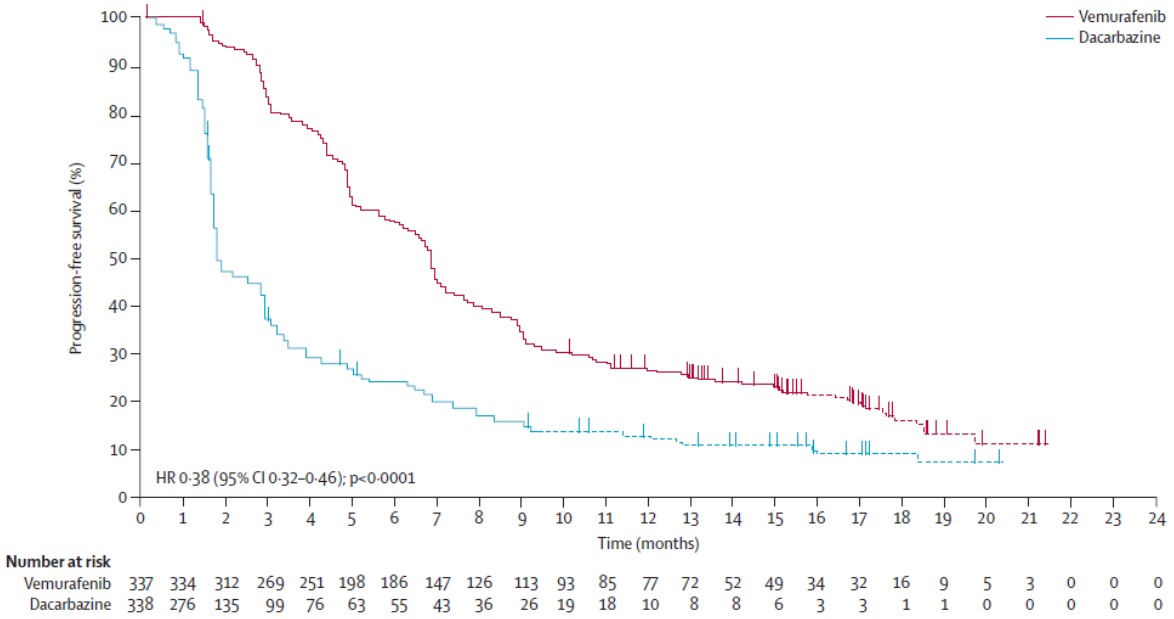


Figure 33. Progression-free survival Kaplan Meier plot for BRIM-3: vemurafenib versus DTIC (CS, pg 99, Figure 33)



The pseudo-PLD for the vemurafenib arm were analysed using parametric survival models. As the company did not have access to the trial PLD, the models did not include covariates. Rather, the baseline characteristics of the BRIM-3 trial were used to adjust the outcomes predicted by the models estimated for combination immunotherapy and ipilimumab.

The AIC and BIC statistics resulting from the parametric survival analysis of the OS are reported in Table 55. The log-normal model resulted having the best relative fit among the tested parametric shapes and was selected for use in the economic model.

Table 55. Model fit estimates for OS, vemurafenib arm data from the BRIM-3 trial (CS, pg 100, Table 30)

Model	AIC	BIC
Exponential	3700.23	3704.05
Generalised Gamma	3647.94	3659.41
Gompertz	3698.01	3705.65
Log-logistic	3651.70	3659.34
Log-normal	**3647.40**	**3655.04**
Weibull	3677.80	3685.44
Abbreviations in table: AIC, Akaike information criteria; BIC, Bayesian information criteria; OS, overall survival.		

The same procedure was used to analyse the PFS pseudo-PLD. A generalised gamma model was selected according to the AIC and BIC measures and visual fit to the Kaplan Meier curves. The relative measures of fit to the data are reported in Table 56.

Table 56. Model fit estimates for OS, vemurafenib arm data from the BRIM-3 trial

Model	AIC	BIC
Exponential	3506.86	3510.68
Generalised Gamma	3410.62	3422.08
Gompertz	3503.35	3510.99
Log-logistic	3428.62	3436.26
Log-normal	3421.30	3428.94
Weibull	3473.10	3480.74
Abbreviations in table: AIC, Akaike information criteria; BIC, Bayesian information criteria; PFS, progression-free survival.		

The resulting model parameters estimated by the company, log-normal and generalised gamma for the OS and PFS, respectively, are reported in Table 57.

Table 57. Parameters for models selected for BRAF inhibitors (adapted from CS, pg 101, Table 32)

Study, Treatment	Endpoint	Chosen Curve	Model estimates
BRIM-3, vemurafenib	OS	Log-normal	Meanlog=6.078 Sdlog=-0.072
	PFS	Generalised gamma	Mu=5.104 Sigma=-0.220 Q=-0.754
Abbreviations in table: OS, overall survival; PFS, progression-free survival.			

5.4.2.8 Long-term mortality, BRAF inhibitors

To model the long-term mortality associated with BRAF inhibitors the company selected the American Joint Committee on Cancer (AJCC) registry survival data for Stage IV melanoma patients (n=1,158), reported by Balch *et al.*[84], "because it provides data with the longest follow-up period, 15 years" (CS, pg 151, Section 5.3.3). The company reported to have digitised the Kaplan Meier curve from the publication and rebased them at 3 years. Details of the parametric survival analysis performed were reported in Appendix 9 of the CS, page 91, Section 9.3.2.

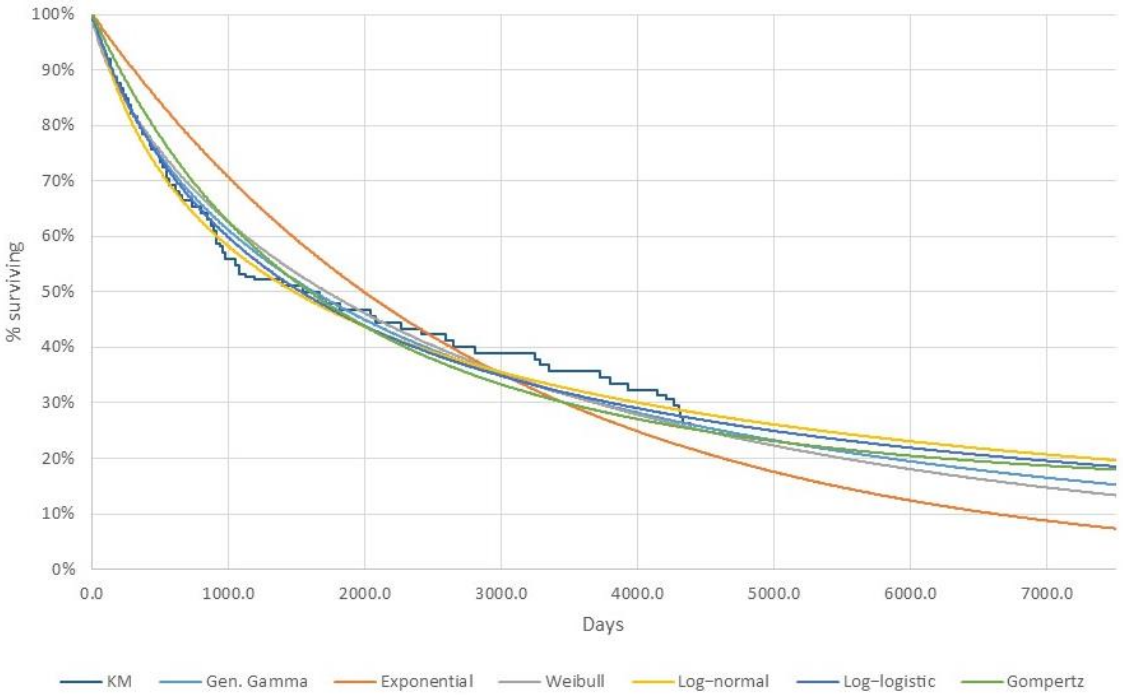
The AIC and BIC statistics resulting from the company's parametric analysis of the registry data are reported in Table 58. The company did not explicitly state in their submission the model selected; a figure was included, comparing Kaplan Meier data for the pseudo-PLD against what was labelled as a log-normal model (CS, pg 151, Figure 55). However, the figure had an inconsistent caption and x-axis label, as they were, "KM and fitted base case OS (rebased at 3 years) using registry data" and, "Time (year, rebased at year 2)" (CS, pg 151, Section 5.3.3). The ERG confirmed in the economic model that the parametric model used in the base case was a Weibull, which resulted having the lowest AIC and BIC statistic among the tested parametric models.

Table 58. Model fit estimates for registry data, rebased at 3 years (Appendix 9 of the CS, pg 91, Table 20)

Model	AIC	BIC
Exponential	2457.99	2461.22
Generalized Gamma	2438.74	2448.42
Gompertz	2445.51	2451.97
Log-logistic	2438.66	2445.11
Log-normal	2442.68	2449.13
Weibull	**2437.91**	**2444.36**
Abbreviations in table: AIC, Akaike information criteria; BIC, Bayesian information criteria.		

Figure 34 shows the fit of the tested curves to the pseudo-PLD. The ERG notes that none of the curves seems to fit the data particularly well.

Figure 34. Parametric OS model fits for registry data, rebased at 3 years (Appendix 9 of the CS, pg 92, Figure 12)



5.4.2.9 Treatment effectiveness modelling

The implementation of the treatment effectiveness in the model is described below, separately for combination immunotherapy and ipilimumab and for the BRAF inhibitors, as two different model structures were adopted.

- Combination immunotherapy and ipilimumab ($BRAF^-$ and $BRAF^+$ subpopulations):
    - TTP (Section 5.4.2.2):
        - TTP pre-84 days: Kaplan Meier curves from the CheckMate 067 trial, adjusted for the patients' baseline characteristics based on the estimates of a Cox proportional hazards model;
        - TTP post-84 days: log-normal parametric model estimated based on the post-84 days CheckMate 067 trial data. Treatment effect was based on the model estimate, assuming proportionality of the hazards;
    - PrePS (Section 5.4.2.3 and Section 5.4.2.4):
        - PrePS from model inception to end of observed follow-up in the CheckMate 067 trial: Kaplan Meier curves from the CheckMate 067 trial,

adjusted for the patients' baseline characteristics based on the estimates of a Cox proportional hazards model. The treatment effect estimated in the Cox model was not considered in the adjustment, and it was accounted for by the difference in the area under the Kaplan Meier curves. The maximum follow-up periods differed between the two model arms and were equal to 551 days and 513 days for combination immunotherapy and ipilimumab, respectively;

        - PrePS from end of maximum follow-up in the CheckMate 067 trial to end of time horizon: patients were assumed to die at the same rate of the general population. The age-specific mortality was based on the UK life tables;

    - PPS (Section 5.4.2.5 and Section 5.4.2.6):

        - PPS from model inception to year 3: log-logistic model estimated based on the nivolumab arm of the CheckMate 066 trial and the pooled ipilimumab and ipilimumab plus gp100 arms of the MDX010-20 trial.

        - PPS from year 3 to end of time horizon: Gompertz parametric model estimated based on the pooled ipilimumab data reported by Schadendorf *et al.*[4]

- BRAF inhibitors, i.e. vemurafenib and dabrafenib ($BRAF^+$ subpopulation only):

    - PFS (Section 5.4.2.7):

        - PFS from model inception to end of time horizon: generalised gamma parametric model estimated based on the pseudo-PLD based on the BRIM-3 trial. The OS was set as upper bound for the PFS;

    - OS (Section 5.4.2.7 and Section 5.4.2.8):

        - OS from model inception to year 3: log-normal parametric model based on the pseudo-PLD extracted from the BRIM-3 trial results;

        - OS from year 3 to end of time horizon: Weibull parametric model fitted on pseudo-PLD extracted from the AJCC registry for melanoma-specific mortality, in addition to age-matched general population mortality from the Life Table for England (years 2012-2014).

Baseline patients' characteristics

The company's model relied on the characteristics of patients at baseline to determine the adjustment of the survival curves. The baseline characteristics were set equal to the ones observed in the CheckMate 067 in the $BRAF^-$ subpopulation and to the characteristics of patients in the BRIM-3 trial in the analysis of $BRAF^+$ patients.[3, 31]

Table 59. Patient characteristics at baseline influencing treatment effectiveness (adapted from CS, pg 138, Table 51 and pg 147, Table 52)

Characteristics	BRAF-	BRAF+
Mean age	62	59
% male	66.2%	59.0%
% under 65	53.3%	100%
% stage M1c	59.2%	66.0%
ECOG status = 0	70.4%	68.0%
% elevated LDH (>ULN)	38.4%	58.0%
% with brain metastases	3.9%	0%

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of the normal range.

TTP: base case model inputs

The resulting curve, combining the Kaplan Meier pre-84 days data and the extrapolated parametric models for combination immunotherapy and ipilimumab in the $BRAF^-$ and $BRAF^+$ subpopulation are shown in Figure 35 and Figure 36, respectively.

Figure 35. Time to progression in the base case model for BRAF^{-} analysis over 3 years (CS, pg 139, Figure 45)

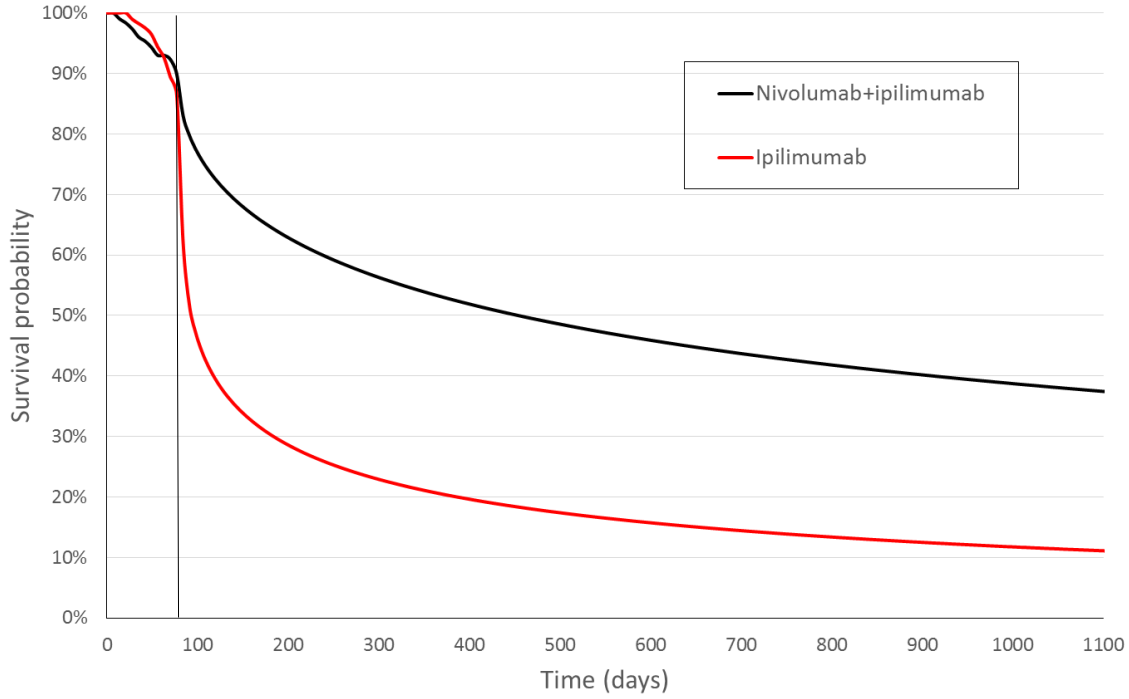
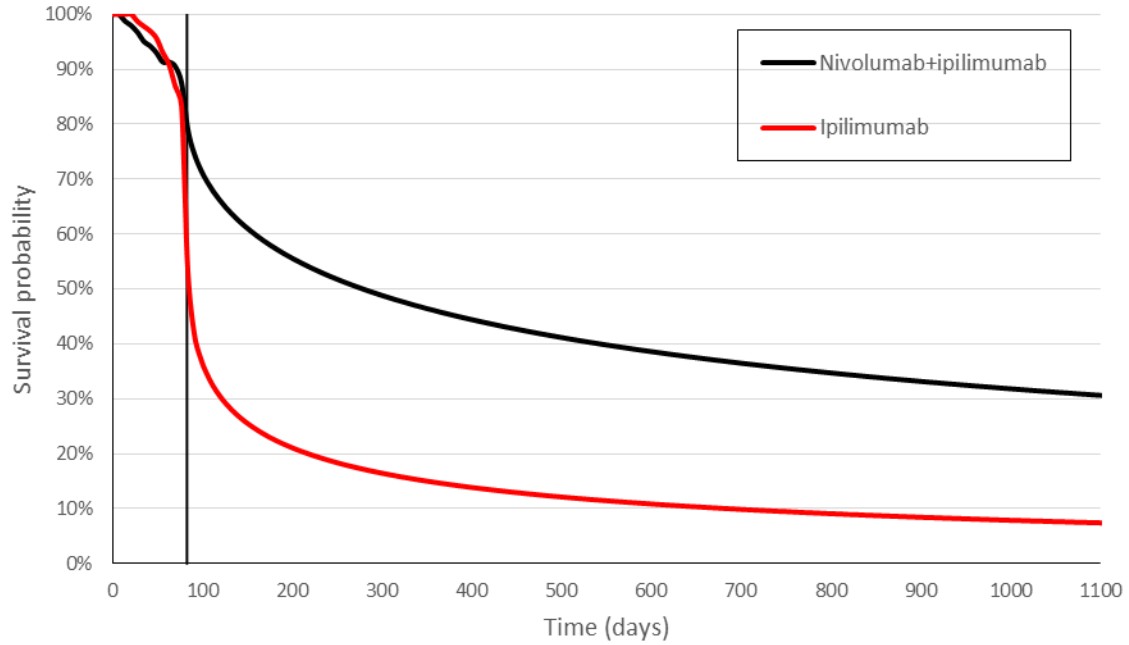


Figure 36. Time to progression in the base case model for BRAF^{+} analysis over 3 years



PrePS: base case model inputs

The PrePS curves adopted in the company's base case model are shown in Figure 37 and Figure 38, respectively for the BRAF- and BRAF^{+} subpopulations. The general population mortality was applied at the end of the Kaplan Meier curves until the end of the time horizon. As the maximum observed follow-up for the two intervention strategies was different (551 days and 513 days for combination

immunotherapy and ipilimumab, respectively), the general population mortality is applied earlier in the ipilimumab model arm.

Figure 37. Pre-progression survival in the base case model BRAF$^-$ analysis over 3 years

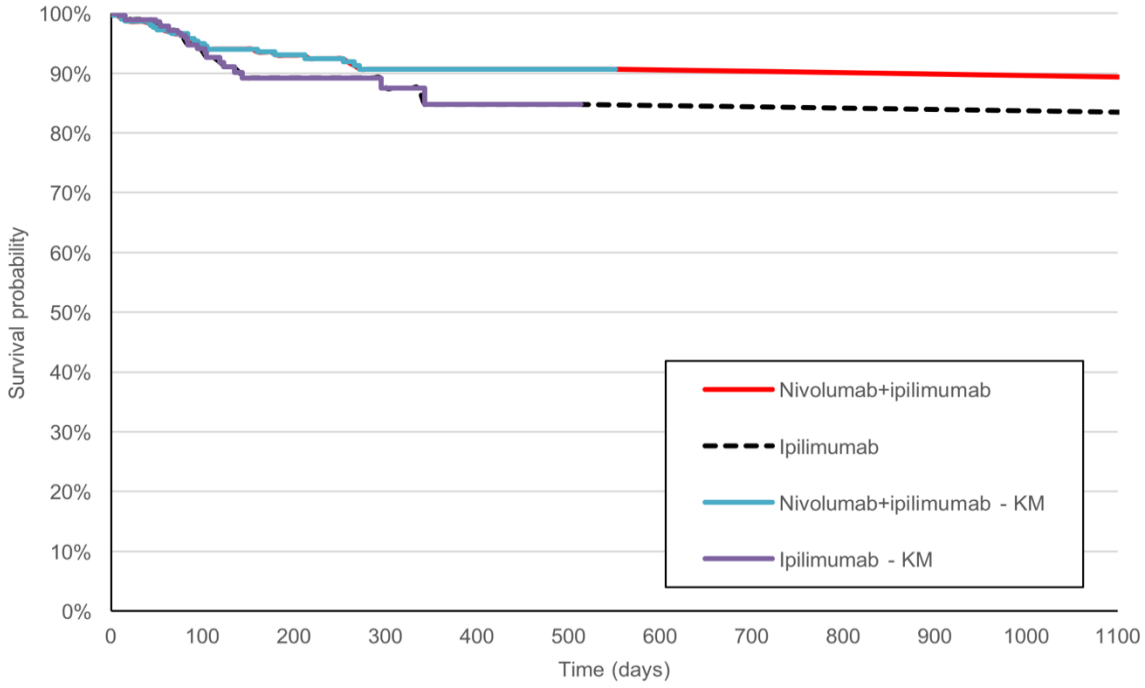
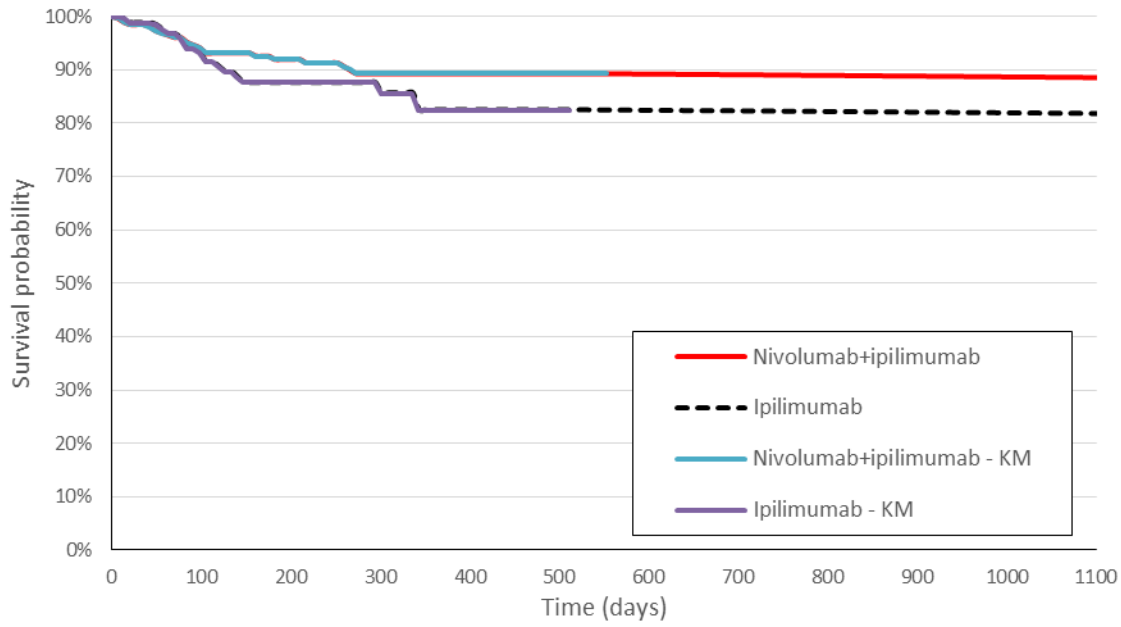


Figure 38. Pre-progression survival in the base case model BRAF$^+$ analysis over 3 years



The Kaplan Meier survival estimates for PrePS are reported in Table 60; these were extracted from the economic model provided by the company. The unadjusted curves were used in the $BRAF^-$ subpopulation analysis were the same as the observed results in the CheckMate 067 RCT[a].[80] The adjusted Kaplan Meier estimates for the $BRAF^+$ patients at the end of the observed follow-up in Table 60 were extracted from the company's model adjusted weekly estimates.

Table 60. Kaplan Meier PrePS estimates at end of follow-up

Treatment	Time of last event	Maximum follow-up	Survival estimate at end of follow-up, $BRAF^-$	Survival estimate at end of follow-up, $BRAF^+$
Combination immunotherapy	271 days	551 days	90.7%	89.3% (at day 553)
Ipilimumab	343 days	513 days	84.7%	82.4% (at day 511)

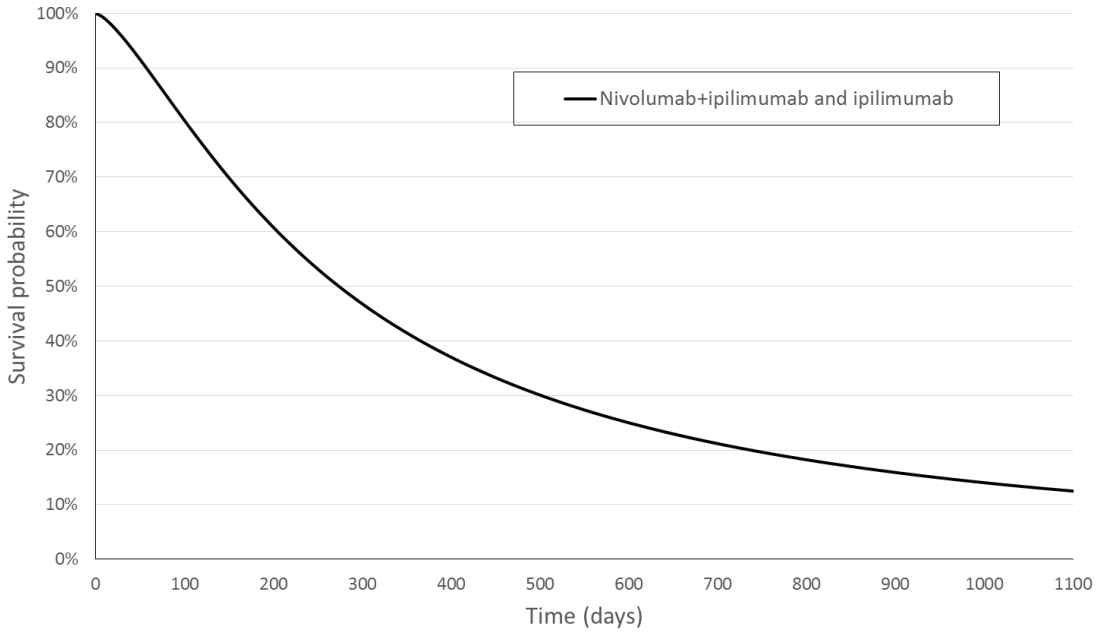
Before the general population mortality was applied in the two arms, the tail of the Kaplan Meier curves were used even though no events were recorded for 280 and 170 days for the combination immunotherapy and ipilimumab, respectively (based on no observed variations in the Kapan Meier estimator). As a consequence, in the model no mortality was assumed in correspondence of the flat portions of the curves. The general population mortality applied from the end of the maximum follow-up period in the CheckMate 067 trial was based on the life tables for England (years 2012-2014), as reported in Section 5.4.2.4.

PPS: base case model inputs

As described in Section 5.4.2.5, a log-logistic parametric survival curve was selected to model the post-progression survival data from the CheckMate 066 and MDX010-20 trials. The model was adjusted based on the baseline patients' characteristics in the CheckMate 067 and BRIM-3 trials in the $BRAF^-$ and $BRAF^+$ analysis, respectively.[3, 80] This model was used to extrapolate the trial data and model the survival in post-progression of patients progressed up to 3 years.

[a] More precisely, as the baseline characteristics in the trial and in the model were the same the adjustment did not produce any difference. Therefore in the base case model for the BRAF-negative subpopulation the unadjusted and adjusted curves coincide.

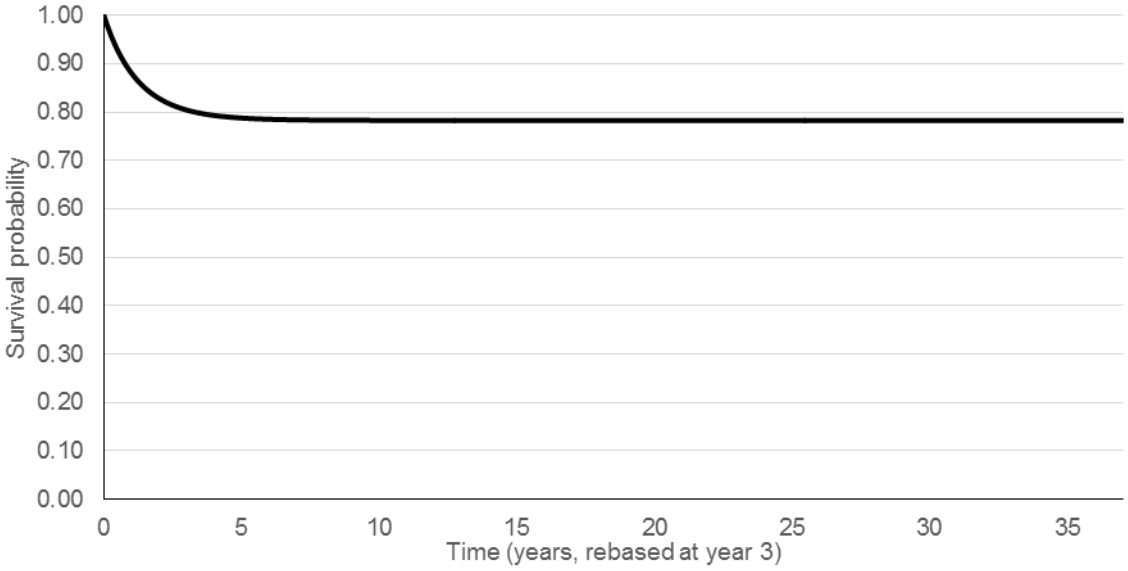
Figure 39. Post-progression survival in the base case model for BRAF^{-} analysis over 3 years (CS, pg 143, Figure 49)



The same mortality was assumed for all patients at progression, independently from first-line or subsequent treatment received (if any). The log-logistic model was applied starting from the moment of progression up to 3 years since first-line treatment initiation; i.e. the x axis in Figure 39 represents time since progression. The mortality curve shown in Figure 39 was applied in full for patients who would have progressed during the first cycle; however, none or only a portion of it was applied to patients who would progress after that, as the long-term mortality was plugged in at the third year since beginning of model time and not since patient progression.

After 3 years since model beginning, all patients are assumed to follow the post-progression mortality based on the pooled ipilimumab OS reported by Schadendorf *et al.* (Section 5.4.2.6).[4] The long-term model extrapolation is reported in Figure 40. The company limited the minimum probability of death to be equal or higher than the one for the age-specific general population, not accounted for in Figure 40.

Figure 40.Gompertz model for long-term PPS based on the data reported by Schadendorf *et al.*[4]



BRAF inhibitors: base case efficacy inputs

The modelling approach used for modelling the efficacy of BRAF inhibitors differed from the one adopted for combination immunotherapy and ipilimumab, as described in Section 5.4.1. The data analysis performed by the company is detailed in Section 5.4.2.7. The partitioned survival (or area under the curve) approach was based on the PFS and OS parametric models reported in Table 57.

Similarly to the data used to model combination immunotherapy and ipilimumab, survival data from the AJCC melanoma registry were used to model mortality from year 3 onwards.[84] As the survival curves reported in the Balch *et al.* publication represented melanoma-specific mortality[84], the company applied additional general population mortality to the parametric mortality estimates. The company reported using general population mortality extracted from the, "Life Table for England (2011-2013) as a weighted average of male and female mortality risks using the gender distribution of participants in the BRIM-3 trial" (CS, pg 151, Section 5.5.3). However, the ERG confirmed that the source for mortality were based on data for the years 2012-2014 and not 2011-2013 as reported in the CS.

5.4.3 Adverse events

The company included the following treatment-related adverse events (TRAEs) based on clinical expert opinion: endocrine disorders (any grade), diarrhoea (grade 2 or higher) and other events of grade 3 or higher. There was no restriction based on the proportion of patients experiencing the events for the inclusion of grade 3 or higher TRAEs.

The proportions of patients assumed to experience TRAEs for combination immunotherapy and ipilimumab were based on patient-level data from CheckMate 067.[80] The estimated number of

patients expected to experience TRAEs when receiving dabrafenib and vemurafenib was based on published results from the dabrafenib arm and vemurafenib arms of the BREAK-3 and BRIM-3 trials, respectively.[2, 27]

According to clinical expert opinion sought by the company, the majority of costs associated with management of TRAEs are associated to TRAE-related hospitalisations. Data on TRAE-related hospitalisations collected in CheckMate 067 were analysed and the results utilised in the model.

TRAE-related hospitalisation associated to BRAF inhibitors were estimated based on the relative ratios (RR) for the comparison versus ipilimumab. Vemurafenib and dabrafenib data from the BREAK-3 and BRIM-3 trials, respectively, were compared to the ipilimumab arm in the CheckMate 067 trial to estimate the RRs.[2, 27, 80] The hospitalisation durations for BRAF inhibitors were assumed to be the equal to the observed durations in the ipilimumab arm of the Checkmate 067 trial.[80]

The proportions of patients requiring outpatient visits were assumed to be: 25% of patients with endocrine disorders, 19.2% for diarrhoea and 17.2% for other TRAEs, based on a longitudinal study analysing costs associated with management of patients with advanced melanoma.[85] A summary of TRAEs included in the model, and associated resource use is presented in Table 61.

An average utility decrement due to TRAEs was applied to patients on respective treatments. As for costs of management of TRAEs, they were applied as an upfront cost at the beginning of treatment and at week 54 for patients still on treatment which was the mean follow-up of patients in the CheckMate 067 trial.[80]

Table 61. Summary of TRAEs included in economic model (adapted from CS, pg 156, Table 53)

Treatment-related adverse event category	**Combination immunotherapy[80]**	**Ipilimumab[80]**	**Dabrafenib[2]**	**Vemurafenib[27]**
Patient numbers for TRAE analysis	313	311	187	336
Endocrine disorder (any grade)				
Percentage of patients	30.0%	11.3%[a]	0%[b]	0%[b]
Percentage of patients hospitalised	8.6%	2.6%	0%[c]	0%[c]
Total hospitalisation days	194	43	0	0
Mean hospitalisation days per patient (hospitalised patients)	7.2	5.4	5.4[d]	5.4[d]
Mean hospitalisation days per patient (all safety patients)	0.6	0.1	0	0
Percentage of patients requiring outpatient visits	7.7%	2.9%	0%	0%
Diarrhoea (Grade 2+)				
Percentage of patients	24.6%	18.6%	0%[b]	5.5%

Treatment-related adverse event category	Combination immunotherapy[80]	Ipilimumab[80]	Dabrafenib[2]	Vemurafenib[27]
Percentage of patients hospitalised	10.5%	7.4%	0%[c]	2.2%[c]
Total hospitalisation days	411	351	0	112
Mean hospitalisation days per patient (hospitalised patients)	12.5	15.3	15.3[c]	15.3[c]
Mean hospitalisation days per patient (all safety patients)	1.3	1.1	0	0.3
Percentage of patients requiring outpatient visits	4.7%	3.6%	0%	1.1%
Other TRAEs (Grade 3+)				
Percentage of patients	49.5%	27.0%	32.0%	44.5%
Percentage of patients hospitalised	25.6%	14.8%	17.5%[c]	24.4%[c]
Total hospitalisation days	1,051	537	383	956
Mean hospitalisation days per patient (hospitalised patients)	13.1	11.7	11.7[d]	11.7[d]
Mean hospitalisation days per patient (all safety patients)	3.4	1.7	2.0	2.8
Percentage of patients requiring outpatient visits	8.5%	4.6%	5.5%	7.6%

Abbreviations in table: TRAE, treatment-related adverse events.

Notes: [a] [redacted]; [b] based on conservative assumption because no published data is identified; [c] estimated by apply the relative ratio (% of patient hospitalised vs % of patient) for the ipilimumab arm; [d] assumed to be the same for the ipilimumab arm.

5.4.4 Health-related quality of life

This section outlines the systematic review carried out by the company to identify sources of evidence on health-related quality of life (HRQoL) in the target disease area. It also describes how HRQoL is included and evaluated in the economic analysis, the data sources used and finally the methods used to translate patients' HRQoL into quality-adjusted life years (QALYs) in the economic model. The systematic literature review is described in Section 5.4.4.1, with the modelling approach discussed in Section 5.4.4.2.

The main source of evidence for the estimation of HRQoL in the base case analysis was the EQ-5D data collected in the pivotal phase III randomised controlled trial (RCT) CheckMate 067.[80] The company also carried out a scenario analysis using EQ-5D data collected in the phase III RCT CheckMate 066.[86]

5.4.4.1 Systematic literature review for HRQoL

The company carried out a systematic literature review to identify evidence sources for HRQoL in patients with advanced melanoma. The first search was performed in May 2013 as part of the STA TA319[62], and was updated using the same methods and terms in November 2014 for the nivolumab

monotherapy NICE submission ID845[61] and in October 2015 for the current submission. The company searched the following electronic databases:

- MEDLINE;
- Embase;
- EconLit;
- NHS Economic Evaluation Database (EED);
- Cochrane Database of Systematic Reviews (CDSR);
- Health Technology Assessment (HTA) Database;
- Database of Abstracts of Reviews of Effects (DARE);
- Cumulative Index to Nursing & Allied Health Literature (CINAHL).

An overview of the search was reported in Section 5.4.2 of the CS and details of the search strategies in Appendix 10 of the CS. Details of the original searches carried out in November 2014 and March 2013 were provided by the company at clarification stage. The inclusion and exclusion criteria applied by the company are reported in Table 62, along with the rationale for each criterion. The search strategy and terms used by the company are deemed reasonable by the ERG.

Table 62. Eligibility criteria for the HRQoL search (CS, pg 158, Table 54)

Inclusion criteria		
Category	**Inclusion criteria**	**Rationale**
Study type	Studies reporting utilities or HRQoL data	The aim of the review was to identify relevant utility data
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant population
Interventions	No restriction to intervention	To allow all relevant papers to be identified
Comparators	No restriction to comparators	To allow all relevant papers to be identified
Outcomes	Any reported measurement in the form of utilities was included; and utility values mapped from a measure of HRQoL	The aim of the review was to identify relevant utility studies
Exclusion criteria		
Category	**Exclusion criteria**	**Rationale**
Publication year	Studies before 1970	The earliest melanoma trial was published in 1972
Language	Non-English language literature	Time and resource required for translation
Publication type	Letters, editorials and review studies	Primary study articles are required
Abbreviations in table: HRQoL, health-related quality of life.		

The company reported hand-searching the reference lists of the included HRQoL studies for additional publications of interest. Across the three searches, a total of 21 studies were included: 11 were primary utility studies while 10 were cost-effectiveness studies using utility values published in the literature. Thirteen studies were identified in the systematic review carried out in May 2013[26, 87-98], and an additional two and six studies in the November 2014[99, 100] and October 2015 updates[55, 86, 101-104], respectively. The reasons cited by the company for excluding papers after full text review across the three searches were: "Wrong study type" (n=11), "Wrong population" (n=21), "Did not include enough information to derive utilities" (n=49) and "Duplicate/review" (n=3). An overview of the included studies and values reported is presented in Table 63.

Table 63. Overview of included HRQoL studies (Adapted from CS, pg 158, Table 55 and Appendix 11; Table 25-29)

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td rowspan="4">Systematic review update (October 2015)</td><td>Abernethy et al. 2015[55],
Global</td><td>Patients with naïve advanced melanoma</td><td>Primary: EORTC QLQC30 and EQ-5D questionnaire was used during the CheckMate 069.</td><td>Progression-free survival, post-progression
Combination immunotherapy and ipilimumab had similar mean EORTC QLQ-C30 global health scores at baseline (76.9 vs 80.9), Week 7 (69.2 vs74.5) and Week 13 (78.5 vs 72.2), and similar mean EQ-5D utility index scores at baseline (0.861 vs 0.847), Week 7 (0.788 vs 0.789) and Week 13 (0.894 vs 0.834)
A transient deterioration in EQ-5D utilities was noted at Week 7 for combination immunotherapy (-0.071; n = 53; P= 0.023) and ipilimumab (-0.055; n = 35; P= 0.140), but scores returned to baseline levels at Week 13 and were maintained with combination immunotherapy beyond Week 13 after the switch to nivolumab monotherapy. Similar results were noted with EORTC QLQ-C30 scales</td></tr>
<tr><td>Long et al.,, 2015[86],
Global</td><td>Patients with naïve advanced melanoma</td><td>Primary: EORTC QLQC30 and EQ-5D questionnaire was used during the CheckMate 066.</td><td>Progression-free survival, post-progression
Mean baseline HRQoL scores were similar for nivolumab versus DTIC (EQ-5D utilities: 0.778 vs 0.711; EQ-5D Visual Analogue Scale [VAS] scores: 70.9 vs 69.1; EORTC Global Health: 68.9 vs 66.2)
No HRQoL change was noted for DTIC prior to study dropout. For nivolumab, improvements from baseline were noted in EQ-5D utilities from Week 7 (0.027; n = 132; P= 0.011) through Week 49 (0.045; n = 38; P= 0.034), and in EQ-5D VAS scores at Weeks 25, 31, 37, 49 and 61 (P≤ 0.03). EORTC subscale scores did not change over time</td></tr>
<tr><td>Delea et al. 2014[101],
Not specified</td><td>Patients with BRAF+ unresectable or metastatic melanoma</td><td>Secondary: cost-effectiveness paper primarily using utilities (EQ-5D) from BREAK-3 trial data</td><td>Progression-free survival, post-progression
<table>
<tr><th>Health state,</th><th colspan="3">Utility value (SE)</th><th>Source data</th></tr>
<tr><td></td><td>Dabrafenib</td><td>Dacarbazine</td><td>Vemurafenib</td><td></td></tr>
<tr><td>PFS</td><td>0.233 (0.024)</td><td>0.250 (0.046)</td><td>0.233 (0.024)</td><td>BREAK-3 EQ-5D data</td></tr>
<tr><td>PPS</td><td>0.090 (0.056)</td><td>0.073 (0.04)</td><td>0.091 (0.056)</td><td>BREAK-3 EQ-5D data</td></tr>
</table></td></tr>
<tr><td>Li et al. 2015[102],
USA</td><td>Patients with metastatic melanoma, compared with a single-site BRAF V600 mutation test</td><td>Secondary: cost-effectiveness paper primarily using Beusterien et al.[91], 2009</td><td>Progression-free survival, post-progression
<table>
<tr><th>Health state</th><th>Utility</th><th>Source data</th></tr>
<tr><td>Progression-free</td><td>0.8 (0.64-0.96)</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Progression</td><td>0.52 (0.42-0.62)</td><td>Beusterien et al. 2009</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td></td><td>Matter et al. 2015[103], USA</td><td>Patients with metastatic melanoma</td><td>Secondary: cost-effectiveness paper primarily using Amdahl et al. 2014 and Beusterien et al. 2009[91, 105]</td><td>Progression-free survival, post-progression
<table>
<tr><th>Health state</th><th>Utility</th><th>Source data</th></tr>
<tr><td colspan="3">Dabrafenib + Trametinib</td></tr>
<tr><td>Progression-free</td><td>0.78 (0.73-0.83)</td><td>Amdahl et al. 2014</td></tr>
<tr><td>Progression</td><td>0.72 (0.56-0.87)</td><td>Amdahl et al. 2014</td></tr>
<tr><td colspan="3">Vemurafenib</td></tr>
<tr><td>Progression-free</td><td>0.80 (0.78-0.82)</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Progression</td><td>0.52 (0.48-0.56)</td><td>Beusterien et al. 2009</td></tr>
</table></td></tr>
<tr><td></td><td>Shih et al. 2015[104], USA</td><td>Patients with metastatic melanoma</td><td>Secondary: cost-effectiveness paper primarily using Beusterien et al. 2009[91],</td><td>Progression-free survival, progression
<table>
<tr><th>Health state</th><th>Utility</th><th>Source data</th></tr>
<tr><td colspan="3">Dacarbazine</td></tr>
<tr><td>Stable</td><td>0.69</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Progression</td><td>0.45</td><td>Beusterien et al. 2009</td></tr>
<tr><td colspan="3">Dabrafenib</td></tr>
<tr><td>Stable</td><td>0.79</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Progression</td><td>0.52</td><td>Beusterien et al. 2009</td></tr>
<tr><td colspan="3">Vemurafenib</td></tr>
<tr><td>Stable</td><td>0.73</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Progression</td><td>0.49</td><td>Beusterien et al. 2009</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td>Systematic review update (November 2014)</td><td>Porter et al. 2014[100],
Global (111 sites in Africa, Australia, Europe, North America and South America)</td><td>Previously untreated patients with unresectable malignant melanoma</td><td>Primary: EORTC QLQ-C30 responses were mapped to a generic, preference-based measure (EORTC-8D) using the mapping algorithm developed by Rowen et al.[106], 2011</td><td>Pre-progression, post-progression and time to death
<table>
<tr><th rowspan="2">Treatment arm</th><th colspan="2">Pre-progression</th><th colspan="2">Post-progression</th></tr>
<tr><th>n</th><th>Mean utility (SD)</th><th>n</th><th>Mean utility (SD)</th></tr>
<tr><td>Placebo + DTIC</td><td>843</td><td>0.845 (0.138)</td><td>160</td><td>0.838 (0.143)</td></tr>
<tr><td>Ipilimumab + DTIC</td><td>694</td><td>0.840 (0.137)</td><td>168</td><td>0.830 (0.136)</td></tr>
<tr><td>All patients</td><td>1537</td><td>0.843 (0.137)</td><td>328</td><td>0.834 (0.139)</td></tr>
</table>
<table>
<tr><th>Time to death</th><th>DTIC</th><th>Ipilimumab + DTIC</th></tr>
<tr><td>< 1 month</td><td>0.631</td><td>0.610</td></tr>
<tr><td>1-3 months</td><td>0.739</td><td>0.719</td></tr>
<tr><td>3-6 months</td><td>0.810</td><td>0.790</td></tr>
<tr><td>6-9 months</td><td>0.854</td><td>0.834</td></tr>
<tr><td>9-12 months</td><td>0.880</td><td>0.859</td></tr>
<tr><td>>12 months</td><td>0.885</td><td>0.865</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td></td><td>Hatswell et al. 2014[99],
Global (125 sites in Africa, Europe, North America and South America) [107] [78]</td><td>Previously treated unresectable advanced melanoma, at Stage III or IV</td><td>Primary: generating EORTC-8D utilities from the EORTC QLQ-C30 results using the mapping algorithm developed by Rowen et al.[106], 2011</td><td>Pre-progression, post-progression and time to death
<table>
<tr><th>Model</th><th>Health state</th><th>EORTC-8D</th><th>SF-6D</th></tr>
<tr><td>Model 1</td><td>Pre-progression</td><td>0.813</td><td>0.648</td></tr>
<tr><td></td><td>Post-progression</td><td>0.776</td><td>0.626</td></tr>
<tr><td>Model 2</td><td>180 or more days to death</td><td>0.840</td><td>0.667</td></tr>
<tr><td></td><td>120-179 days to death</td><td>0.767</td><td>0.610</td></tr>
<tr><td></td><td>90-119 days to death</td><td>0.756</td><td>0.600</td></tr>
<tr><td></td><td>60-89 days to death</td><td>0.723</td><td>0.574</td></tr>
<tr><td></td><td>30-59 days to death</td><td>0.670</td><td>0.541</td></tr>
<tr><td></td><td>Under 30 days to death</td><td>0.651</td><td>0.531</td></tr>
<tr><td>Model 3</td><td>Pre-progression</td><td></td><td></td></tr>
<tr><td></td><td>180 or more days to death</td><td>0.848</td><td>0.677</td></tr>
<tr><td></td><td>120-179 days to death</td><td>0.777</td><td>0.615</td></tr>
<tr><td></td><td>90-119 days to death</td><td>0.759</td><td>0.591</td></tr>
<tr><td></td><td>60-89 days to death</td><td>0.738</td><td>0.588</td></tr>
<tr><td></td><td>30-59 days to death</td><td>0.690</td><td>0.554</td></tr>
<tr><td></td><td>Under 30 days to death</td><td>0.629</td><td>0.518</td></tr>
<tr><td></td><td>Post-progression</td><td></td><td></td></tr>
<tr><td></td><td>180 or more days to death</td><td>0.820</td><td>0.661</td></tr>
<tr><td></td><td>120-179 days to death</td><td>0.742</td><td>0.595</td></tr>
<tr><td></td><td>90-119 days to death</td><td>0.750</td><td>0.623</td></tr>
<tr><td></td><td>60-89 days to death</td><td>0.693</td><td>0.547</td></tr>
<tr><td></td><td>30-59 days to death</td><td>0.643</td><td>0.521</td></tr>
<tr><td></td><td>Under 30 days to death</td><td>0.675</td><td>0.547</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td rowspan="3">First systematic review (May 2013)</td><td>Askew et al. 2011[87], USA[108][79]</td><td>Melanoma Stages I/II, III, IV</td><td>Primary: mapping study for FACT-M to EQ-5D</td><td>Melanoma Stage I/II, Stage III or Stage IV and on active treatment, on surveillance
<table>
<tr><th>Patient distribution</th><th>n</th><th>EQ-5D utility</th><th>SD</th></tr>
<tr><td>Stage I/II</td><td>102</td><td>0.91</td><td>0.14</td></tr>
<tr><td>Stage III</td><td>100</td><td>0.85</td><td>0.13</td></tr>
<tr><td>Stage IV</td><td>71</td><td>0.86</td><td>0.11</td></tr>
<tr><td>Active treatment</td><td>75</td><td>0.83</td><td>0.11</td></tr>
<tr><td>Surveillance</td><td>198</td><td>0.89</td><td>0.13</td></tr>
<tr><td>Total</td><td>273</td><td>0.88</td><td>0.13</td></tr>
</table></td></tr>
<tr><td>Barzey et al. 2013[88], USA[88][80]</td><td>Pre-treated advanced melanoma</td><td>Secondary: cost-effectiveness paper primarily using utilities by Beusterien et al. 2009[91][81][91]</td><td>Complete/partial response, stable disease, progressive disease, death, inpatient treatment, outpatient treatment
<table>
<tr><th>Health state, event, complication</th><th>Utility value</th><th>Source data, as cited in Barzey et al. 2013[88]</th></tr>
<tr><td>Complete/partial response</td><td>0.88</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Stable disease</td><td>0.80</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Progressive disease</td><td>0.52</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Death</td><td>0</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Inpatient treatment (utility decrement)</td><td>-0.17</td><td>Beusterien et al. 2009</td></tr>
<tr><td>Outpatient treatment (utility decrement)</td><td>-0.13</td><td>Beusterien et al. 2009</td></tr>
</table></td></tr>
<tr><td>Batty et al. 2011, [89]
Global (125 sites in Africa, Europe, North America and South America)</td><td>Previously treated advanced melanoma</td><td>Primary: comparison of mapping techniques (SF-6D and EORTC-8D)</td><td>Progression free and post-progression
<table>
<tr><th>Health state</th><th>SG</th><th>EORTC-8D</th><th>SF-6D</th></tr>
<tr><td>Progression free</td><td>0.77</td><td>0.80</td><td>0.64</td></tr>
<tr><td>Post-progression</td><td>0.59</td><td>0.76</td><td>0.62</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td></td><td>Batty et al. 2012[90],
Global (125 sites in Africa, Europe, North America and South America)</td><td>Previously treated advanced melanoma & general population</td><td>Primary: comparing patient (EORTC-8D) and general-population utilities</td><td>Progression free and post-progression with different treatments, and utilities for different times before death
<table>
<tr><th rowspan="2">Treatment arm</th><th rowspan="2">Progression status</th><th colspan="3">EORTC-8D derived</th><th colspan="3">SF-6D derived</th></tr>
<tr><th>n</th><th>Mean</th><th>SD</th><th>n</th><th>Mean</th><th>SD</th></tr>
<tr><td rowspan="2">Ipilimumab + GP100</td><td>Pre-progression</td><td>131</td><td>0.802</td><td>0.134</td><td>131</td><td>0.647</td><td>0.122</td></tr>
<tr><td>Post-progression</td><td>68</td><td>0.760</td><td>0.149</td><td>69</td><td>0.630</td><td>0.132</td></tr>
<tr><td rowspan="2">Ipilimumab only</td><td>Pre-progression</td><td>393</td><td>0.804</td><td>0.141</td><td>391</td><td>0.649</td><td>0.115</td></tr>
<tr><td>Post-progression</td><td>185</td><td>0.781</td><td>0.161</td><td>182</td><td>0.608</td><td>0.114</td></tr>
<tr><td rowspan="2">GP100 only</td><td>Pre-progression</td><td>133</td><td>0.789</td><td>0.135</td><td>131</td><td>0.620</td><td>0.108</td></tr>
<tr><td>Post-progression</td><td>61</td><td>0.719</td><td>0.161</td><td>59</td><td>0.599</td><td>0.136</td></tr>
<tr><td rowspan="2">All patients</td><td>Pre-progression</td><td>657</td><td>0.801</td><td>0.138</td><td>653</td><td>0.640</td><td>0.118</td></tr>
<tr><td>Post-progression</td><td>314</td><td>0.763</td><td>0.160</td><td>310</td><td>0.619</td><td>0.130</td></tr>
</table>
<table>
<tr><th rowspan="2">Time before death (days)</th><th colspan="3">EORTC-8D derived</th><th colspan="3">SF-6D derived</th></tr>
<tr><td>n</td><td>Mean</td><td>SD</td><td>n</td><td>Mean</td><td>SD</td></tr>
<tr><td>≥180</td><td>433</td><td>0.826</td><td>0.128</td><td>418</td><td>0.655</td><td>0.108</td></tr>
<tr><td>120-179</td><td>108</td><td>0.763</td><td>0.149</td><td>96</td><td>0.608</td><td>0.107</td></tr>
<tr><td>90-119</td><td>66</td><td>0.742</td><td>0.149</td><td>61</td><td>0.598</td><td>0.112</td></tr>
<tr><td>60-89</td><td>63</td><td>0.716</td><td>0.130</td><td>59</td><td>0.572</td><td>0.098</td></tr>
<tr><td>30-59</td><td>71</td><td>0.661</td><td>0.132</td><td>68</td><td>0.538</td><td>0.101</td></tr>
<tr><td><30</td><td>35</td><td>0.608</td><td>0.143</td><td>34</td><td>0.505</td><td>0.135</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td></td><td>Beusterien et al.* 2009[91],
UK and Australia</td><td>General public evaluating outcomes for advanced melanoma</td><td>Primary: HRQoL outcomes study</td><td>Partial response, stable disease, progressive disease and best supportive care. Also utility decrement for 8 toxicity states included
<table>
<tr><th colspan="2">Health state</th><th>All
Mean (SE)</th><th>UK
Mean (SE)</th></tr>
<tr><td colspan="4">Clinical response states</td></tr>
<tr><td></td><td>Partial response</td><td>0.88 (0.01)</td><td>0.85 (0.02)</td></tr>
<tr><td></td><td>Stable disease</td><td>0.80 (0.01)</td><td>0.77 (0.02)</td></tr>
<tr><td></td><td>Progressive disease</td><td>0.52 (0.02)</td><td>0.59 (0.02)</td></tr>
<tr><td></td><td>Best supportive care</td><td>0.52 (0.02)</td><td>0.59 (0.02)</td></tr>
<tr><td colspan="4">Utility decrement for toxicity states</td></tr>
<tr><td></td><td>Hair loss (grade I/II)</td><td>-0.03 (0.01)</td><td>-0.03 (0.01)</td></tr>
<tr><td></td><td>Skin reaction (grade I/II)</td><td>-0.06 (0.01)</td><td>-0.03 (0.01)</td></tr>
<tr><td></td><td>Diarrhoea (grade I/II)</td><td>-0.09 (0.01)</td><td>-0.06 (0.01)</td></tr>
<tr><td></td><td>Nausea/vomiting (grade I/II)</td><td>-0.10 (0.01)</td><td>-0.07 (0.01)</td></tr>
<tr><td></td><td>Flu-like syndrome (grade I/II)</td><td>-0.11 (0.01)</td><td>-0.09 (0.01)</td></tr>
<tr><td></td><td>Stomatitis (grade I/II)</td><td>-0.13 (0.01)</td><td>-0.10 (0.02)</td></tr>
<tr><td></td><td>1-day in-/outpatient stay for severe toxicity (grade III/IV)</td><td>-0.13 (0.01)</td><td>-0.11 (0.02)</td></tr>
<tr><td></td><td>Symptomatic melanoma</td><td>-0.16 (0.01)</td><td>-0.11 (0.02)</td></tr>
<tr><td></td><td>2-5-day hospitalisation for severe toxicity (grade III/IV)</td><td>-0.17 (0.01)</td><td>-0.13 (0.02)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td></td><td>Cormier et al. 2007[92], USA [109][82]</td><td>Previously treated, metastatic melanoma</td><td>Secondary: cost-effectiveness paper primarily using utilities by Kilbridge et al.[110], 2001</td><td>NED, NED with HDI treatment, salvage LR, salvage DR, LR, DR
<table>
<tr><th>Health state</th><th>Utility</th><th>Range tested in sensitivity analysis</th></tr>
<tr><td>NED</td><td>0.96</td><td>0.77-1.00</td></tr>
<tr><td>NED with HDI treatment</td><td>0.87</td><td>0.69-1.00</td></tr>
<tr><td>Salvage LR</td><td>0.85</td><td>0.68-1.00</td></tr>
<tr><td>Salvage DR</td><td>0.80</td><td>0.64-0.96</td></tr>
<tr><td>LR</td><td>0.80</td><td>0.64-0.96</td></tr>
<tr><td>DR</td><td>0.61</td><td>0.49-0.73</td></tr>
<tr><td>Source data, as cited in Cormier et al. 2007[92]</td><td>Kilbridge et al. 2001</td><td>Mooney et al. 1997 and Hillner et al. 1997[98, 111]</td></tr>
</table></td></tr>
<tr><td></td><td>Dixon et al. 2006[93], UK</td><td>Malignant melanoma</td><td>Primary: cost-effectiveness study also measuring HRQoL</td><td>Follow-up after interferon-alpha treatment. Years 1-5.
 </td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td></td><td>Hirst et al. 2012[94], Australia</td><td>No melanoma, and different stages of melanoma</td><td>Secondary: cost-effectiveness analysis paper using utilities published by Chen et al. 2004,** Kilbridge et al. 2001, Stratton et al. 2000 and Morton et al. 2009, and Beusterian et al.,2003[110-114]</td><td>Melanoma in situ, melanoma Stages I, II, III and IV. For all stages utilities are given for ‘at diagnosis’ and for ‘stable disease’
<table>
<tr><th colspan="2">Health state</th><th>Utility</th><th>Source data, as cited in Hirst et al. 2012[94]</th></tr>
<tr><td colspan="2">No melanoma</td><td>1.000</td><td>Assumption</td></tr>
<tr><td rowspan="2">Melanoma in situ</td><td>At diagnosis</td><td>0.950</td><td>No source provided</td></tr>
<tr><td>Stable disease</td><td>1.000</td><td>No source provided</td></tr>
<tr><td rowspan="2">Melanoma Stage I</td><td>At diagnosis</td><td>0.937</td><td>Chen et al. 2004**</td></tr>
<tr><td>Stable disease</td><td>0.960</td><td>Kilbridge et al. 2001</td></tr>
<tr><td rowspan="2">Melanoma Stage II</td><td>At diagnosis</td><td>0.753</td><td>Chen et al. 2004**</td></tr>
<tr><td>Stable disease</td><td>0.930</td><td>Stratton et al. 2000</td></tr>
<tr><td rowspan="2">Melanoma Stage III</td><td>At diagnosis</td><td>0.520</td><td>Chen et al. 2004**</td></tr>
<tr><td>Stable disease</td><td>0.930</td><td>Stratton et al. 2000</td></tr>
<tr><td rowspan="2">Melanoma Stage IV</td><td>At diagnosis</td><td>0.470*</td><td>Beusterien et al. 2003</td></tr>
<tr><td>Stable disease</td><td>0.650</td><td>Morton et al. 2009</td></tr>
<tr><td colspan="4">*This value could not be traced to the source paper.</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td></td><td>Hodi et al. 2010[26], Canada**</td><td>General public</td><td>Primary: HRQoL outcomes study</td><td>Partial response, stable disease, progressive disease and best supportive care. Also utility decrement for 8 toxicity states included
<table>
<tr><th colspan="2">Health state</th><th>Utility</th><th>SE</th></tr>
<tr><td colspan="4">Clinical response state</td></tr>
<tr><td></td><td>Partial response</td><td>0.84</td><td>0.02</td></tr>
<tr><td></td><td>Stable disease</td><td>0.79</td><td>0.02</td></tr>
<tr><td></td><td>Progressive disease</td><td>0.55</td><td>0.02</td></tr>
<tr><td></td><td>Best supportive care</td><td>0.54</td><td>0.02</td></tr>
<tr><td colspan="4">Utility decrement for toxicity states</td></tr>
<tr><td></td><td>Skin reaction</td><td>-0.04</td><td>0.01</td></tr>
<tr><td></td><td>Hair loss</td><td>-0.05</td><td>0.01</td></tr>
<tr><td></td><td>Diarrhoea</td><td>-0.06</td><td>0.01</td></tr>
<tr><td></td><td>Nausea/vomiting</td><td>-0.07</td><td>0.01</td></tr>
<tr><td></td><td>Flu-like syndrome</td><td>-0.08</td><td>0.01</td></tr>
<tr><td></td><td>Stomatitis</td><td>-0.09</td><td>0.01</td></tr>
<tr><td></td><td>1 day out/inpatient care for grade 3/4 toxicity</td><td>-0.11</td><td>0.01</td></tr>
<tr><td></td><td>Hospitalisation for grade 3/4 toxicity</td><td>-0.15</td><td>0.01</td></tr>
</table></td></tr>
<tr><td></td><td>King et al. 2011[95], USA [115][83]</td><td>Melanoma</td><td>Primary: HRQoL outcomes study</td><td>Stages I, II, III and IV disease. New diagnoses and established diagnoses
<table>
<tr><th rowspan="2">Stage</th><th colspan="2">New diagnoses</th><th colspan="2">Established diagnoses</th><th colspan="2">Overall</th></tr>
<tr><th>n</th><th>Mean (SD)</th><th>n</th><th>Mean (SD)</th><th>n</th><th>Mean (SD)</th></tr>
<tr><td>I</td><td>15</td><td>0.904 (0.129)</td><td>80</td><td>0.931 (0.118)</td><td>95</td><td>0.926 (0.119)</td></tr>
<tr><td>II</td><td>4</td><td>0.956 (0.052)</td><td>11</td><td>0.900 (0.145)</td><td>15</td><td>0.915 (0.127)</td></tr>
<tr><td>III</td><td>8</td><td>0.534 (0.291)</td><td>10</td><td>0.908 (0.123)</td><td>18</td><td>0.720 (0.282)</td></tr>
<tr><td>IV</td><td>11</td><td>0.693 (0.329)</td><td>24</td><td>0.527 (0.339)</td><td>25</td><td>0.580 (0.340)</td></tr>
</table></td></tr>
<tr><td></td><td>Lee et al. 2012[96], UK [116][84]</td><td>Previously treated, metastatic melanoma</td><td>Secondary: cost-effectiveness paper primarily using utilities from MDX010-20 trial</td><td>Ipilimumab and best supportive care
<table>
<tr><th>Health state</th><th>Utility</th><th>Source data, as cited by Lee et al. 2012[96]</th></tr>
<tr><td>Progression free disease</td><td>0.80</td><td>MDX010-20 trial</td></tr>
<tr><td>Progressive disease</td><td>0.76</td><td>MDX010-20 trial</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Systematic review</th><th>Reference, study location</th><th>Population</th><th>Study type</th><th>Utilities included</th></tr>
<tr><td></td><td>Losina et al. 2007[97], USA</td><td>Melanoma</td><td>Secondary: Cost-effectiveness paper primarily using utilities by Chen et al. 2004[113]</td><td>Stages I/II and Stages III/IV
<table>
<tr><td>Health state</td><td>Utility (TTO)</td><td>Source data, as cited by Losina et al. 2007[97]</td></tr>
<tr><td>Stages I and II</td><td>0.937</td><td>Chen et al. 2004[113]</td></tr>
<tr><td>Stages III and IV</td><td>0.520</td><td>Chen et al. 2004[113]</td></tr>
</table></td></tr>
<tr><td></td><td>Mooney et al. 1997[98], USA[98][85]</td><td>Melanoma</td><td>Secondary: Cost-effectiveness paper using utilities published by Hillner et al. 1992 and Wong et al. 1995[111, 117]</td><td>Complete remission and metastatic melanoma
<table>
<tr><td>Health state</td><td>Utility</td><td>Source data, As cited by Mooney et al. 1997[98]</td></tr>
<tr><td>Surgical patients (complete remission)</td><td>0.90</td><td>Hillner et al. 1992 and Wong et al. 1995[111, 117]</td></tr>
<tr><td>Relative utility for patients with progressive disease (metastatic)</td><td>0.40</td><td>Hillner et al. 1992 and Wong et al. 1995[111, 117]</td></tr>
</table></td></tr>
<tr><td colspan="5">Abbreviations in table: BSC, best supportive care; CXR, chest x-ray; DR, Distant recurrence; DTIC, dacarbazine;EORTC-QLQ-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC-8D, The European organization for research and treatment of cancer 8 dimension; EQ-5D, European Quality of Life-5 Dimensions; HDI, high-dose interferon alpha; HRQoL, health-related quality of life; LR, local recurrence; NED, no evidence of disease; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SD, standard deviation; SE, standard error; SF-36, Short Form 6 dimensions questionnaire; SG, standard gamble; TTO, time trade-off; VAS, Visual Analog Scale.
* Only UK values were reported separately in this table.
** The correct reference is Chen et al. 2004 and not Bendeck et al. 2004 as is reported in the CS.
*** The correct reference is Hodi et al. 2010 and not Hogg et al. 2010 as is reported in the CS.</td></tr>
</table>

5.4.4.2 HRQoL data and modelling approach used in the economic analysis

The company used EQ-5D data that was collected in CheckMate 067[80], as described in Box 22. Details of the statistical analysis performed to derive the utility scores applied in the economic model were provided in Appendix 8 of the CS.

Box 22. HRQoL data collection in CheckMate 067 (CS, pg 157)

In the CheckMate 067 trial, HRQL was assessed using the EQ-5D, which is consistent with the NICE reference case. On-study assessments of EQ-5D were scheduled during week 1 and week 5 of the first 2 treatment cycles and for on study assessments up to 6 months. After 6 months the on study EQ-5D assessments occurred during week 1 of the treatment cycle only. During the follow-up phase (when the decision to discontinue a subject from study therapy is made i.e., no further treatment with study therapy) EQ-5D assessments continued to be taken every three months for the next 12 months, and then every six months thereafter. A total of 5,244 visits involving 827 study patients where the EQ-5D was administered were included in a statistical analysis to derive the utilities used in the model.
Abbreviations in box: HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence.

The mean utility values recorded at baseline for all patients are presented in Table 64. There was an average of 7.1, 6.9 and 8.7 mean EQ-5D observations recorded for combination immunotherapy, ipilimumab, and nivolumab respectively.[80] The company deemed the difference in the number of observations plausible, given the different rates of discontinuation across the three trial arms.[80]

Table 64. Mean utility values at first visit (CS, pg 140, Table 32 in Appendix 8)

Treatment arm	***Baseline utility value***		
	N	***Mean***	***SD***
Nivolumab plus ipilimumab	304	0.7736	0.2393
Ipilimumab	304	0.7733	0.2429
Nivolumab	301	0.7792	0.2562
Abbreviations in table: SD, standard deviation.			

EQ-5D data from all three treatment arms in CheckMate 067 were included in the statistical analysis.[80] The nivolumab monotherapy arm was used as the reference category, reported to be, "considerably less toxic" (CS, pg 163) than the other two treatment regimens. A longitudinal mixed-effects linear model was fitted in SAS/STAT® to the trial data. This model was selected to account for within-patient correlation.

The following covariates were included:

- Baseline EQ-5D;
- Progression status (with pre-progression status as reference);

- Treatment received (with nivolumab monotherapy as reference).

The results of the statistical model are presented in Table 65.[80]

Table 65: Statistical model results using EQ-5D data from CheckMate 067 (CS, pg 163, Table 57)

Parameter	Coefficient	95% confidence interval	p-value
Intercept	0.42590	[0.37870; 0.47320]	<.0001
Post-progression	-0.03291	[-0.04577; -0.02005]	<.0001
Baseline EQ-5D	0.47650	[0.42390; 0.52920]	<.0001
Treatment: ipilimumab	-0.03136	[-0.05900; -0.00372]	0.0262
Treatment: combination immunotherapy	-0.03373	[-0.06121; -0.00626]	0.0161
Sample size: 5,244 EQ-5D observations from 827 patients; Baseline EQ-5D = 0.7754.			

As reported in Table 66, utility values of 0.80 and 0.76 were associated with the progression-free and progressed health states respectively. Patients receiving treatment were assumed to have a reduced HRQoL as a result of treatment-related adverse events (TRAEs). The average utility decrements compared to nivolumab monotherapy were 0.033 and 0.031 for combination immunotherapy and ipilimumab, respectively.[80] The impact of TRAEs on the HRQoL of patients treated with BRAF inhibitors was assumed to be comparable to nivolumab, thus no relative decrement was applied to the HRQoL of patients on treatment with dabrafenib or vemurafenib.

Table 66. Summary of utility values used in the cost-effectiveness analysis (CS, pg 164, Table 57)

Health state/ Treatment received	Utility value	Justification
Health state		
Progression free	0.7954	Based on statistical models fitted using EQ-5D data collected in CheckMate 067 trial[80]
Progressed	0.7625	
Treatment received		
Combination immunotherapy	-0.03373	Based on statistical models fitted using EQ-5D data collected in CheckMate 067 trial[80]
Ipilimumab	-0.03136	
Dabrafenib	0	Assumption: equal to nivolumab monotherapy
Vemurafenib	0	

5.4.5 Resources and costs

In this Section the ERG outlines the systematic review carried out by the company to identify resource use and cost evidence in advanced melanoma to use within the economic model, as well as the assumptions and estimates used in the economic model submitted by the company. The

company's model included costs associated with advanced melanoma from the perspective of the NHS and Personal Social Services (PSS), according to the NICE reference case.[81] Resource use and costs considered in the model consisted of:

- Intervention and comparator's costs, described in Section 5.4.5.2;
- Drug resource use for nivolumab in combination immunotherapy based on time on treatment, Section 5.4.5.3;
- Treatment initiation and end of life costs, described in Section 5.4.5.4;
- Follow-up costs, described in Section 5.4.5.5;
- Adverse event costs, described in Section 5.4.5.6;
- Subsequent therapy costs, described in Section 5.4.5.7.

5.4.5.1 Systematic literature review to identify resource use and costs

An overview of the systematic literature review conducted to identify studies reporting on costs associated with advanced melanoma was reported in Section 5.5 of the CS and details of the search strategy in Appendix 10 of the CS. The company carried out a systematic review as part of the TA319 submission in May 2013.[62] The review was updated in November 2014 and October 2015. The following electronic databases were searched:

- MEDLINE;
- Embase;
- EconLit;
- NHS Economic Evaluation Database (EED);
- Cochrane Database of Systematic Reviews (CDSR);
- Health Technology Assessment (HTA) Database;
- Database of Abstracts of Reviews of Effects (DARE);
- Cumulative Index to Nursing & Allied Health Literature (CINAHL).

The company reported hand-searching and scanning studies included in the parallel costs and resource search for additional publications. The inclusion and exclusion criteria applied in the search, with

rationale for each criterion are presented in Table 67. The ERG considers the search strategy and terms used to be reasonable and in line with SIGN guidelines.[78]

Table 67. Eligibility criteria for study inclusion and exclusion (CS, pg 165, Table 58)

Inclusion criteria		
Category	**Inclusion criteria**	**Rationale**
Study type	Studies reporting costs and resource use	The aim of the review was to identify relevant costs and use of resources
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population
Interventions	There was no restriction to intervention	To allow all relevant evidence to be identified
Comparators	There was no restriction to comparators	To allow all relevant evidence to be identified
Outcomes	Studies reporting the resource use and costs associated with the treatment and ongoing management of advanced melanoma	The aim of the review was to identify relevant costs and data about resource use
Country of study	UK and Ireland	Costs and use of resources from a UK or Irish perspective were required
Exclusion criteria		
Category	**Exclusion criteria**	**Rationale**
Publication year	Studies before 1970	The earliest melanoma trial was published in 1972
Language	Non-English language literature	Time and resource required for translation and relevance to UK setting
Publication type	Letters, editorials and review studies	Primary study articles are required

The company identified five studies in the original search, two of which were cost-effectiveness studies, one was an economic impact studies and the remaining two were cost analysis studies. Three additional studies were identified in the November 2014 and none in the October 2015 update. The reasons cited for excluding studies after reviewing full text were: "Wrong population (disease)" (n=1),"Wrong population (country)" (n=15), Wrong study type (irrelevant outcomes)" (n=17), "Duplicate/review" (n=3), and "More recent data available" (n=1). An overview of the included studies is presented in Table 68.

Table 68. Summary of included resource and costs studies (CS, pg 167, Table 59)

Systematic review	**Reference**	**Country**	**Population**	**Study type**	**Resource use and costs included**
Systematic review	Hatswell *et al.* 2014[99]	UK	Metastatic melanoma	Cost analysis	Costs for drugs

Systematic review	Reference	Country	Population	Study type	Resource use and costs included
update (November 2014)	NIHR 2013[118]	UK	Malignant melanoma	Summary safety, efficacy or effectiveness of new drugs	Costs for drugs
	NIHR 2013[119]	UK	Advanced melanoma	Summary safety, efficacy or effectiveness of new drugs	Costs for drugs
First systematic review (May 2013)	Dixon *et al.* 2006[93]	UK	Malignant melanoma	Cost-effectiveness analysis	Inpatient costs, outpatient costs, GP, costs, nurse visit costs and interferon costs for two groups (observation and interferon)
	Johnston *et al.* 2012[120]	UK, Italy and France	Advanced melanoma	Economic impact	Hospitalisation and outpatient costs, use of hospital and hospice
	Lee *et al.* 2012[96]	UK	Previously treated metastatic melanoma	Cost-effectiveness analysis	Costs for drugs, treatment, palliative and terminal care
	Lorigan *et al.* 2010[121]	UK	Advanced melanoma	Healthcare resource utilisation study	Hospitalisation rates and duration of hospitalisation
	Morris *et al.* 2009[122]	UK	Malignant melanoma	Cost analysis	Costs of GP consultations, inpatient care, day cases, and outpatient attendances. NHS costs, patient costs and indirect costs

Abbreviations in table: GP, general practitioner; NHS, National Health Service; NIHR, National Institute for Health Research.

5.4.5.2 Pharmacological costs of combination immunotherapy and ipilimumab monotherapy

In this section the ERG describes the methods the company used to estimate resource use and costs associated with combination immunotherapy and ipilimumab monotherapy.

Treatment-related cost categories in the model included drug acquisition and treatment administration. Drug cost was based on the mean number of vials per patient for both combination immunotherapy and ipilimumab. The company estimated the number of vials per patient using the method of moments, as described in Box 23.

Box 23. Mean dose calculation (CS, pg 169, Section 5.5.2)

> For the [combination immunotherapy] and ipilimumab, dosing based on the method of moments using patient weight data is applied to estimate the mean number of vials required in the base case using UK patient-level weight data from trials CheckMate 067, CheckMate 066, CheckMate 037 and CA184-024. The method assumes a log-normal distribution for body weight and calculates the proportion of patients requiring each possible number of vials based upon the log-normal distribution derived from the individual patient weights. This calculation is an accurate method of accounting for wastage, assuming that no vial sharing occurs.

Table 69 and Table 70 present the unit costs and dosages for nivolumab and ipilimumab, respectively. The company assumed that patients would receive the same number of doses of ipilimumab as observed in the CheckMate 067 trial. Table 71 shows the percentages of patients who received ipilimumab by dose number. These percentages were applied to the respective treatment cycles in the model, and were assumed not to depend on the proportion of patients alive or non-progressed. The average number of ipilimumab doses was [redacted] and [redacted], respectively for combination immunotherapy ipilimumab monotherapy.

The company also assumed that patients would receive only 90.2% of the planned doses of nivolumab within combination therapy at each treatment administration, based on CheckMate 067 trial data.[80]

Table 69. Unit costs for nivolumab and ipilimumab (CS, pg 168, Table 60)

Drug	Concentration	Vial volume	Dose per vial/pack (mg/MU)	Price per vial/pack	PAS price	Source for price
Nivolumab	10mg/ml	4ml	40	£439.00	n/a	Bristol Myers Squibb
		10ml	100	£1,097.00	n/a	
Ipilimumab	5mg/ml	10ml	50	£3,750.00	[redacted]	MIMS November 2015[123]
		40ml	200	£15,000.00	[redacted]	
Abbreviations in table: mg, milligram; ml, millilitre; n/a, not applicable; PAS, patient access scheme.						

Table 70. Dosage for combination immunotherapy and ipilimumab monotherapy (adapted from CS, pg 169, Table 61)

Drug	Dosing regimen	Dose	Number of vials	Vial size	Cost per administration (list price)	Cost per administration (PAS)
Nivolumab (first 4 doses)	1mg/kg, every 3 weeks IV	80mg	[redacted]	[redacted]	£1,082	n/a
Nivolumab (after first 4 doses)	3mg/kg, every 2 weeks IV	239mg	[redacted]	[redacted]	£2,840	n/a
Ipilimumab	3 mg/kg	239mg	[redacted]	[redacted]	£19,786	[redacted]
Abbreviations in table: IV, intravenously; mg, milligram; ml, millilitre; n/a, not applicable; PAS, patient access scheme.						

Table 71. Ipilimumab doses received in CheckMate 067[80]

Treatment arm	Dose 1	Dose 2	Dose 3	Dose 4	Average doses received	Sample size
	Percentage of patients					
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	311
Combination immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	313

Administration costs for both combination immunotherapy and ipilimumab monotherapy included the cost of intravenous treatment delivery in an outpatient setting, and the cost of a full metabolic panel which was assumed to be carried out for all patients. The unit costs applied were obtained from NHS Schedule of Reference costs 2014-2015, and are presented in Table 72.[124]

Table 72. Administration costs for nivolumab and ipilimumab (CS, pg 169, Table 62)

Resource use element	Unit cost	Source[124]
Complex parenteral chemotherapy - 1st attendance	£329.32	NHS National Schedule of Reference Costs 2014-2015. (SB13Z)
Laboratory tests – complete metabolic panel	£1.19	NHS National Schedule of Reference Costs 2014-2015. (DAPS04)
Abbreviations in table: NHS, National Health Service.		

Vemurafenib and dabrafenib were included as comparators in the $BRAF^+$ population in line with the NICE Final Scope.[1] The dosage for dabrafenib was estimated based on data from the BREAK III trial[2], while it was based on the NICE single technology assessment TA269 for vemurafenib.[125] The doses and drug cost per administration are presented in Table 73 with and without the assumed drug cost in the PAS scenario analysis. The cost of oral chemotherapy was applied as a one-off administration cost at treatment initiation with BRAF inhibitors. This cost was assumed equal to £192.32 the cost of exclusive oral chemotherapy reported in the National Schedule of Reference Costs 2014-2015 (code SB11Z).

Table 73. Dosage and costs for BRAF inhibitors (CS, page 168-169, Table 60 and 61)

Drug	Dosing regimen	Dose per admin	Drug cost per admin	Drug cost per admin (including PAS)
Dabrafenib	300mg, daily oral	300mg	£200 per day	[redacted]
Vemurafenib	1920mg, daily oral	1920mg	£250 per day	[redacted]
Abbreviations in table: mg, milligram; PAS, patient access scheme.				

5.4.5.3 Nivolumab resource use based on time on treatment

Pharmacological resource use for nivolumab was based on time on treatment observed in the CheckMate 067 trial. The proportion of patients treated was limited to the proportion of patients alive, but was assumed not to depend on the proportion of patients in the PFS health state at each point in time.

A parametric survival analysis of the CheckMate 067 trial data was conducted, reported in Section 5.3.4 and Appendix 9 of the CS. The company stated that model selection was based on AIC, BIC and

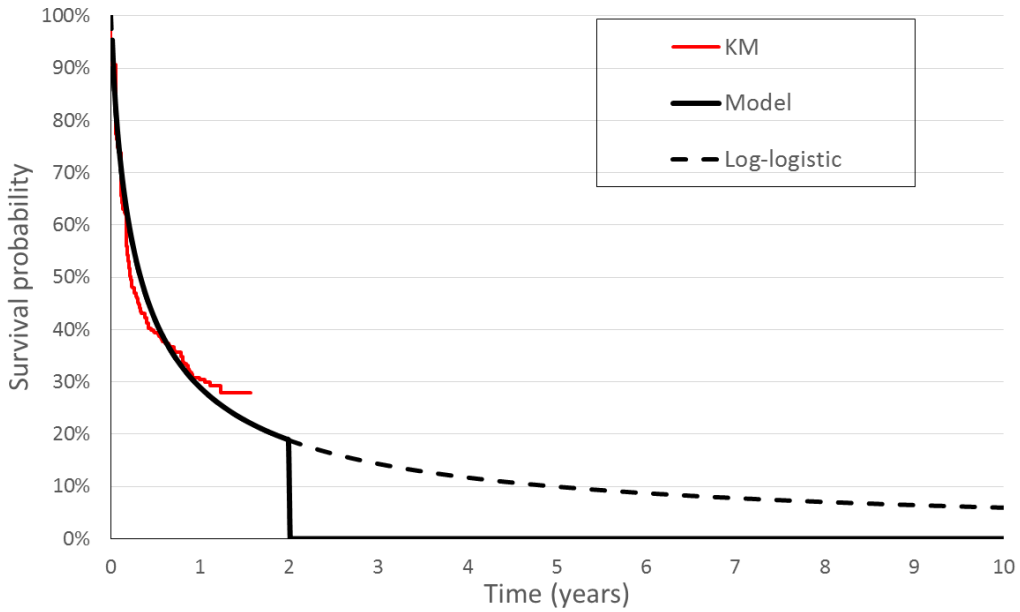
clinical validity; however, the AIC and BIC measures were not reported in the CS. The company reported the estimates of the parameters for the tested model, shown in Table 74.

Table 74. Model estimates for time on treatment (Appendix 9 of the CS, pg 89, Section 9.2)

Model parameter	Exponential	Weibull	Gompertz	Log-normal	Gamma	Log-logistic
ECOG: 0 vs ≥1	-0.443	0.603	-0.345	0.783	0.723	0.703
M stage: M1c vs 'M0 or M1a or M1b'	-0.041	0.028	-0.005	-0.262	-0.148	-0.182
Aged under 65: Yes/No	-0.109	0.130	-0.062	0.075	0.087	0.020
Sex: Male vs Female	-0.551	0.727	-0.428	0.656	0.693	0.650
History of brain metastases: Yes/No	-0.458	0.728	-0.457	0.395	0.591	0.813
High LDH: Yes/No	0.719	-0.934	0.538	-0.875	-0.915	-0.885
Shape	n/a	-0.508	-0.007	n/a	n/a	-0.216
Rate	-4.986	n/a	-4.268	n/a	n/a	n/a
Scale	n/a	4.835	n/a	n/a	n/a	4.226
Meanlog	n/a	n/a	n/a	4.168	n/a	n/a
Sdlog	n/a	n/a	n/a	0.792	n/a	n/a
Mu	n/a	n/a	n/a	n/a	4.409	n/a
Sigma	n/a	n/a	n/a	n/a	0.710	n/a
Q	n/a	n/a	n/a	n/a	0.344	n/a
Abbreviations in table: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; M, metastases.						

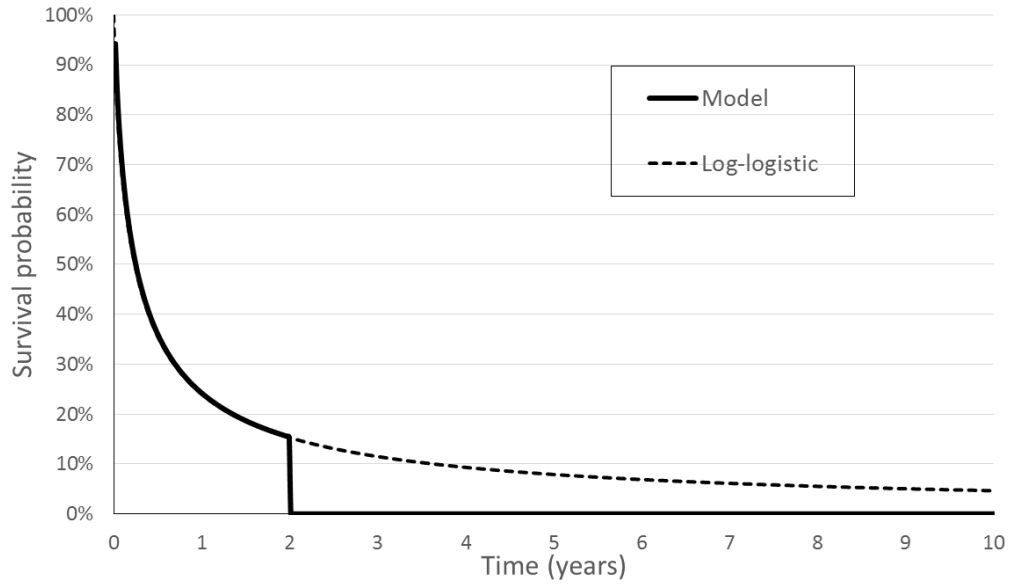
The company reported choosing a log-logistic parametric shape as, "it has the lowest AIC/BIC scores and has plausible prediction at the tail" (CS, pg 154, Section 5.3.4). The company used the OS as an upper limit for the proportion of patients on treatment, and assumed a maximum treatment duration of 2 years, "in line with expected clinical practice" (CS, pg 154, Section 5.3.4).

Figure 41. Log-logistic model used for the analysis of the BRAF^{-} subpopulation for time on treatment with nivolumab in the combination immunotherapy arm (CS, pg 154, Figure 57)



Covariate adjustment, based on the patient characteristics in the BRIM-3 trial, was included to account for the effect of differences at baseline between the trials for comparability purposes. The resulting model is shown in Figure 42. The adjustment resulted in a shorter average time on treatment compared to the BRAF^{-} subpopulation.

Figure 42. Adjusted log-logistic model used for the analysis of the BRAF^{+} subpopulation for time on treatment with nivolumab in the combination immunotherapy arm (CS, pg 155, Figure 58)



5.4.5.4 Treatment initiation and end of life costs

Resource use was assumed at treatment initiation and end of life based on the data collected in the MELODY study. MELODY was a longitudinal, observational study on healthcare resource utilisation associated with the treatment of individuals with melanoma in Italy, UK and France. Data were separately analysed and reported for a total of [redacted] UK patients with advanced melanoma.[126] These costs were applied as one-off costs in the model, at beginning of treatment and at death. Resource use estimates at treatment initiation are presented in Table 75.

Table 75. One-off resource use for treatment initiation (adapted from CS, pg 171, Table 63)

Resource use item	Unit cost	Percentage of patients	Resource use (number)	Source of costs
Outpatient visits				
Medical oncologist outpatient visit	£158.54	81.0%	3.6	NHS National Schedule of Reference Costs 2014-2015. Medical Oncology (Total OPATT service code 370)[124]
Radiation oncologist outpatient visit	£134.48	6.0%	2.3	NHS National Schedule of Reference Costs 2014-2015. Clinical Oncology Previously Radiotherapy (Total OPATT service code 800)[124]
General practitioner visit	£38.00	4.0%	2.0	PSSRU 2014: pg195 without qual. with indirect costs
Palliative care physician outpatient visit	£96.80	1.3%	1.0	NHS National Schedule of Reference Costs. Weighted average of total for SD04A and SD05A[124]
Psychologist outpatient visit	£138.00	0.5%	1.0	PSSRU 2014: pg183 per hour of client contact. 1 hour visit assumed[127]
Plastic surgeon outpatient visit	£92.69	2.0%	1.5	NHS National Schedule of Reference Costs 2014-2015. Plastic Surgery (Total OPATT service code 160)[124]
Inpatient (resource use and unit cost measured by days)				
Oncology/general ward – inpatient	£302.97	6.0%	2.8	NHS National Schedule of Reference Costs 2014-2015. Weighted average of excess bed days for elective and non-elective inpatients for all HRGs.[124]
Laboratory tests				
Complete blood count	£3.01	100.0%	1.2	NHS National Schedule of Reference Costs 2014-2015. Haematology (TOC currency code DAPS05)[124]
Complete metabolic panel	£1.19	100.0%	1.2	NHS National Schedule of Reference Costs 2014-2015. Clinical biochemistry (TOC currency code DAPS04)[124]
Lactate dehydrogenase	£1.19	100.0%	1.2	NHS National Schedule of Reference Costs 2014-2015. Clinical biochemistry (TOC currency code DAPS04)[124]
Radiological examinations				
CT scan (any)	£96.57	100.0%	1.0	NHS National Schedule of Reference Costs 2014-2015. Ave of total for RD20A/RD21A/RD22Z[124]
MRI of brain	£141.06	14.5%	1.0	NHS National Schedule of Reference Costs 2014-2015. Ave of total for RD01A/RD02A/RD03Z[124]

Resource use item	Unit cost	Percentage of patients	Resource use (number)	Source of costs
PET scan	£517.00	5.0%	1.0	NHS Reference costs 2014/2015. Positron Emission Tomography (PET), 19 years and over RN07A (Total HRG)[124]
Bone scintigraphy	£188.77	16.8%	1.0	NHS National Schedule of Reference Costs 2014-2015. Nuclear Bone Scan of two or three phases, 19 years and over RN15A (Total HRG)[124]
Echography	£55.39	4.5%	1.0	NHS National Schedule of Reference Costs 2014-2015. Average of total for RA23Z/RA24Z/RA25Z/RA26Z/RA27Z[124]
Chest x-ray	£102.03	17.5%	1.0	NHS National Schedule of Reference Costs 2014-2015. Contrast Fluoroscopy Procedures with duration of less than 20 minutes RA16Z (Total HRG) [124]
Abbreviations in table: CT, computerised tomography; HRG, health resource group; IV, intra-venous; MRI, magnetic resonance imaging; NHS, National Health Service; NSAID, non-steroidal anti-inflammatory drugs; PET, positron emission tomography; TOC:, total other currencies..				

A cost associated with end of life care was attributed to patients transitioning to the death health state. A total of 23.1% of patients were assumed to die in a hospice [126] for a cost of £6773.20 per patient. The cost of hospice stay was obtained from a 2008 report [128] analysing costs at the end of life in the UK, and then adjusted to 2014-2015 prices using inflation indices reported by the PSSRU.[129]

5.4.5.5 Follow-up costs (pre-palliative and palliative care)

Follow-up resource use and costs were based on the data from the MELODY study.[126] They were applied to patients depending on time since treatment initiation: first, second, and third and subsequent years after treatment initiation. Palliative care costs were attributed to patients in the twelve weeks before death. The following components were part of the follow-up costs: inpatient care, outpatient visits, laboratory tests, radiological tests and pain control medication. Monthly resource use and costs estimates are presented in Table 76 and Table 77, respectively for the time since treatment initiation and palliative care.

Table 76. Resource use and costs for pre-palliative care (adapted from CS, pg 173, Table 64)

Resource use item (monthly)	Unit cost	Year 1		Year 2		Year 3 and beyond		Source
		% patients	Monthly use	% patients	Monthly use	% patients	Monthly use	
Outpatient								
Medical oncologist outpatient visit	£158.54	79.3%	1.9	39.6%	1.9	23.8%	1.9	NHS National Schedule of Reference Costs 2014-2015. Medical Oncology (Total OPATT service code 370)[124]
Radiation oncologist outpatient visit	£134.48	6.0%	1.0	3.0%	1.0	1.8%	1.0	NHS National Schedule of Reference Costs 2014-2015. Clinical Oncology Previously Radiotherapy (Total OPATT service code 800)[124]
General practitioner visit	£38.00	4.0%	2.0	2.0%	2.0	1.2%	2.0	PSSRU 2014: pg195 without qual. with indirect costs[127]
Plastic surgeon outpatient visit	£92.69	2.0%	1.5	1.0%	1.5	0.6%	1.5	NHS National Schedule of Reference Costs 2014-2015. Plastic Surgery (Total OPATT service code 160)[124]
Nurse visit	£37.26	12.5%	1.0	6.3%	1.0	3.8%	1.0	NHS National Schedule of Reference Costs 2014-2015. District Nurse, Adult, Face to face (TOC currency code N02AF)[124]
Inpatient (resource use and unit cost measured by days)								
Oncology/general ward – inpatient	£302.97	5.0%	1.3	2.5%	1.3	1.5%	1.3	NHS National Schedule of Reference Costs 2014-2015. Weighted average of excess bed days for elective and non-elective inpatients for all HRGs.[124]

Resource use item (monthly)	Unit cost	Year 1		Year 2		Year 3 and beyond		Source
		% patients	Monthly use	% patients	Monthly use	% patients	Monthly use	
Laboratory tests								
Complete blood count	£3.01	100.0%	1.3	50.0%	1.3	30.0%	1.3	NHS National Schedule of Reference Costs 2014-2015. Haematology (TOC currency code DAPS05)[124]
Complete metabolic panel	£1.19	95.0%	1.3	47.5%	1.3	28.5%	1.3	NHS National Schedule of Reference Costs 2014-2015. Clinical biochemistry (TOC currency code DAPS04)[124]
Lactate dehydrogenase	£1.19	95.0%	1.3	47.5%	1.3	28.5%	1.3	NHS National Schedule of Reference Costs 2014-2015. Clinical biochemistry (TOC currency code DAPS04)[124]
Radiological examinations								
CT scan (any)	£96.57	£96.57	£96.57	£96.57	£96.57	£96.57	£96.57	NHS National Schedule of Reference Costs 2014-2015. Ave of total for RD20A/RD21A/RD22Z[124]
MRI of brain	£141.06	£141.06	£141.06	£141.06	£141.06	£141.06	£141.06	NHS National Schedule of Reference Costs 2014-2015. Ave of total for RD01A/RD02A/RD03Z[124]
PET scan	£517.00	£517.00	£517.00	£517.00	£517.00	£517.00	£517.00	NHS Reference costs 2014/2015. Positron Emission Tomography (PET), 19 years and over RN07A (Total HRG)[124]
Bone scintigraphy	£188.77	£188.77	£188.77	£188.77	£188.77	£188.77	£188.77	NHS National Schedule of Reference Costs 2014-2015. Nuclear Bone Scan of two or three phases, 19 years and over RN15A (Total HRG)[124]
Echography	£55.39	£55.39	£55.39	£55.39	£55.39	£55.39	£55.39	NHS National Schedule of Reference Costs 2014-2015. Ave of total for

Resource use item (monthly)	Unit cost	Year 1		Year 2		Year 3 and beyond		Source
		% patients	Monthly use	% patients	Monthly use	% patients	Monthly use	
								RA23Z/RA24Z/RA25Z/RA26Z/RA27Z[124]
Chest x-ray	102.03	27.5%	1.1	13.8%	1.1	8.3%	1.1	NHS National Schedule of Reference Costs 2014-2015. Contrast Fluoroscopy Procedures with duration of less than 20 minutes RA16Z (Total HRG) [124]
Abbreviations in table: CT, computerised tomography; IV, intra-venous; MRI, magnetic resonance imaging; NHS, National Health Service; NSAID, non-steroidal anti-inflammatory drugs; OPATT, outpatient attendance; PET, positron emission tomography; TOC, total other currencies.								

Table 77. Resource use and costs for palliative care (adapted from CS, pg 173, Table 64)

Resource use item	Unit cost	% Patients	Monthly resource use	Source
Outpatient				
Medical oncologist outpatient visit	£158.54	62.3%	0.9	NHS National Schedule of Reference Costs 2014-2015. Medical Oncology (Total OPATT service code 370)[124]
Radiation oncologist outpatient visit	£134.48	7.0%	1.5	NHS National Schedule of Reference Costs 2014-2015. Clinical Oncology Previously Radiotherapy (Total OPATT service code 800[124]
General practitioner visit	£38.00	78.5%	1.9	PSSRU 2014: pg195 without qual. with indirect costs[127]
Palliative care physician outpatient visit	£96.80	23.0%	1.2	NHS National Schedule of Reference Costs 2014-2015. Weighted average of total for SD04A and SD05A[124]
Psychologist outpatient visit	£138.00	3.5%	3.0	PSSRU 2014: pg183 per hour of client contact. 1 hour visit assumed[127]
Inpatient (resource use and unit cost measured by days)				
Oncology/general ward – inpatient	£302.97	13.0%	3.6	NHS National Schedule of Reference Costs 2014-2015. Weighted average of excess bed days for elective and non-elective inpatients for all HRGs. [124]
Palliative care unit – inpatient	£180.05	24.5%	4.0	NHS National Schedule of Reference Costs 2014-2015. Ave of total for SD01A and SD03A[124]

Resource use item	Unit cost	% Patients	Monthly resource use	Source
Home care				
Palliative care physician – home care	£124.00	21.8%	1.0	PSSRU 2014: pg111 Outpatient - non medical specialist palliative care attendance (adults and children)[127]
Palliative care nurse – home care	£78.67	61.0%	1.4	NHS National Schedule of Reference Costs 2014-2015. Specialist Nursing, Palliative/Respite Care, Adult, Face to face (TOC currency code N21AF[124]
Home aide visits	£153.00	25.5%	7.3	PSSRU 2014: pg111 Outpatient - medical specialist palliative care attendance (adults and children)[124]
Radiological examinations				
CT scan (any)	£96.57	3.8%	1.0	NHS National Schedule of Reference Costs 2014-2015. Ave of total for RD20A/RD21A/RD22Z[124]
MRI of brain	£141.06	1.3%	1.0	NHS National Schedule of Reference Costs 2014-2015. Average of total for RD01A/RD02A/RD03Z[124]
Chest x-ray	£102.03	1.3%	1.0	NHS National Schedule of Reference Costs 2014-2015. Contrast Fluoroscopy Procedures with duration of less than 20 minutes RA16Z (Total HRG) [124]
Pain control				
Morphine – Oral	£10.88	51.0%	1.0	Oxford outcomes Melanoma Resource Use report,[126] PSSRU 2014 [127]
Morphine – IV	£118.00	22.0%	1.0	Oxford outcomes Melanoma Resource Use report,[126] PSSRU 2014[127]
Morphine – Transdermal patch	£40.31	15.0%	1.0	Oxford outcomes Melanoma Resource Use report,[126] PSSRU 2014[127]
NSAIDs (Ibuprofen)	£0.75	47.5%	1.0	Oxford outcomes Melanoma Resource Use report,[126]
Other – Paracetamol	£4.60	36.0%	1.0	PSSRU 2014[127]
Abbreviations in table: CT, computerised tomography; IV, intra-venous; MRI, magnetic resonance imaging; NHS, National Health Service; NSAID, non-steroidal anti-inflammatory drugs; OPATT; PET, positron emission tomography; TOC, total other currencies.				

A summary of costs estimated for all the health states is presented in Table 78.

Table 78. Health states and associated costs (CS, pg 175, Table 65)

Defined health states	Value
Treatment initiation – one off	£740.77
Year 1 (per week)	£96.80
Year 2 (per week)	£48.40
Year 3 and beyond (per week)	£29.04
Palliative care period – 12 weeks before death (per week)	£217.16
End of life care – one off	£1,463.89

5.4.5.6 Treatment-related adverse event costs

The resource use for treating TRAEs was based on patient-level CheckMate 067 trial data analysis and considered for endocrine disorder (any grade), diarrhoea (Grade 2+) and other AEs (Grade 3+).[80]. The resources contributing to costs considered by the company were TRAE-related hospitalisations and outpatient visits.

The unit costs and respective sources for the cost of inpatient stays and outpatient visits are presented in Table 79. These were applied to the number of hospital days and outpatient visits in each treatment arm.

Table 79. Treatment-related adverse event costs (CS, pg 175, Table 66)

Items	Value	Reference
Hospital stay for endocrine disorders (day)	£255.35	NHS National Schedule of Reference Costs 2014-2015 (Other Endocrine Disorders with CC Score 4+ (KA08A)(Non elective excess bed days)[124]
Hospital stay for other TRAEs (day)	£295.80	NHS National Schedule of Reference costs 2014-2015 (Non Elective Inpatients - Excess Bed Days (NEL_XS)[124]
Unit cost for outpatient visit (endocrine disorder)	£413.17	Oxford Outcomes Report[85]
Unit cost for outpatient visit (diarrhoea)	£575.98	
Unit cost for outpatient visit (other TRAEs)	£348.75	
Abbreviations in table: CC, complication or comorbidity; NHS, National Health Service, TRAE, treatment-related adverse event.		

An average per-patient TRAE-related cost was calculated for each treatment arm, taking into account the proportion of patients experiencing the events. A summary of the resulting costs is presented in Table 80. TRAE costs were applied to patients alive and on treatment upfront at treatment initiation and then again at 54 weeks, which is the mean follow-up for patients in the CheckMate 067 trial.[80]

As none of the ipilimumab patients was still on treatment at week 54, the TRAE costs were applied only at treatment initiation for the ipilimumab arm of the models (in both subpopulations).

Table 80. Summary of per patient TRAE costs in the economic model (CS, pg176, Table 67)

Cost component	Combination immunotherapy	Ipilimumab	Dabrafenib	Vemurafenib
Hospitalisation costs – endocrine disorder (any grade)	£158.27	£35.31	£0.00	£0.00
Hospitalisation costs – diarrhoea (Grade 2+)	£388.42	£333.85	£0.00	£98.46
Hospitalisation costs – other TRAEs (Grade 3+)	£993.25	£510.76	£605.13	£841.50
Hospitalisation costs – subtotal	**£1,539.93**	**£879.91**	**£605.13**	**£939.96**
Outpatient costs – endocrine disorder (any grade)	£31.62	£11.85	£0.00	£0.00
Outpatient costs – diarrhoea (Grade 2+)	£27.21	£20.62	£0.00	£6.08
Outpatient costs – other TRAEs (Grade 3+)	£29.66	£16.18	£19.17	£26.65
Outpatient costs – subtotal	**£88.48**	**£48.65**	**£19.17**	**£32.74**
Total cost	**£1,628.42**	**£928.56**	**£624.29**	**£972.70**
Abbreviations in table: TRAE, treatment-related adverse events.				

5.4.5.7 Subsequent treatment costs

The proportion of patients receiving subsequent therapies after discontinuing first treatment was estimated based on data from CheckMate 067 for combination immunotherapy and ipilimumab[80], and from the BRIM-3 trial for BRAF inhibitors.[3] Subsequent therapies included: ipilimumab, dabrafenib, vemurafenib and pembrolizumab. BRAF+ patients, receiving BRAF inhibitors as first line treatment were assumed to only have ipilimumab as second line treatment option. The assumed proportions of patients receiving subsequent therapies in the model and details of how costs were estimated are presented in Table 81 and Box 24, respectively.

Table 81. Proportions of patients receiving subsequent therapies (CS, pg 176, Table 68)

Sequence	Ipilimumab	Dabrafenib	Vemurafenib	Pembrolizumab
$BRAF^-$ patients				
After combination immunotherapy	4.7%	0.9%	0.0%	4.7%
After ipilimumab	1.8%	0.9%	0.9%	34.4%
$BRAF^+$ patients				
After combination immunotherapy	3.0%	19.8%	11.9%	1.0%
After ipilimumab	1.0%	36.1%	27.8%	17.5%
After dabrafenib	22.0%*	0.0%	0.0%	0.0%
After vemurafenib	22.0%*	0.0%	0.0%	0.0%

Sequence	Ipilimumab	Dabrafenib	Vemurafenib	Pembrolizumab
Notes: * the values were found not to correspond with the referenced publication by McArthur *et al.*, where a value of 18% was reported.[3]				

Box 24. Estimation of cost of subsequent therapy in economic model (CS, pg 177, Section 5.5.5)

These one-off costs were applied to the patients who discontinue treatments in the model and the estimated proportions of patients using each drug as subsequent treatment (see Table 68). The mean number of ipilimumab doses used for previously treated patients is 3.3 which was based on the NICE TA268. The mean duration of treatment was assumed to be 7 months for vemurafenib based on the costing template from NICE TA269. The same treatment duration was used for dabrafenib due to absence of alternative data. The mean number of pembrolizumab doses was assumed to be 13.3 which was based on the reported mean life years of 0.762 in the pre-progression state for previously treated patients in the pembrolizumab arm in NICE TA357.

Abbreviations in box: NICE, National Institute of Health and Care Excellence.

A breakdown of costs and the total for each subsequent therapy are presented in Table 82.

Table 82. Cost of subsequent treatment use (CS, pg 177, Table 69)

Resource use element	Value	Sources
Ipilimumab		
Mean duration (doses)	[redacted]	NICE TA268[69]
Drug cost	[redacted]	Same as first line calculation
Administrative cost	£1,091	Same as first line calculation
Adverse event cost	£929	Same as first line calculation
Total	[redacted]	
Dabrafenib		
Mean duration (day)	213.1	Assumed same as vemurafenib
Drug cost	£42,612	Same as first line calculation
Administrative cost	£192	Same as first line calculation
Adverse event cost	£624	Same as first line calculation
Total	**£43,429**	
Vemurafenib		
Mean duration (day)	213.1	NICE TA269[125]
Drug cost	£53,266	Same as first line calculation
Administrative cost	£192	Same as first line calculation
Adverse event cost	£973	Same as first line calculation
Total	**£54,431**	
Pembrolizumab		
Mean duration (doses)	13.3	NICE TA357[28]

Resource use element	Value	Sources
Drug cost	£64,180	Same as first line calculation
Administrative cost	£4,380	Same as first line calculation
Adverse event cost	£624	Assumed same as dabrafenib
Total	**£69,184**	

5.4.6 Discounting

Discounting was applied at each weekly cycle. The company used an annual discount rate of 3.5% for both costs and health effects, in line with the NICE Reference Case.[81]

5.4.7 Sensitivity analysis

The company performed deterministic and probabilistic sensitivity analyses around the base case, as well as deterministic scenario analyses by testing the robustness of the results to variations in the base case scenario assumptions. Results from the company's sensitivity analyses were reported in Section 5.8 of the CS. The company reported the results from deterministic sensitivity analyses (DSA) both as ICERs and incremental net benefits (INB), calculated assuming a willingness to pay threshold of £50,000 per QALY.

The results of the company's deterministic and probabilistic sensitivity analyses are reported in Section 5.6.2.

5.4.8 Model validation

The company reported that several methodologies and inputs used in the economic model were validated by health economics and clinical experts. The validated model aspects and the feedback incorporated into the analyses are reported in Box 25.

Box 25. Model validation (CS, pg 213, Section 5.9)

The following key aspects of the model methods and inputs were validated by health economics and clinical experts:

- The Markov state-transition method to estimate OS and PFS using TTP, PPS and PrePS;
- Extrapolation beyond trial period and the use of external data for long-term survival;
- The modelling of time on treatment for nivolumab within the [combination immunotherapy] arm and the treatment continuation rule;
- The use of utilities derived from the pivotal clinical trial based on progression status;
- Modelling costs and resource use (excluding drug costs) for advanced melanoma patients; and
- Modelling impacts of safety and AEs on resource use and utilities.

The experts were in agreement with the modelling methods, and the key feedback for other aspects

has been incorporated into the analysis, including:

- The use of external long-term survival evidence so that modelled long-term survival for immunotherapy is in line with published long-term clinical data;
- The use of a clinically plausible and practical treatment continuation rule for nivolumab within the [combination immunotherapy] arm;
- Modelling resource use to reflect longer survival of advanced melanoma patients and the potential decreased resource use over time of long-term survivors;
- The use of resource use data collected within trials for modelling AEs and the importance of capturing all serious AEs.

Abbreviations in box: AE, adverse event; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival; TTP, time to progression.

The company compared the ipilimumab OS estimations from the economic model and from a pooled analysis of trial data reported by Schadendorf *et al*.[4] The company reported that, "The OS estimated by the model for ipilimumab […] has a similar shape and is broadly comparable with the observed OS in clinical trials" (CS, pg 214, Section 5.9).

5.5 Critique of the company's economic evaluation

5.5.1 NICE reference case checklist

Table 83 and Table 84 summarise the ERG's quality assessment of the company's economic evaluation. Table 83 summarises the ERG's appraisal of the economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope outlined in Section 3.[1] Table 84 reports the ERG's appraisal of the company's *de novo* economic models using the Philips checklist.[130]

Table 83. NICE reference case checklist for the base case analysis

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes.
Comparator(s)	Alternative therapies routinely used in the NHS	No. Pembrolizumab was considered a relevant in the NICE Final Scope; however, it was not included as a comparator in the base case analysis presented in the CS. The company produced a scenario analysis including pembrolizumab as part of the clarification responses.[1]
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D.
Benefit valuation	Time-trade off or standard gamble	Not reported.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Data were collected during the CheckMate 067 RCT. Valuation methodology was not reported in the CS.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	A probabilistic sensitivity analysis around the base case was performed, however details regarding the parameters that were varied in the analysis were not provided.
Abbreviations used in the table: HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; RCT, randomised clinical trial.		

Table 84. Philips checklist[130]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2: Statement of scope/perspective	Stated correctly.
S3: Rationale for structure	The company stated clearly the rationale for the modelling structure chosen. A semi-Markov state-transition model was adopted because of the immaturity of the OS data from the CheckMate 067 trial. The company therefore modelled OS as a function of TTP, PrePS and PPS. PPS and the long-term extrapolation of PrePS were based on sources other than the phase III CheckMate 067 RCT.
S4: Structural assumptions	The company did not state clearly the structural assumptions. Under the modelling approach taken, the company implied surrogacy between TTP and OS over the entire time horizon.

Dimension of quality	Comments
	The company also implicitly assumed that PPS would depend on the time of progression only between model inception and year 3. Mortality in post-progression after year 3 was assumed to depend on model time, and not on time of progression.
S5: Strategies/ comparators	Combination immunotherapy (i.e. nivolumab and ipilimumab) was compared to: ipilimumab in $BRAF^-$ patients; to ipilimumab, vemurafenib and dabrafenib in $BRAF^+$ patients. The company did not include a comparative analysis against pembrolizumab in the CS, albeit this was included in the NICE Final Scope.
S6: Model type	Semi-Markov state-transition model.
S7: Time horizon	Lifetime horizon, defined as 40 years of maximum follow-up from treatment initiation.
S8: Disease states/pathways	The model included three health states: PFS, PPS and death. The health states considered are deemed appropriate and were validated by the ERG's clinical experts.
S9: Cycle length	Weekly cycles were chosen, and are deemed appropriate by the ERG.
Data	
D1: Data identification	The company updated systematic literature reviews that were carried out for previous submissions to identify evidence on cost-effectiveness, resource use, costs and health-related quality of life. Details of studies included in the original searches and update search were provided. The ERG deems the searches to be relevant and appropriate. Data from the studies identified in the HRQoL searches were not included in the model or in sensitivity analyses.
D2: Pre-model data analysis	Data analysis was performed using an indirect comparison to compare immunotherapies to BRAF inhibitors. The results were used to adjust the models resulting from parametric survival analysis by patients' baseline characteristics.
D2a: Baseline data	Baseline characteristics of $BRAF^-$ patients were based on baseline data in the CheckMate 067 trial, while for $BRAF^+$ patients they were based on BRIM-3 trial population.[2, 80]
D2b: Treatment effects	Data on short-term treatment effects of combination immunotherapy and ipilimumab were extracted from the double-blind phase III CheckMate 067 trial.[80] Long-term data were derived from: general population mortality, pooled analysis of ipilimumab trial data, parametric extrapolation of clinical data. Treatment effects for BRAF inhibitors were derived based on pivotal trial and integrated using an indirect comparison adjusting for patients' baseline characteristics.
D2c: Costs	Resource use for treatment of advanced melanoma was mainly based on a longitudinal observational study (MELODY) and was the best available data, and the ERG clinical experts confirmed that overall the estimates seemed fair. The ERG disagrees with the way a constant rate of dose reduction of 90.2% was assumed for nivolumab as part of combination immunotherapy when calculating drug costs in the model, when no evidence was provided to support this assumption. Costs were obtained from the National Schedule of Reference Costs and from the PSSRU database.[124, 127]
D2d: Quality of life weights (utilities)	The HRQoL weights adopted in the model were based on EQ-5D collected in the phase III trial CheckMate067.[80]
D3: Data incorporation	Data incorporation is not considered appropriate for the long-term PPS associated to combination immunotherapy and ipilimumab because of the chosen nesting structure. Short-term PPS depends on time of progression while long-term PPS depends on model time only. This associates substantially and implausibly longer PPS times to patients progressing later in model time.
Assessment of uncertainty	
D4a: Methodological	The ERG considers the methodological uncertainty associated with the chosen modelling structures (i.e. semi-Markov state-transition model; separation of PrePS and PPS components) to be substantial, given that very different results may be expected using different assumptions. This source of uncertainty was not explored by the

	company.
D4b: Structural	Structural uncertainty was assessed through a series of scenario analyses exploring the impact of changing assumptions based on pre-model data analysis, e.g. alternative survival parametric functions.
D4c: Heterogeneity	Uncertainty associated to heterogeneity was not assessed. Patients' baseline characteristics were not included in sensitivity analyses (e.g. PSA), leading to underestimating the uncertainty and variability in the results.
D4d: Parameter	Parametric uncertainty was explored through deterministic sensitivity analyses and a probabilistic sensitivity analysis around the base case. Patients' baseline characteristics, which influenced key efficacy outcomes through the adjustment of survival models, were not included in the analysis of the parametric uncertainty.
Consistency	
C1: Internal consistency	The model is generally sound. However, the ERG considers the nesting of long-term mortality in PPS to be inappropriate and producing results with no face validity, thus negating internal validity.
C2: External consistency	Appropriate. The model results were compared to trial data, which however had relatively short follow-up times compared to the lifetime horizon assumed in the model.
Abbreviations used in table: CS, company's submission; ERG, evidence review group; HRQoL, health-related quality of life; NHS, National Health System; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival; PSA, probabilistic sensitivity analysis; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; RCT, randomised clinical trial; TTP, time to progression.	

5.5.2 Modelling approach and model structure

The company based the choice of the modelling approach on the strategy used in the efficacy data analysis. The justification reported by the company for the modelling choice is reported in Box 26 (replicating Box 17).

Box 26. Company's justification for the modelling approach used for immunotherapies (CS, pg 85, Section 4.10)

> Mature OS data is not available for [combination immunotherapy], and therefore OS data from CheckMate 066 and MDX010-20 has been used as a proxy assuming equal efficacy between ipilimumab, nivolumab and [combination immunotherapy]. This assumption is unlikely to hold for OS, but when adopting a Markov state-transition approach, as used in the nivolumab monotherapy submission, only post-progression survival (PPS) relies on OS data, and the assumption of equal efficacy is considered conservative for PPS. Additionally, using this approach, and in particular PPS rather than OS, allows increased validity and robustness of survival extrapolations for long-term estimation of treatment effects when data are relatively immature (i.e. the do not reach the median survival point). As a result, the economic model has been designed to adopt a Markov-based state-transition approach using time to progression (TTP), pre-progression survival (PrePS), and PPS for modelling survival.

Abbreviations in box: OS, overall survival; PPS, post-progression survival; PrePS, pre-progression survival; TTP, time to progression.

The ERG finds this justification insufficient and imprecise to support the effectiveness modelling approach taken. In particular, the ERG's opinion is that:

- It is not correct that, "only post-progression survival relies on OS data", as pre-progression survival (PrePS) relies on OS data as well;
- The fact that a similar approach has been used in a previous submission is not a sufficient justification to support assumptions or methodologies;
- The statement, "using this approach […] allows increased validity and robustness of survival extrapolations for long-term estimation of treatment effects […]" is unjustified. In fact the proposed approach greatly increases both model complexity and the number of model parameters compared to a simpler approach such as partitioned survival modelling. As a result the two statistical modelling criteria of parsimony and interpretability are hardly respected;
- The impact of the methodological and parametric uncertainty arising from mixing together, integrating and extrapolating on a lifetime horizon several data sources and statistical models is vast and largely unexplored;
- The sentence, "the assumption of equal efficacy is considered conservative for PPS" is unjustified and the ERG strongly disagrees with it. In fact setting the same PPS for all treatments equates to imply a surrogacy assumption between TTP and OS, i.e. longer time without progression determines longer time alive. This hypothesis was not tested nor explicitly stated by the company. It has been observed that combination immunotherapy extends TTP, PFS and OS compared ipilimumab; however it has not been demonstrated that the extension in OS is determined by the longer TTP. The ERG would consider conservative to assume a reduced PPS for combination immunotherapy compared to ipilimumab, with the reduction directly proportional to the time elapsed since treatment initiation (i.e. model inception).

As such, the ERG finds that the company's analysis strategy might have favoured the treatment with the longer TTP, i.e. combination therapy, because of the non-justified surrogacy assumption between TTP and OS. However, the ERG is unable to separate the survival benefit due to the treatment effects and to the surrogacy assumption. The issue is discussed further in Section 5.5.5.3.

The ERG deems the cycle length and time horizon to have been chosen appropriately.

5.5.3 Population

The ERG sought clinical expert advice to assess the generalisability of the population modelled in the economic evaluation submitted by the company. The ERG's clinical experts confirmed that the population analysed in the CheckMate 067 and 069 trials were sufficiently similar to patients routinely seen in English clinical practice.

The company made ample use of survival models adjusted by patients' baseline characteristics in the indirect treatment comparison (Section 5.4.2). In particular the adjustment allowed the company to increase the degree of comparability of the effectiveness and cost-effectiveness profiles of the interventions in the $BRAF^+$ subpopulation.

The ERG notes that variations in the baseline characteristics had non-negligible effects on the prediction and extrapolation of clinical outcomes in the economic model. The ERG agrees with the reasons for the adjustment for prognostic factors. However the ERG also considers that the comparability was compromised by the use of two different modelling approaches for the two types of drug (i.e. immunotherapies and BRAF inhibitors). As such the ERG only looks at the $BRAF^-$ subpopulation for the comparison between combination immunotherapy. This approach is consistent with the company's assumptions of equal effectiveness associated to the immunotherapies regardless of BRAF status.

The ERG found an inconsistency in the company's model when looking at the $BRAF^+$ subpopulation, which did not seem to influence the results. The adjustment was partially based on the difference between the baseline characteristics of patients in the BRIM-3 trial and CheckMate 067 trial. The company did not hard-code the values associated with the CheckMate 067 trial in the model but linked them to the user-chosen baseline patients' profile for the $BRAF^-$ subpopulation (selected in the "Controls" sheet of the model). This implementation choice led to the results of the $BRAF^+$ subpopulation to change when only the baseline characteristics of the $BRAF^-$ subpopulation were varied.

5.5.4 Interventions and comparators

The company did not comply with the NICE Final Scope, as it did not include pembrolizumab as a comparator in the CS.[(1)] The exclusion was justified as reported in Box 27.

Box 27. Company's justification for the exclusion of pembrolizumab as a comparator intervention (CS, pg 14, Table 1)

> Pembrolizumab is not included in the current clinical pathway of care having only been recommended by NICE for use in NHS England after disease progression with ipilimumab in October 2015; and for use in patients not previously treated with ipilimumab in November 2015.
>
> Recent prescribing data indicate that there is virtually no pembrolizumab usage in a first-line setting and it is not

in routine use in clinical practice. Pembrolizumab is not therefore established standard of care for advanced melanoma in NHS England and thus is not a relevant comparator to [combination immunotherapy].
Abbreviations in box: NHS, National Health Service.

The ERG disagrees with the company's justification, with particular reference to Section 6.2 of the NICE Guide to the Methods of Technology Appraisal.[81] The ERG asked the company to provide a comparison of combination immunotherapy against pembrolizumab as part of the clarification questions. As a response, the company conducted a meta-analysis of the hazard ratios for OS and PFS based on the CheckMate 067, Keynote 006 and Keynote 002 trials to compare combination immunotherapy, ipilimumab and pembrolizumab (at two dosages, i.e. 10 mg/kg q3w and 2 mg/kg q3w). The results are discussed as part of the scenario analyses performed by the company in Section 5.6.2.3.

5.5.5 Treatment effectiveness

In this section the ERG focuses on the choice of data, extrapolation and modelling approach chosen to model treatment effectiveness in the company's model. Treatment effectiveness determined time spent by patients in the three health states of the model, i.e. PFS, PPS and death.

The ERG divides the section in four separate parts to appraise each component of the company's effectiveness modelling approach in detail. The first part of the section will be focused on the company's data analysis strategy. In the second the ERG looks at individual analyses performed on clinical data for all treatments and both subpopulations and at how the individual components contribute to the overall projection of the effectiveness of immunotherapies in the model. The third subsection is centred on the surrogacy assumption between TTP and OS. The final subsection is centred on the comparability and validity of the comparison between BRAF inhibitors and immunotherapies based on the different modelling approaches taken.

5.5.5.1 Company's data analysis strategy

Overall, the ERG finds that each individual piece of the data analysis was carried out reasonably and appropriately, reporting results and interpretations clearly.

In Section 4.10 of the CS, the company reported using the *flexsurv* R library to perform the analyses.[82, 83] However, it was not explained why the PPS model reported in Table 27, Section 4.10 of the CS, referred to the model parameterisation of the SAS software. When carrying out parametric survival analysis, the company tested six models according to the NICE DSU Technical Support Document 14.[63] The choice of the models tested is considered appropriate by the ERG, even though the company might have also included the generalised F model as this is implemented in the *flexsurv* library and would have required little additional effort in conducting the analysis.

The company included six baseline covariates, reportedly based on the meta-analysis by Korn *et al.*[19] As LDH levels were available for only 136 patients out of the total 2,100 patients, it was not considered in the analysis by Korn *et al.* Its inclusion in the company's models is therefore reasonable, as PLD from RCTs were available. However, the ERG notes that the results on the prognostic factors (other than LDH) identified by Korn *et al.* were not followed. The company included all prognostic variables considered in the analyses by Korn *et al.* instead of using the factors which resulted to have statistically significant associations with the outcomes. In the study by Korn *et al.*, the factors associated with the outcomes in multivariate regression models were:

- Performance status, presence of visceral disease, gender and presence of brain metastases for OS;

- Performance status, gender and age for PFS (a statistically significant interaction between performance status and age resulted in the 6-month PFS analysis).[19]

Additionally, the company ignored the following variables considered as trial-level parameters in the Korn *et al.* study: "exclusion of patients with liver metastases, exclusion of patients with visceral metastases, previous treatment for metastatic disease and the year during which accrual was completed".[19] The company implicitly assumed equivalence between the variable set the study by Korn *et al.* and the one used to perform the analyses. The two sets are reported in Table 85.

Table 85. Comparison of prognostic factors in the Korn *et al.* study and in the company's analysis

Parameter	**Korn *et al.*[19]**	**Company's analysis**
Age	Continuous variable	Dichotomous variable: Above or below 65 years of age
Gender	Dichotomous variable: Male or female	Dichotomous variable: Male or female
Disease	Dichotomous variable: Visceral disease or not	Dichotomous variable: M1c; or M0, M1a or M1b
Performance status	Three-level variable: ECOG PS 0, 1 or 2-3	Dichotomous variable: ECOG PS 0 or ≥1
Brain metastases	**Trial-level variable** Dichotomous variable: Inclusion or exclusion of patients with brain metastases	**Individual-level variable** Dichotomous variable: Brain metastases or not
LDH level	Not included	Dichotomous variable: Above or below ULN
Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; ULN, upper limit of normal (range).		

The ERG notes that the codification of the prognostics factors (with the exception of gender and LDH) did not correspond between the two analyses. In detail:

- Age was considered as a dichotomous variable. The company did not justify the choice of the 65 years of age cut-off value;

- Presence of visceral disease was assimilated to stage M1c, as opposed to stages M0, M1a or M1b. According to the AJCC melanoma staging and classification, using this categorisation the company mixed together Stage III patients (M0, i.e. no distant metastases; as the CheckMate RCTs included only Stage III or IV melanoma patients and that all Stage IV patients have distant metastases, these are only Stage III patients) and Stage IV patients with non-visceral metastases (M1a) and lung metastases (M1b). However lung metastases are visceral, and thus a categorisation more in line with the one used by Korn *et al.* wold have been to partition patients in 3 separate groups: M1b and M1c; M1a; and M0.[14, 19, 84] M0 patients should have been included separately as the analysis reported by Balch *et al.* 2001, showed that Stage III patients have a better prognosis compared to Stage IV patients[84];

- Performance status was grouped differently in the two analyses. A marked increase in the effect was reported in the study by Korn *et al.* for increasing levels of ECOG performance score.[131] This effect was not considered by the company, and no justification of the choice was reported in the CS;

- The Korn *et al.* study considered the exclusion of patients with brain metastases a trial-level covariate in the models.[19] The company used the presence of brain metastases as an individual-level covariate, without justifying the choice in the CS.

Additionally, the inclusion of the LDH levels as a covariate might have introduced collinearity in the models. This is because, according to the AJCC melanoma and staging classification, elevated LDH levels in Stage IV patients determine M1c categorisation.[14] In the CheckMate 067, 36.1% of patients resulted having elevated LDH, while 58.0% of all patients had metastasis stage M1c.[31] The company did not include in the CS any goodness of fit test, graphical analysis or other model statistics for the ERG to be able to evaluate further this issue. The potential presence of collinearity in the models would not be a problem for reasonably short extrapolations of the models or under the CheckMate 067 parameter values. However, it might have introduced severe bias in the long-term extrapolation of the outcomes under a different setting, in particular the $BRAF^{+}$ analysis, which included adjustment based on the BRIM-3 RCT baseline characteristics.[3]

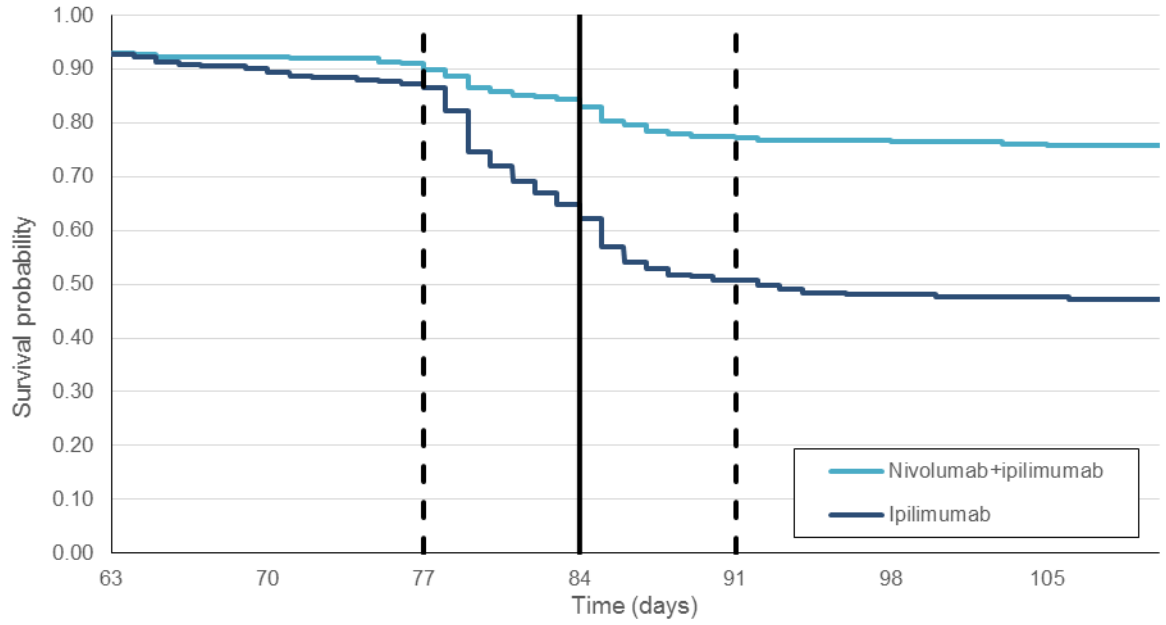
5.5.5.2 Company's survival analysis of efficacy outcomes

Time to progression data analysis

The analysis of the CheckMate 067 TTP trial data was performed by partitioning the Kaplan Meier curve in pre- and post-84 days since treatment initiation. This was because the first assessment of progression in the CheckMate 067 trial was scheduled at 12 weeks and in the company's interpretation caused an, "unrealistic clustering of progression time" (CS, pg 87, Section 4.10) at about 3 months since the start of the trial. In the company's analysis, the cut-off time point was set to exactly 12 weeks (i.e. 84 days). The ERG notes that the choice of this cut-off is inappropriate because:

- The study protocol reports that the first assessment was planned at 12±1 weeks;[31]
- The visual inspection of the Kaplan Meier curve, reported in Figure 43, clearly shows that the steep drop in the proportion of patients alive and not progressed is centred around 84 days, but reaches a plateau later in time.

Figure 43. Comparison of TTP Kaplan Meier curves at 77, 84 and 91 days



The ERG disagrees with the company's choice of the 84 days cut-off time point. In the ERG's opinion this should have been set either earlier in time (e.g. at 11 weeks, or 77 days), thus completely avoiding the cluster of events, or after the cluster, e.g. at 13 weeks, or 91 days. This choice is expected to influence substantially the parameter estimation for the post-cut off parametric model and therefore the extrapolation of outcomes over time. However, the company did not conduct any sensitivity analysis around this assumption.

A comparison of the survival estimates at 77, 84 and 91 days is presented in Table 86. In the ERG's opinion, the estimated probabilities highlight that the choice of setting the cut-off at 84 days was sub-optimal as it did not avoid the cluster of progression events.

Table 86. Comparison of survival estimates at 77, 84 and 91 days

Survival estimate at time	Combination immunotherapy	Ipilimumab
77 days	0.910	0.873
84 days	0.844	0.648
91 days	0.774	0.506
Note: time to progression Kaplan Meier estimates extracted from the curves reported in the company's electronic model.		

Time to progression: pre-84 days

The company modelled the pre-84 days TTP using the Kaplan Meier curves from CheckMate 067. These corresponded to the unadjusted curves in the $BRAF^-$ subpopulation, while they were adjusted based on the BRIM-3 trial characteristics in the $BRAF^+$ subpopulation. The adjustment was performed based on a Cox PH model, described in Section 5.4.2.2.

Based on the 84-day argument described above, it would be expected to see no difference between the lines, with very few or no progression events. The company did not provide any justification as to why progression events were assumed to occur prior to the first assessment at 12(±1) weeks in the model; the occurrence of events between day 77 and 84 is, in the ERG's opinion, in contradiction with the 84-days cut off approach taken by the company.

The PH assumption between treatments did not hold in the company's Cox model, as correctly noted. However, the global and covariate-specific PH assumptions were not tested, and it is unclear whether they are verified or not. The assumptions could not be tested by the ERG as the PLD were not available (nor were requested to the company).

Time to progression: post-84 days

The company carried out a parametric survival analysis. Model fit was assessed using relative fit statistics (i.e. AIC and BIC) and visual inspection. The ERG considers the analysis to have been carried out appropriately; however, residual analysis would have been informative to assess the behaviour of the parametric functions especially around the tails of the curves. The ERG notes that it is unclear whether the tail of the Kaplan Meier curve associated with combination immunotherapy might be suggestive of a "catch-up" effect, as the information observed in the trial was not sufficient to test for this effect (with a number of patients at risk equal to 60 and 7 patients at day 300 and 400, respectively).

The ERG notes that, had the cut-off date been different, the post-84 days parametric models might have been substantially different, and that even small differences in the effects would have influenced the extrapolated outcomes substantially.

In conclusion, the ERG is not satisfied with the TTP analysis carried out by the company, in particular given the lack of flexibility around the cut-off time assumption. The ERG considers that allowing for progression events to occur pre-cut off date is not consistent with the assumption of all patients having a first assessment at 84 days as described by the company.

Pre-progression survival

The company fitted a Cox PH model to the observed PrePS observed in the CheckMate 067 trial. The PH assumptions were not tested, but used in the covariate adjustment. Even though no difference was found between the treatment arms, the company assumed the existence of a difference between the curves during the follow-up period and then equal to the difference in the tails of the curves at the end of the maximum follow-up. Moreover, the general population mortality was not used as bound for the mortality rates during the CheckMate 067 follow-up period, even though there were very few patients at risk at later follow-up times. General population mortality rates were nested on the adjusted Kaplan Meier curves earlier on in the ipilimumab arm compared to the combination immunotherapy arm by about 1 month of model time, as described in Section 5.4.2.9.

The ERG disagrees with the company's approach for modelling PrePS. Very little information was contained in the Kaplan Meier curves and no difference between the two treatments emerged to both graphical analysis (Figure 27) and formal testing (via the Cox model, Table 50). A more reasonable approach would be to pool together the two curves and assume equal mortality between the treatments. This would remove the assumption of a PrePS survival benefit carried over along the entire time horizon which was not justified. Additionally, the age- and gender-matched general population mortality should have been set as a lower bound for the mortality rates. In the ERG opinion the assumption of an extrapolated survival benefit equal to the difference in the tails of the curves is inappropriate.

The company assumed that long-term pre-progression survival would be equal to the general population mortality. This assumption implies that patients with advanced, metastatic melanoma, alive and not progressed after about 2 years, would have the same mortality rate as the age- and gender-matched general English population. The expected survival in PrePS projected in the company's base case model is reported in Table 87.

Table 87. Average progression-free survival time for immunotherapies compared to matched general population

Expected survival (years)	BRAF- subpopulation	BRAF+ subpopulation

Combination immunotherapy	20.01	24.23
Ipilimumab	18.73	22.41
Matched general population	21.77	26.92
Note: average times estimated based on the area under the PrePS curve in the company's base case.		

In the ERG's opinion, these estimates are overly optimistic. However, given the company's modelling choice of separating the PrePS and PPS components of the OS, it is not possible to easily compare survival times as external sources do not report the two measures separately. The projected pre-progression survival over the model time horizon projected in the company's base case is shown in Figure 44 and Figure 45, respectively for the $BRAF^-$ and the $BRAF^+$ subpopulation. As the survival associated with BRAF inhibitors was modelled using a different approach, it is not directly comparable to immunotherapies for $BRAF^+$ patients.

Figure 44. PrePS for immunotherapies in the $BRAF^-$ subpopulation

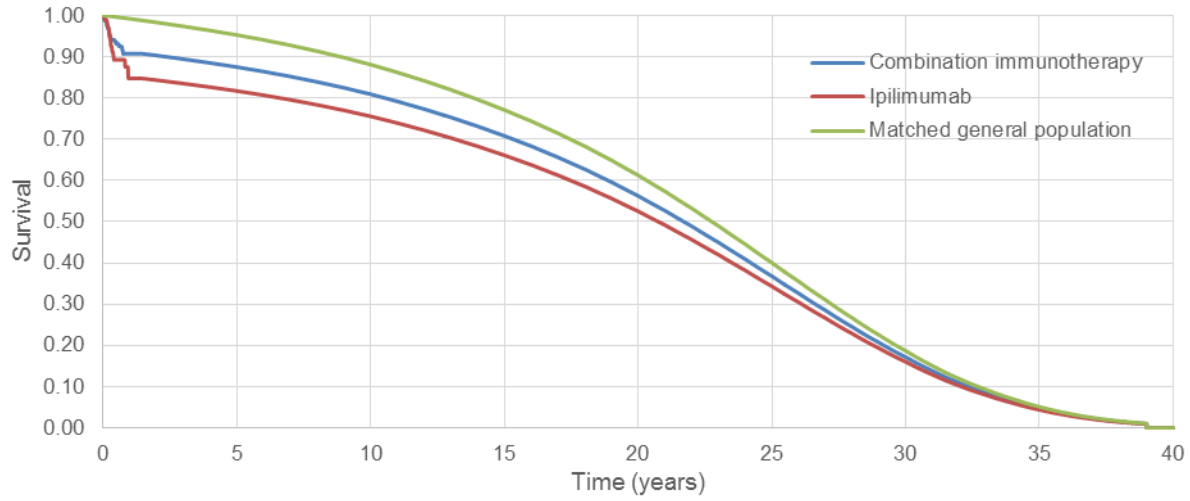
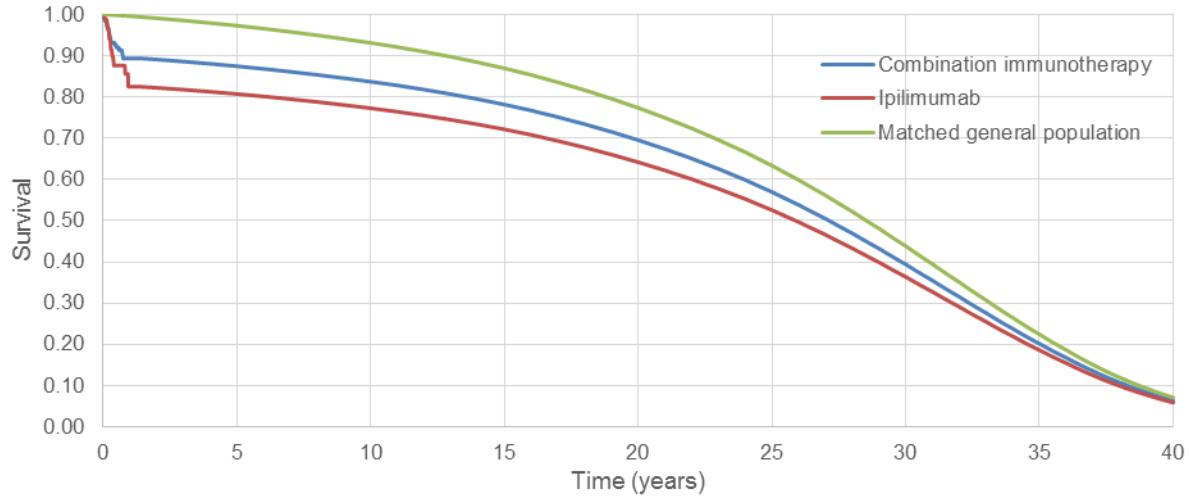


Figure 45. PrePS for immunotherapies in the $BRAF^+$ subpopulation



Post-progression survival

The company assumed equal post-progression survival for ipilimumab and combination immunotherapy. PPS was based on a log-logistic model as described in Section 5.4.2.5.

As already mentioned in Section 5.5.2, the ERG disagrees with the company's statement that, "It is conservatively assumed that PPS is the same for all immunotherapies" (CS, pg 143, Section 5.3.2). While the assumption would be conservative *per se*, it is not in the context of the sequentiality of the health states in the semi-Markov model. This is because survival depends on a combination of treatment-specific factors, specifically PrePS and TTP. An assumption of equal PPS among immunotherapies would imply an assumption of surrogacy between TTP and OS, i.e. an extension in TTP would translate into an extension in OS. This assumption was not explicitly stated, justified or proved by the company, and is not considered a conservative assumption by the ERG.

The company assumed that the log-logistic curve would be used to estimate mortality for the first 3 years of the model, and not the first 3 years since occurrence of progression. After 3 years, PPS was determined by ipilimumab long-term mortality data, rebased at 3 years where a plateau in mortality was observed. Given the steep drop in survival in the first weeks, this produced an increased PPS over time; this effect which was not explored by the company. Additionally, the log-logistic curve was applied at time of progression, i.e. the mortality rate for the i^{th}cycle after progression was determined based on the rate calculated based on the i^{th} weekly portion of the curve. The long-term PPS was applied differently, as after 3 years the mortality rate for the j^{th} cycle of the model, and not for the j^{th} after progression (with time at cycle $j >$3 years), was determined by the rate calculated based on the j^{th} portion of the curve. That is, the short-term mortality (i.e. based on the log-logistic curve estimated from trial data) depended on time since progression, but the long-term mortality did not, as it depended only on model time.

Figure 46. PPS curves at different times of progression (BRAF$^-$ patients)

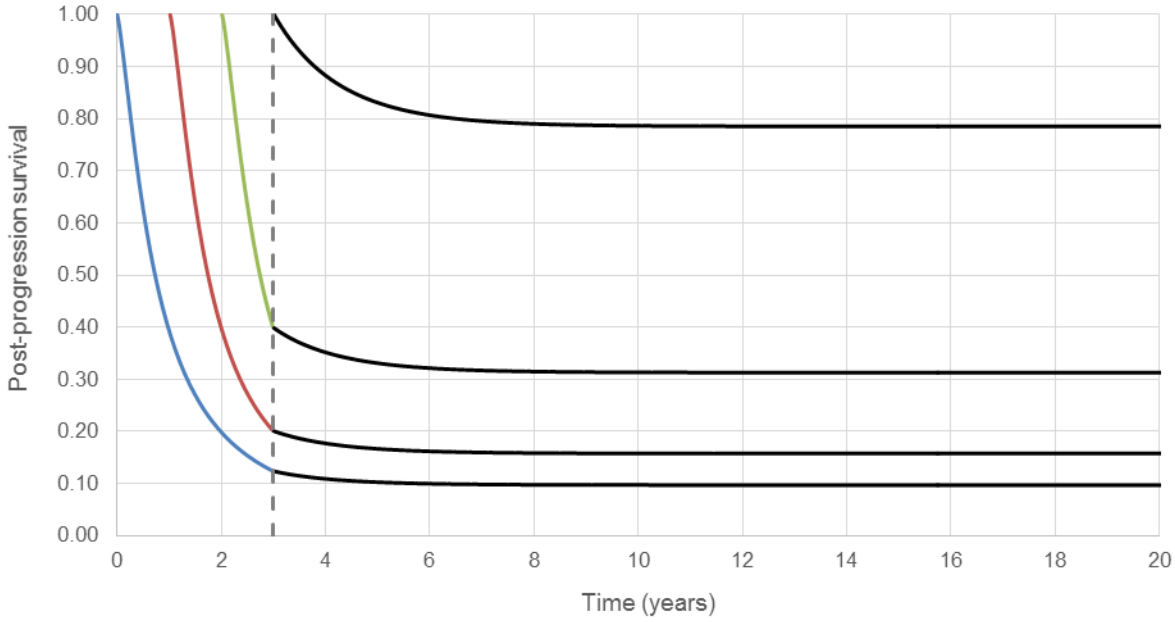
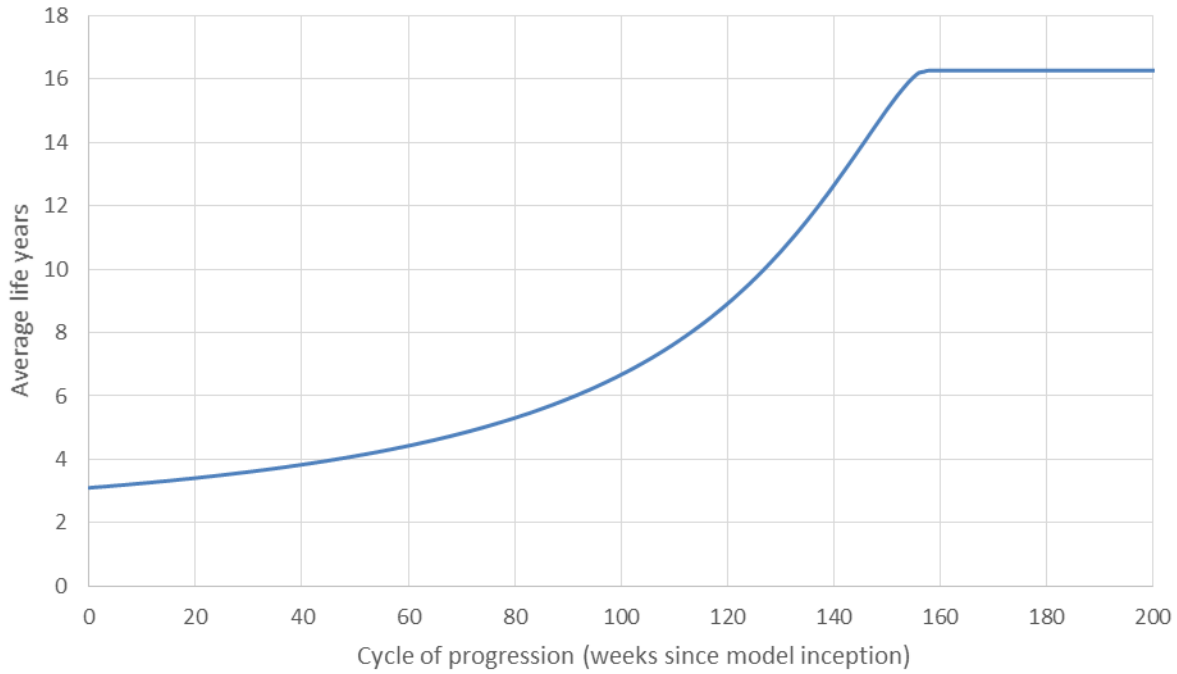


Figure 46 shows the PPS applied in the company's base case (for the BRAF$^-$ subpopulation). The first part of the curves (coloured) depends on time since progression, while the second portion (black) depends only on time since model inception. It is clear how patients progressing later would be expected to live in the post-relapse health state considerably longer than early-progressing patients.

This inconsistent integration of the two curves produced average PPS times increasing with the time at which patients progress, as the long-term mortality plateau (from the ipilimumab long-term mortality) would be applied earlier to patients progressing later in time. This effect was not explored by the company in the CS. The average years of life projected for progressed patients by time of progression are shown in Figure 47. The average life years were calculated by the ERG based on the area under the survival curves by cycle of progression in the company's model. The same holds for BRAF$^+$ patients although the estimates (not shown) differ slightly due to the short-term PPS covariate adjustment.

Figure 47. Average PPS life years by cycle of progression for BRAF^{-} patients



As a consequence of this modelling choice, mortality in post-progression is not equal between immunotherapies as it has been demonstrated to depend on TTP, even though this assumption was not reported, justified or demonstrated by the company. The ERG also notes that statements such as, "It is conservatively assumed that PPS is the same for all immunotherapies" (CS, pg 143, Section 5.3.2) are misleading or incorrect, depending on the interpretation. Strictly speaking the PPS inputs are the same for all immunotherapies, however the model-predicted PPS or PPS outputs, being dependent on TTP, are different between them and the average PPS time associated with combination immunotherapy is substantially longer than the one for ipilimumab in both subpopulations.

As this assumption arising from the modelling choice was not clearly stated and justified, the ERG considers it an unwanted artefact of the implementation in the model and as such an error.

Efficacy of BRAF inhibitors

The ERG considers the survival analysis, including the pseudo-PLD generation from literature, to be appropriate and clearly reported. Even though a long-term curve was attached to the OS curve estimated form the BRIM-3 trial, the methodology does not suffer from the same inconsistency discussed for the immunotherapy PPS in Section 5.5.5.2. This is because model time- and time lag-dependent curves were not mixed. The company did not explain nor justify clearly why a different data source for long-term mortality was used for the BRAF inhibitors and the immunotherapies other than, "because no OS trial data exist for the BRAF inhibitors after 3 years" and, "registry survival data for Stage IV reported by Balch *et al.* was used as the melanoma registry OS because it provides data with the longest follow-up period, 15 years" (CS, pg 151, Section 5.3.3). The same cut-off time

point of 3 years used in the immunotherapy PPS extrapolation was chosen for the long-term BRAF inhibitors OS curve nesting. The company did not justify the choice of the nesting time point of 3 years.

5.5.5.3 Surrogacy assumption for immunotherapies

The company's modelling approach to treatment effectiveness implies a surrogacy assumption between TTP (or PFS) and OS, which was neither stated nor justified explicitly in the CS. In particular this is verified in two aspects:

1. The base case model-predicted PPS was found to vary based on time of progression, with a longer TTP corresponding to a longer projected life in post-progression;

2. The model structure, through the health state transition structure, defines mortality as a function of TTP, as the probability of moving to the post-progression health state, associated with higher mortality (particularly for quickly progressing patients) compared to the PFS health state.

The ERG finds that the company did not provide sufficient evidence to support the surrogacy assumption between TTP and OS. This assumption was hard-wired into the company's model for immunotherapies because of the modelling approach adopted.

5.5.5.4 Comparison across different modelling approaches in the BRAF+ subpopulation

As described, among others, in Section 5.4.1 and Section 5.4.2.9, the company compared immunotherapies and BRAF inhibitors in the $BRAF^+$ subpopulation using two different modelling approaches: a semi-Markov model (modelling transition between the health states) for immunotherapies and a partitioned survival model (modelling health state occupancy) for the BRAF inhibitors.

The main difference between these two approaches is that the surrogacy assumption between TTP and OS was present only in the semi-Markov model, and that there was no difference in mortality between progressed and non-progressed patients in the partitioned survival model. Therefore the ERG does not consider the comparison to produce robust results as the exogenous effect associated to the different modelling approach was not taken into account. The results are not considered probative of the comparative cost-effectiveness but constitute an exploratory analysis of the profiles of the interventions.

The ERG notes that it cannot be determined with certainty whether one of the two modelling approach produced results more favourable than the other.

5.5.6 Adverse events

The company included the following treatment-related adverse events (TRAEs) in the model: endocrine disorders of any grade, diarrhoea (grade 2 or higher) and all other grade 3 adverse events. The 'other' grade 3 TRAEs were included regardless of the proportion of patients experiencing them in order to take a more conservative approach. The ERG's clinical experts confirmed that the TRAEs included in the model were sufficient and reflect what they would see in clinical practice.

The rates of adverse events were based on data collected on all patients who received treatment in the CheckMate 067 trial. The ERG identified a discrepancy between the CS and the CSR in the proportion of ipilimumab patients who experienced endocrine disorders when comparing the model and the value reported in Table 8.1-2 of the CheckMate 067 trial CSR. The CSR reported [redacted] while a value equal o 11.3% was used in the model.[80]

The ERG considers the approach taken by the company to incorporate TRAEs in the model to be reasonable but not particularly accurate.

5.5.7 Health-related quality of life

The health state utility values in the model were based on EQ-5D data collected in the CheckMate 067 trial from 827 patients.[80] The data were analysed using a longitudinal mixed-effects linear model including the following covariates: baseline EQ-5D, progression status and treatment arms. The ERG considers the methods of assessment of HRQoL reported in the trial to be appropriate.

However, the ERG notes that:

- The methodology used for the valuation (e.g. time trade-off, standard gamble) was not reported in the CS;
- The utility scores could not be verified based on the data provided by the company;
- No comparison with data retrieved in the literature review was performed.

In Section 4.7 of the CS, the company referenced a document containing HRQoL output tables from the CheckMate 067 RCT. This document contained EQ-5D utility index measurements only for, "patients with non-missing PRO [patient-reported outcome] data at baseline and non-missing PRO data at one additional post-baseline visit".[132] The company reported however that, "Patients in CheckMate 067 with at least one EQ-5D observation were used for the utility analysis" (Appendix 12 of the CS, pg 140). The ERG noted that the two sets of values, albeit similar, did not match, and that fewer patients were included in the analysis reported in the cited document.

The company stated in Appendix 12 of the CS that BRAF and PD-L1 status were not significant predictors for utility over time when they were tested as covariates in separate models. The company did not provide details on any goodness of fit analysis testing that was carried out.

The company included a total of 21 studies in the systematic literature review for health-related quality of life (HRQoL) and utilities for patients with advanced melanoma. However, no comparison was made between the HRQoL values observed in the trial and data identified in the systematic literature review.[80]

The utility values estimated based on the CheckMate 067 data and used in the model for pre-progression and post-progression health states were 0.80 and 0.76, respectively.[80] Clinical expert opinion sought by the ERG stated that the difference in the utility scores associated to the health states might have been underestimated according to their experience. The pre-progression and post-progression utility values in the model are similar to values reported in other studies identified as part of the company's systematic literature review.[55, 100, 105] A single study identified in the literature review, by Beusterein *et al.* 2011, reported values of 0.77 and 0.59 for stable and progressed disease UK patients, respectively.[91]

5.5.8 Resources and costs

The company estimated resource use in the model mainly based on data from the MELODY study, which is a longitudinal observational study analysing costs associated with management of melanoma.[126] Unit costs were based on NHS Reference costs and PSSRU costs, in line with the NICE reference case. [81, 124, 127] The ERG checked that the prices were correctly inflated when necessary and that discounting was correctly applied. The formulae were generally correct and sound in the electronic model.

5.5.8.1 Subsequent therapy

The ERG looks at the way in which the costs associated with patients receiving subsequent treatments after progression were estimated in the model, as these were found to be a substantial proportion of the total projected costs associated with the interventions. The proportions of patients receiving subsequent therapies after combination therapy and ipilimumab were based on data from the CheckMate 067 trial.[80] However, the proportions of patients who did not receive second line treatment were unbalanced in the trial across treatment arms, as presented in Table 88. $BRAF^-$ patients receiving combination therapy as first line treatment have limited treatment options in second line as they would not generally be treated with a PD-1inhibitor (i.e. nivolumab or pembrolizumab) according to clinical expert opinion. The treatment pathway for $BRAF^+$ patients however includes BRAF inhibitors.

Table 88. Proportion of patients who did not receive second line therapy at disease progression

First line therapy	Proportion of patients untreated after disease progression	Source
$BRAF^-$ patients		
Combination immunotherapy	89.70%	CheckMate 067 RCT[80]
Ipilimumab	62.00%	
$BRAF^+$ patients		
Combination immunotherapy	64.30%	CheckMate 067 RCT[80]
Ipilimumab	17.60%	
Dabrafenib	78.00%	BRIM-3 RCT[3]
Vemurafenib	78.00%	

When asked at the clarification stage, the company replied that, "The cost-effectiveness model only included subsequent treatment which are both potentially effective in increasing survival and further progression and which are associated with significant costs. Therefore, only four subsequent treatments are considered in the model which are ipilimumab, dabrafenib, vemurafenib and pembrolizumab. Consequently, the sum of the proportions are less than 100% […] and the proportions of patients not treated by these four treatments […] also vary across treatments" (company's response to clarification questions, pg 37, question B4). The ERG finds the justification reasonable and appropriate.

The proportion of $BRAF^+$ patients on BRAF inhibitors who were assumed to progress to receive ipilimumab were reported to be based on data from the BRIM-3 trial. According to the paper by McArthur *et al*. 18% of patients in the BRIM-3 trial went on to receive ipilimumab after vemurafenib.[3] However, in the model, the corresponding assumed proportion was 22% and not 18%. Applying the correct proportion of 18% increases the base case ICER by £835, from £11,284 to £12,119 per QALY and by £556, from [redacted] to [redacted] per QALY in the list price and PAS base case scenarios, respectively.

As pembrolizumab and nivolumab were not part of the treatment pathway at the time of the BRIM-3 trial, patients did not receive them as second-line after BRAF inhibitors. As the model is based on the trial second-line treatment data, pembrolizumab, nivolumab or nivolumab in combination with ipilimumab were not considered as treatment alternatives.

The company reported that, "It was assumed that patients in dabrafenib and vemurafenib do not receive the four chosen subsequent treatments apart from ipilimumab. Although this may not represent current treatment pathway (patients progressed on dabrafenib and vemurafenib may receive subsequent pembrolizumab), [the company] thinks that the assumption made is more consistent with

the OS/PFS used in the model for the BRAF inhibitors because these were directly estimated using digitised OS/PFS from the BRIM-3 trial reflecting treatment pathway at the time the trial was conducted" (company's response to clarification questions, pg 37, question B4). The ERG does not completely consider this justification to be appropriate. While the ERG appreciates the company's effort to represent the knowledge currently available from RCTs, the ERG considers the introduction of pembrolizumab to have shifted the *status quo*, and as such an analysis including the health effects and costs associated with pembrolizumab might have formed a more informative analysis than the one presented as base case. Additionally, based on the company's justification, the ERG would expect that both costs and QALYs associated to the BRAF inhibitors are underestimated by an unknown quantity in the company's base case.

The ERG notes that the subsequent therapy data from both the CheckMate 067 and BRIM-3 trials seem to be implemented incorrectly in the model. This is because the proportions of the total patients who received subsequent therapy are used as an estimate of the probability of receiving treatment after progression.[3, 80] The ERG notes that the results from the CheckMate 067 could not be validated as the subsequent therapy by treatment arm and BRAF status were not available, and that assuming equal propensity of treatment between the two subpopulations would have been inappropriate.

The proportions of patients not receiving subsequent therapy after progression were compared between the model and data from the CheckMate 067 CSR.[80] The results of the comparison showed that the proportion of patients not receiving subsequent therapy was indeed overestimated in the combination immunotherapy arm, both considering any treatment or only the 4 treatments included in the analysis by the company (i.e. pembrolizumab, ipilimumab, dabrafenib, vemurafenib). This is because the company seems to have used the proportion of patients who have received a specific subsequent therapy out of all patients, rather than out of the patients who have progressed. Data on subsequent therapies, extracted from the RCT CSR, are showed in Table 89. As already mentioned, these data were not available separately for $BRAF^-$ and $BRAF^+$ patients.

Table 89. Subsequent therapies by treatment[80]

Subsequent therapies	Combination immunotherapy	Ipilimumab
Progressed patients	[redacted]	[redacted]
Proportion of progressed patients who received subsequent therapies		
Any subsequent therapy	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]
Proportion of progressed patients who did not received subsequent therapies		
Did not receive any subsequent therapy	[redacted]	[redacted]

Subsequent therapies	Combination immunotherapy	Ipilimumab
Did not receive subsequent pembrolizumab, ipilimumab dabrafenib, dabrafenib or vemurafenib	[redacted]	[redacted]
[redacted]		

As different proportions of patients had progressed in the two arms at the time of the data collection, it is implausible to assume that the proportions of the total patients who had received subsequent therapies could be used as estimates of the probabilities of receiving specific subsequent treatments, and additionally assume that these would be constant over time. The ERG notes that the sensitivity of the model to variations of these data was not explored satisfactorily by the company, while the results are likely to change substantially when varying the underlying assumptions.

5.5.8.2 Dose calculations

The company reported that, "Dose interruption was included within the model using data from the CheckMate 067 trial […] These analyses showed that, on average, 90.2% of patients on nivolumab within [combination immunotherapy] received their expected doses" (CS, pg 169, Section 5.5.2). It is unclear to the ERG how the company derived this figure, as this information could not be found in the CheckMate 067 CSR. The company assumed that 9.8% (i.e. 100%-90.2%) of the total quantity of nivolumab estimated to be used would not be administered to patients and consequently not paid for. Additionally it was assumed that [redacted] and [redacted] doses of ipilimumab would be received by patients in the monotherapy and combination immunotherapy arm, respectively, as observed in the CheckMate 067 trial.[80]

The ERG finds that the application of the mean doses of ipilimumab received by patients in the trial is appropriate, as it is expected to be a good reflection of what would happen in clinical practice. However, the flat dose reduction assumed for nivolumab as part of combination immunotherapy was not sufficiently and not clearly explained and justified. The company did not provide sufficient evidence to prove that this reduction would be constant over time (beyond the trial follow-up) and that it is correctly applied to the proportion of patients on treatment as estimated using the parametric survival analysis proposed by the company (Section 5.4.5.3). Furthermore, the ERG notes that the actual value applied in the model was 90.16% and not 90.2% as reported by the company (most likely because of rounding); applying 90.20% in the model results in a negligible increase in the ICERs of less than £10 per QALY gained. Negating the dose reduction, i.e. assuming all patients receive the planned nivolumab dose while on treatment (based on the time on treatment in the company's base case) increases the discounted total costs associated with combination immunotherapy by approximately £4,000 and £3,500, respectively for the $BRAF^-$ and the $BRAF^+$ subpopulation. This in turn translates into an increase in the ICERs between £1,000 and £2,000 per QALY gained.

5.6 Results included in company's submission

5.6.1 Base case results

The ERG presents the base case results presented by the company for the cost-effectiveness of combination immunotherapy in $BRAF^-$ and $BRAF^+$ patients using both list prices and discounted prices as part of an assumed patient access scheme (PAS) for comparator drugs. The base case results when using list prices are presented for $BRAF^-$ and $BRAF^+$ patients in Table 90 and Table 92, respectively. The base case results using discounted prices as part of the assumed PAS are presented in Table 91 and Table 93 for $BRAF^-$ and $BRAF^+$ patients, respectively.

The company reported that combination immunotherapy was expected to extend patients' lives by about 2 years and 10 months (discounted) in $BRAF^-$ patients, increasing the expected QALYs by 2.2 on average. When list prices were used, combination immunotherapy had an incremental cost per QALY of £10,433 when compared to ipilimumab immunotherapy in $BRAF^-$ patients. An [redacted] was obtained for combination immunotherapy compared to ipilimumab in the PAS scenario.

A fully incremental cost-effectiveness analysis was carried out for $BRAF^+$ patients, comparing combination immunotherapy to ipilimumab monotherapy, vemurafenib and dabrafenib. Vemurafenib and ipilimumab were both dominated and thus excluded from the analysis, while dabrafenib was included as it was the next less costly non-dominated comparator in the list prices scenario [redacted]. Combination immunotherapy compared to dabrafenib was expected to extend patients' lives by about 4 (discounted) life years and increase the expected QALYs by 3.11, on average. When list prices were used, combination immunotherapy had an incremental cost per QALY of £11,284 and an [redacted] in the PAS scenario.

Table 90. Base case results for BRAF^{-} patients (CS, pg 182, Table 71)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
Ipilimumab	[redacted]	3.77	2.90				
Combination immunotherapy	[redacted]	6.55	5.09	£22,826	2.79	2.19	£10,433
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 91. Base case results using PAS prices for BRAF^{-} patients (CS, pg 183, Table 73)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

Table 92. Base case results for BRAF^{+} patients (CS, pg 182, Table 72)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)

Dabrafenib	[redacted]	2.24	1.74						
Vemurafenib	[redacted]	2.24	1.74	£19,070	0.00	0.00	Same QALYs	Dominated	Excluded due to dominance
Ipilimumab	[redacted]	3.38	2.59	£25,161	1.13	0.85	£29,597	Extendedly dominated	Excluded due to dominance
Combination immunotherapy	[redacted]	6.26	4.85	£35,085	4.02	3.11	£11,284		£11,284
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Note: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.									

Table 93. Base case results PAS prices for BRAF^{+} patients (CS, pg 183, Table 74)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

A summary of QALY health gain by health state in $BRAF^-$ and $BRAF^+$ patients is presented in Table 94 and Table 95, respectively. In the $BRAF^-$ population, combination immunotherapy resulted in nearly twice the number of QALYs as ipilimumab with an incremental gain of 2.19 QALYs (43%). Most of the incremental QALY gain (86%) was attributed to different times in the progression-free health state. Total QALYs lost as a result of TRAEs were greater in patients receiving combination immunotherapy when compared to ipilimumab.

In the $BRAF^+$ population, the incremental QALY gain in the progression-free health state for combination immunotherapy was 1.708 (73%) and 1.537 (66%) compared to ipilimumab and BRAF inhibitors, respectively. Combination immunotherapy resulted in a higher QALY differential attributed to time in PPS against BRAF inhibitors (1.592) compared to ipilimumab (0.592).

Table 94. Disaggregated QALY gain by health state for BRAF- patients (Adapted from CS, pg 188, Table 76)

Health state	Combination immunotherapy	Ipilimumab	Incremental QALYs versus ipilimumab	% increment versus ipilimumab
PFS	2.753	0.863	1.891	69%
PPS	2.358	2.045	0.313	13%
TRAEs	-0.023	-0.007	-0.016	69%
Total QALYs	**5.089**	**2.901**	**2.188**	**43%**

Abbreviations in table: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year; TRAE, treatment-related adverse event.

Table 95. Disaggregated QALY gain by health state for $BRAF^+$ patients (Adapted from CS, pg 188, Table 77)

Health state	Combination immunotherapy (1)	Ipilimumab (2)	Dabrafenib (3)	Vemurafenib (4)	Absolute increment (% increment)		
					1 vs 2	1 vs 3	1 vs 4
PFS	2.345	0.637	0.807	0.807	1.708 (73%)	1.537 (66%)	1.537 (66%)
PPS	2.528	1.964	0.936	0.936	0.564 (22%)	1.592 (63%)	1.592 (63%)
TRAEs	-0.020	-0.007	0.000	0.000	-0.013 (64%)	-0.020 (100%)	-0.020 (100%)
Total QALYs	**4.852**	**2.593**	**1.743**	**1.743**	**2.259 (47%)**	**3.109 (64%)**	**3.109 (64%)**

Abbreviations in table: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year; TRAE, treatment-related adverse event.

Table 96 and Table 97 show the life-years gained within different health states for $BRAF^+$ and $BRAF^-$ patients respectively. In both populations, patients spend more time without progressing when receiving combination immunotherapy compared to the other treatments. The incremental gain in life-

years in patients receiving combination immunotherapy was 2.8 life-years compared to ipilimumab in BRAF$^-$ patients. In BRAF$^+$ patients, the corresponding values were 3.38 and 2.24 life-years compared to ipilimumab and BRAF inhibitors, respectively.

Table 96. Summary of life-years gain by health state for BRAF$^-$ patients (CS, pg 188, Table 78)

Health state	Combination immunotherapy	Ipilimumab	Incremental Lys versus Ipilimumab	% increment (versus ipilimumab)
PFS	3.462	1.085	2.377	69%
PPS	3.093	2.682	0.411	13%
Total LYs	**6.554**	**3.767**	**2.788**	**43%**
Abbreviations in table: PFS, progression-free survival; PPS, post-progression survival; LY, life year.				

Table 97. Summary of life-years gain by health state for BRAF$^+$ patients

Health state	Combination immunotherapy (1)	Ipilimumab (2)	Dabrafenib (3)	Vemurafenib (4)	Absolute increment (% increment)		
					1 vs 2	1 vs 3	1 vs 4
PFS	2.948	0.801	1.015	1.015	2.147 (73%)	1.933 (66%)	1.933 (66%)
PPS	3.315	2.576	1.228	1.228	0.740 (22%)	2.087 (63%)	2.087 (63%)
Total LYs	**6.263**	**3.376**	**2.243**	**2.243**	**2.887 (46%)**	**4.020 (64%)**	**4.020 (64%)**
Abbreviations in table: PFS, progression-free survival; PPS, post-progression survival; LY, life year.							

Table 98 and

Table 99 show the disaggregated costs for BRAF$^-$ patients when list prices and discounted prices are used, respectively. Drug costs were the largest component of costs contributing to 76% and [redacted] of total costs for combination immunotherapy when list prices and discounted prices were applied, respectively. The cost of subsequent therapy was nearly four times higher for ipilimumab compared to combination immunotherapy when both list and discounted prices were applied, while the administration cost for nivolumab were nearly five times as much as administration costs for nivolumab monotherapy.

Table 100 and Table 101 show the disaggregated costs for BRAF$^+$ patients when list prices and discounted prices are used, respectively. The contribution of various cost components to total costs followed the same pattern as that seen in BRAF$^-$ patients, with drug costs making up the majority of costs and the administration cost for combination immunotherapy being substantially higher than the

other treatments. The cost of subsequent therapy was also higher for ipilimumab compared to the other treatments.

Table 98. Summary of costs for $BRAF^{+}$ patients using list prices[-] (Adapted from CS, pg 189, Table 80)

Cost component	Combination immunotherapy	Ipilimumab	Absolute increment versus ipilimumab (%)
Drug costs	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Treatment initiation	[redacted]	[redacted]	[redacted]
Pre-palliative care	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]
TRAE costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Abbreviations in table: TRAE, treatment-related adverse events.			

Table 99. Summary of costs for $BRAF^{-}$ patients using PAS drug prices for comparator treatments (Adapted from CS, pg 189, Table 82)

Cost component	Combination immunotherapy	Ipilimumab	Absolute increment versus ipilimumab (%)
Drug costs	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Treatment initiation	[redacted]	[redacted]	[redacted]
Pre-palliative care	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]
TRAE costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Abbreviations in table: TRAE, treatment-related adverse event; PAS, patient access scheme			

Table 100. Summary of costs by health state for BRAF^{+} patients using list prices (Adapted from CS, pg 190, Table 81)

Cost component	Combination immunotherapy	Ipilimumab	Dabrafenib	Vemurafenib	Absolute Increment versus ipilimumab (% increment)	Absolute Increment versus dabrafenib (% increment)	Absolute increment versus vemurafenib (% increment)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment initiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TRAE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: TRAE, treatment-related adverse event; PAS, patient access scheme.							

Table 101. [redacted]

Cost component	Combination immunotherapy	Ipilimumab	Dabrafenib	Vemurafenib	Absolute increment versus ipilimumab (% increment)	Absolute increment versus dabrafenib (% increment)	Absolute increment versus vemurafenib (% increment)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment initiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: TRAE, treatment-related adverse event; PAS, patient access scheme.							

5.6.2 Sensitivity analysis

In this section the ERG presents the deterministic and probabilistic sensitivity analyses carried out by the company. The company provided results for deterministic sensitivity and scenario analyses, reported in Section 5.8.2 and Section 5.8.3 of the CS, respectively. The results of the probabilistic sensitivity analysis were reported in Section 5.8.1.

The ERG requested an additional analysis including pembrolizumab as part of the comparator technologies in both subpopulations. This was provided by the company as part of the clarification responses.

5.6.2.1 One-way sensitivity analysis

The one-way sensitivity analysis was carried out using the net monetary benefit estimation approach, to make interpreting the results more straightforward when treatments were dominated. Net benefit was calculated based on an assumed willingness-to-pay (WTP) threshold of £30,000 per QALY gained. The base case net benefit, using list prices, was estimated to be £42,812 for combination immunotherapy compared to ipilimumab in $BRAF^-$ patients. The net benefit for combination immunotherapy compared to ipilimumab, dabrafenib and vemurafenib resulted equal to £57,849, £58,191, and £77,261, respectively. The results of the one-way sensitivity analyses when using list prices are shown in Figure 48 and Figure 49 (subfigures a-c) for $BRAF^+$ and $BRAF^-$ patients, respectively.

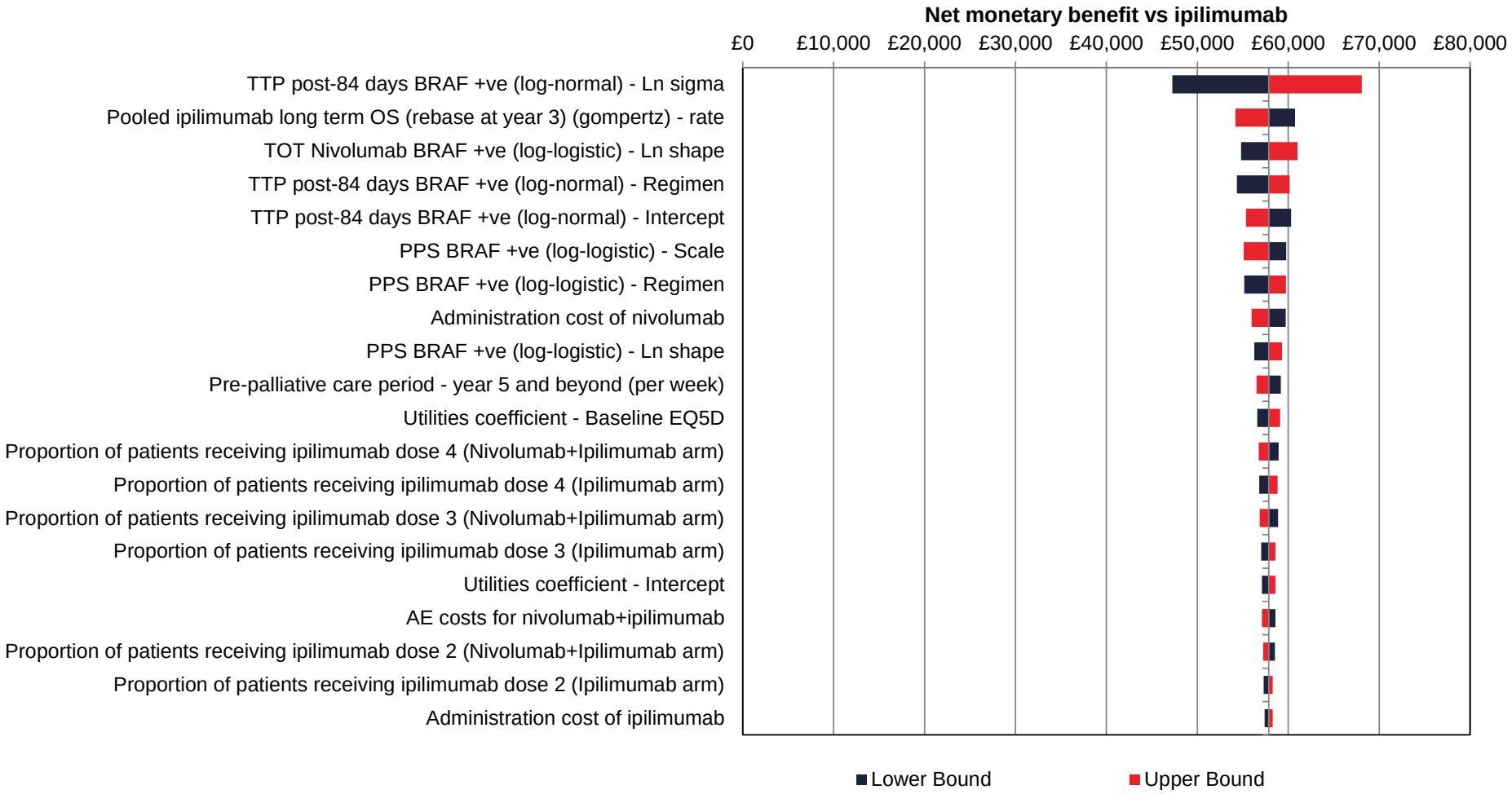
The OWSAs for the comparison against ipilimumab in both populations showed that, among the tested parameters, the cost-effectiveness results were mostly influenced by the parameters determining the post-84 days TTP (in particular, the $\log\sigma$ parameter of the lognormal parametric function used in the base case). Changes in the values of the parameter resulted in net benefit variations of more than £10,000. Other parameters were substantially less influential in the comparison between combination immunotherapy and ipilimumab.

The OWSAs conducted for the comparison between combination immunotherapy and BRAF inhibitors (i.e. dabrafenib and vemurafenib) in the $BRAF^+$ subpopulation highlighted a greater number of influential parameters than the previous analysis. All the parameters associated with the determination and projection of effectiveness (i.e. TTP, PFS, PPS and OS) were found to be influential. This highlighted a high degree of uncertainty associated with the comparison between combination immunotherapy and BRAF inhibitors. This is in line with the lack of head-to-head data, even though the ERG notes that the uncertainty associated to the analysis is in fact substantially greater, as this analysis only looks at univariate variations of a selected set of parameters and does not evaluate structural sensitivity.

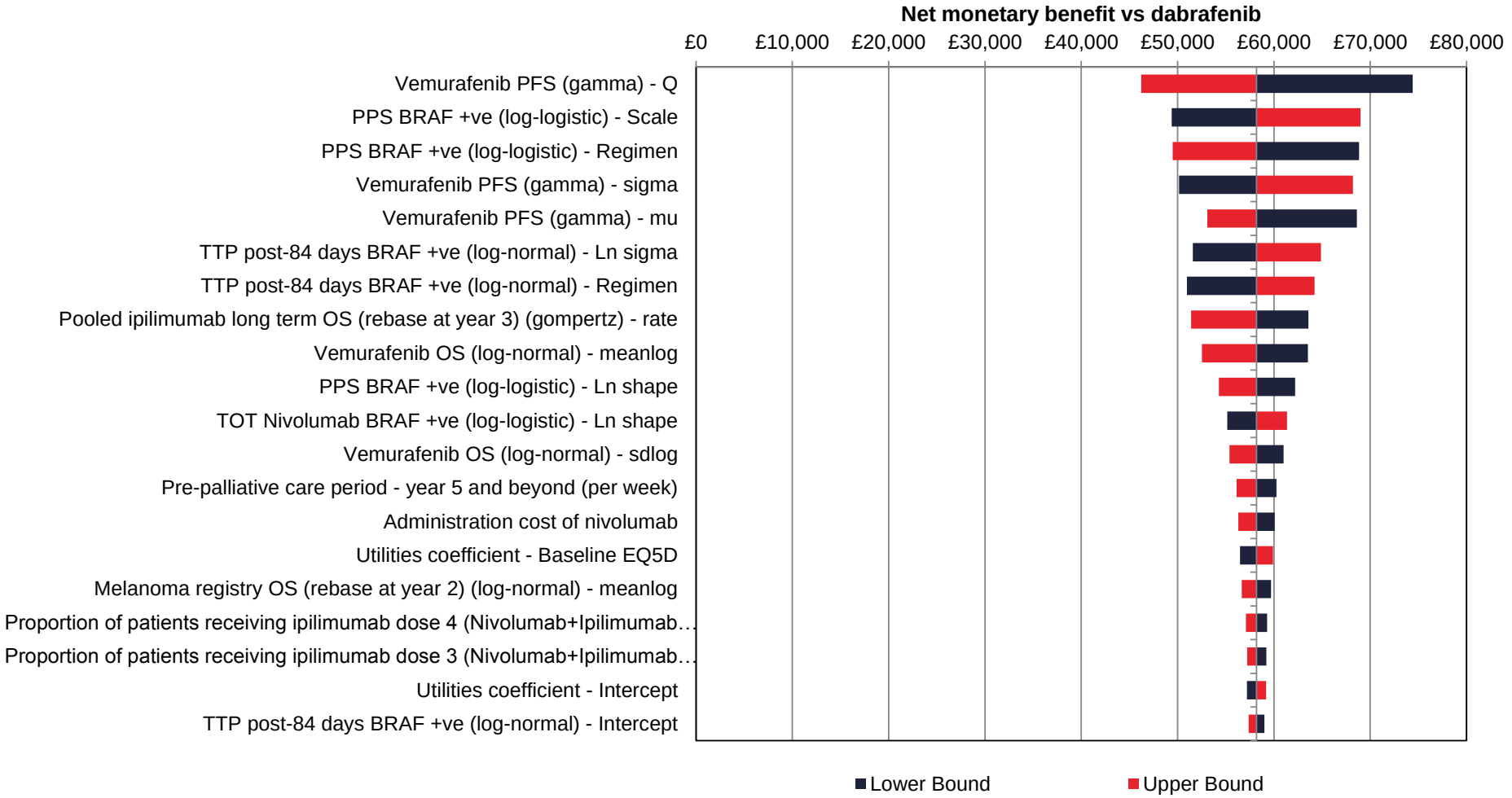
Figure 48. Tornado diagram of OWSA for BRAF^{-} patients with 20 most influential parameters (CS, pg 203, Figure 71)

Figure 49. Tornado diagrams of OWSA for BRAF^{+} patients with 20 most influential parameters (CS, pg 204-206, Figure 72)

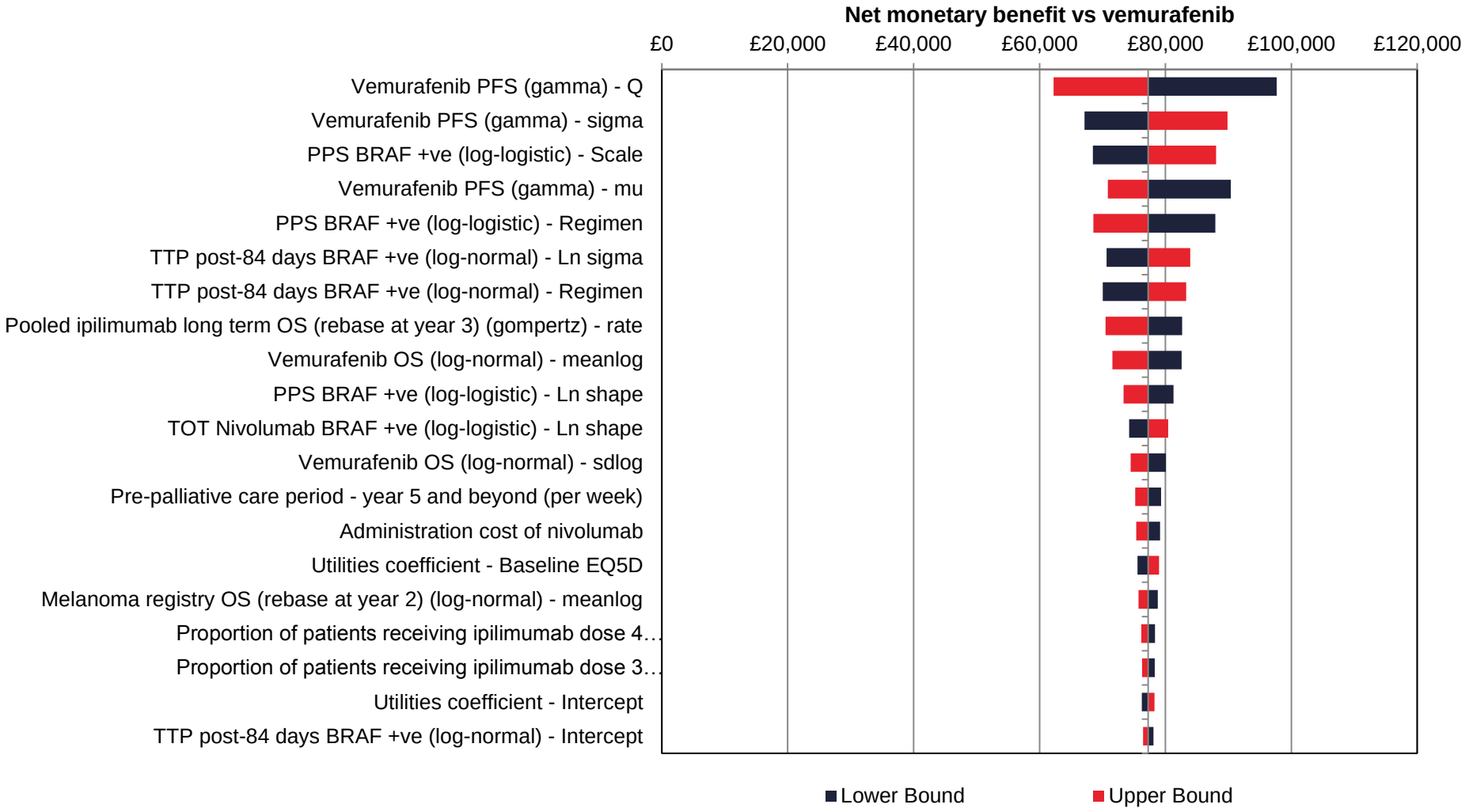
Subfigure 25a: OWSA, combination immunotherapy vs ipilimumab in the BRAF^{+} subpopulation



Subfigure 25b: OWSA, combination immunotherapy vs dabrafenib in the BRAF^{+} subpopulation



Subfigure 25b: OWSA, combination immunotherapy vs vemurafenib in the BRAF^{+} subpopulation



5.6.2.2 Scenario analyses

The impact of changing the following assumptions surrounding the following components of the model was assessed in additional scenario analyses:

- Distribution of parametric curves for parametric curves based on indirect comparisons, pooled long-term overall survival for ipilimumab and the time on treatment (ToT) curve for nivolumab;
- Duration of treatment;
- Dosing methods for drug costs calculation;
- Health state utility values;
- Time horizon;
- Hazard ratios for BRAF inhibitors;
- Discount rate.

The results of the scenario analysis for $BRAF^-$ are presented in Table 102 when both list prices and discounted prices were used. Table 103 and Table 104 show the results of the scenario analysis for $BRAF^+$ patients when list prices and discounted prices were used, respectively. The results of the scenario analysis show that combination immunotherapy is less than £30,000 per QALY across all the scenarios with the exception of two; when no maximum treatment duration is set, and when less patients (0% to 50%) are assumed to discontinue treatment with nivolumab when both list prices and discounted prices are used.

Table 102. Scenario analyses results, $BRAF^-$ patients (adapted from CS, pg 207, Table 88)

Parameter	Base case	Scenario analysis	List price scenario		PAS scenario	
			Combination immunotherapy vs ipilimumab			
			ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)
Base case	**N/A**	**N/A**	**10,433**	**42,812**	[redacted]	[redacted]
Parametric curves based on indirect comparison						
TTP	Log-Normal	Exponential	11,826	33,459	[redacted]	[redacted]
		Weibull	9,639	48,111	[redacted]	[redacted]
		Gompertz	8,961	56,589	[redacted]	[redacted]
		Log-logistic	10,332	43,505	[redacted]	[redacted]
		Generalised Gamma	9,975	45,811	[redacted]	[redacted]
PPS	Log-logistic	Exponential	10,142	44,897	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	List price scenario		PAS scenario	
			Combination immunotherapy vs ipilimumab			
			ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)
		Weibull	10,174	44,657	[redacted]	[redacted]
		Gompertz	10,572	41,800	[redacted]	[redacted]
		Log-Normal	10,689	40,985	[redacted]	[redacted]
		Generalised Gamma	10,543	41,987	[redacted]	[redacted]
Long-term survival						
Pooled ipilimumab long-term survival	Gompertz	Exponential	10,862	39,877	[redacted]	[redacted]
		Weibull	10,327	43,591	[redacted]	[redacted]
		Log-Logistic	10,349	43,422	[redacted]	[redacted]
		Log-Normal	10,343	43,470	[redacted]	[redacted]
		Generalised Gamma	10,326	43,595	[redacted]	[redacted]
Time on treatment						
TOT curve for nivolumab	Log-logistic	Exponential	8,085	47,984	[redacted]	[redacted]
		Weibull	10,198	43,328	[redacted]	[redacted]
		Gompertz	11,134	41,262	[redacted]	[redacted]
		Log-Normal	11,068	41,413	[redacted]	[redacted]
		Generalised Gamma	10,578	42,492	[redacted]	[redacted]
Duration of treatment	100% discontinue at 2 years	75% discontinue at 2 years[b]	20,246	21,250	[redacted]	[redacted]
		50% discontinue at 2 years[b]	30,144	-312	[redacted]	[redacted]
		25% discontinue at 2 years[b]	40,127	-21,874	[redacted]	[redacted]
		0% discontinue at 2 years (no treatment continuation rule)[b]	50,197	-43,436	[redacted]	[redacted]
	Maximum treatment duration of 2 years	Maximum treatment duration of 3 years	15,764	31,075	[redacted]	[redacted]
		Maximum treatment duration of 4 years	19,847	22,123	[redacted]	[redacted]
		Maximum treatment duration of 5 years	23,150	14,904	[redacted]	[redacted]
		No maximum treatment duration	50,197	-43,436	[redacted]	[redacted]
Dosing and drug cost						
Method for dosing for nivolumab and ipilimumab	Method of moment (weight based dosing)	Cost per mg	10,267	43,175	[redacted]	[redacted]
		Round up to the nearest full vial	8,410	47,237	[redacted]	[redacted]
Utilities						
Utility analysis	CheckMate 067 trial analysis	CheckMate 066 trial analysis	10,734	40,972	[redacted]	[redacted]
		Ipilimumab NICE TA319 utilities	9,283	50,943	[redacted]	[redacted]
General model settings						

Parameter	Base case	Scenario analysis	List price scenario		PAS scenario	
			Combination immunotherapy vs ipilimumab			
			ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)
Time horizon	40 years	10 years	17,624	14,754	[redacted]	[redacted]
		20 years	11,731	34,571	[redacted]	[redacted]
		30 years	10,548	41,939	[redacted]	[redacted]
Discount rate	0.035	0.015	8,941	57,357	[redacted]	[redacted]

Abbreviations in table: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; N/A, not applicable; PAS, patient access scheme; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year; TOT, time on treatment; TTP, time-to-progression.

Notes: [a] willingness to pay threshold of £30,000 and was reported incorrectly in the table as £50,000; [b] in these scenario analyses, only a proportion of patients (75% to 0%) who are still on nivolumab treatment at Year 2 will discontinue treatment from Year 2 onwards, with the time on treatment for the remaining patients (25% to 100%) based on extrapolation of the fitted TOT (capped by overall survival).

Table 103: Scenario analyses results, BRAF^{+} patients: list price scenario (Adapted from CS, pg 210, Table 89)

Parameter	Base case	Scenario analysis	List price scenario: combination immunotherapy vs					
			Ipilimumab		Dabrafenib		Vemurafenib	
			ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)
Base case	N/A	N/A	**4,393**	**57,849**	**11,284**	**58,191**	**5,151**	**77,261**
Parametric curves based on indirect comparison								
TTP	Log-Normal	Exponential	4,840	44,553	15,845	29,876	6,810	48,946
		Weibull	3,996	64,506	11,417	57,122	5,213	76,192
		Gompertz	3,991	76,598	9,591	76,925	4,532	95,995
		Log-logistic	4,381	58,548	11,266	58,408	5,149	77,478
		Generalised Gamma	4,171	61,315	11,292	58,179	5,160	77,249
PPS	Log-logistic	Exponential	4,264	60,873	11,617	55,295	5,277	74,365
		Weibull	4,273	60,638	11,563	55,758	5,257	74,827
		Gompertz	4,390	57,724	11,007	60,873	5,057	79,942
		Log-Normal	4,443	56,424	10,779	63,198	4,979	82,268
		Generalised Gamma	4,398	57,521	11,001	60,958	5,057	80,028
Long-term survival								
Registry survival (rebased at 3 years)	Weibull	Exponential	4,393	57,849	11,306	58,175	5,185	77,221
		Gompertz	4,393	57,849	11,347	57,595	5,170	76,667
		Log-Logistic	4,393	57,849	11,344	57,621	5,169	76,694
		Log-Normal	4,393	57,849	11,344	57,621	5,169	76,694
		Generalised Gamma	4,393	57,849	11,296	58,070	5,152	77,142
Pooled	Gompertz	Exponential	4,726	50,430	13,046	44,477	5,777	63,547

Parameter	Base case	Scenario analysis	List price scenario: combination immunotherapy vs					
			Ipilimumab		Dabrafenib		Vemurafenib	
			ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)
ipilimumab long-term survival		Weibull	4,417	57,252	11,405	57,089	5,194	76,158
		Log-Logistic	4,419	57,204	11,415	57,000	5,197	76,070
		Log-Normal	4,408	57,484	11,358	57,519	5,177	76,588
		Generalised Gamma	4,377	58,277	11,199	58,984	5,121	78,053
Time on treatment								
TOT curve for nivolumab	Log-logistic	Exponential	2,004	63,291	9,545	63,633	3,414	82,703
		Weibull	4,054	58,621	11,037	58,963	4,904	78,033
		Gompertz	4,749	57,032	11,544	57,374	5,410	76,444
		Log-Normal	5,319	55,736	11,959	56,078	5,824	75,148
		Generalised Gamma	4,596	57,384	11,432	57,727	5,299	76,797
Duration of treatment	100% discontinue at 2 years	75% discontinue at 2 years[b]	12,014	40,496	16,833	40,838	10,685	59,908
		50% discontinue at 2 years[b]	19,687	23,143	22,410	23,486	16,246	42,555
		25% discontinue at 2 years[b]	27,411	5,791	28,013	6,133	21,835	25,203
		0% discontinue at 2 years (no treatment continuation rule)	35,187	-11,562	33,644	-11,220	27,451	7,850
	Maximum treatment duration of 2 years	Maximum treatment duration of 3 years	8,551	48,367	14,313	48,710	8,172	67,779
		Maximum treatment duration of 4 years	11,707	41,193	16,610	41,535	10,462	60,605
		Maximum treatment duration of 5 years	14,246	35,436	18,457	35,778	12,304	54,848
		No maximum treatment duration	35,187	-11,562	33,644	-11,220	27,451	7,850
Hazard ratios for BRAF inhibitors (dabrafenib vs vemurafenib)								
HR for PFS	HR = 1	HR = 0.97	4,393	57,849	10,225	61,456	5,151	77,261
Dosing and drug cost								
Method for	Method of	Cost per mg	3,976	58,791	8,807	65,893	2,674	84,963

Parameter	Base case	Scenario analysis	List price scenario: combination immunotherapy vs					
			Ipilimumab		Dabrafenib		Vemurafenib	
			ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)
dosing for nivolumab and ipilimumab	moments (weight based dosing)	Round up to the nearest full vial	2,939	61,133	9,593	63,451	3,459	82,521
Utilities								
Utility analysis	CheckMate 067 trial analysis	CheckMate 066 trial analysis[86]	4,547	55,554	11,857	53,689	5,412	72,759
		Ipilimumab NICE TA319 utilities[62]	3,891	66,582	9,876	71,488	4,508	90,558
General model settings								
Time horizon	40 years	10 years	7,080	25,492	28,113	2,319	13,296	20,532
		20 years	4,990	45,153	14,733	35,479	6,633	54,303
		30 years	4,487	55,154	11,880	53,207	5,409	72,208
Discount rate	0.035	0.015	3,966	75,669	8,322	89,926	3,514	109,872

Abbreviations in table: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; N/A, not applicable; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life years; TOT, time on treatment TTP, time-to-progression.

Notes: [a] willingness to pay threshold of £30,000; [b] in these scenario analyses, only a proportion of patients (75% to 0%) who are still on nivolumab treatment at Year 2 will discontinue treatment from Year 2 onwards, with the time on treatment for the remaining patients (25% to 100%) based on extrapolation of the fitted TOT (capped by overall survival).

Table 104. Scenario analysis results, BRAF+ patients: PAS scenarios (Adapted from CS, pg 210, Table 89)

Parameter	Base case	Scenario analysis	PAS scenario: combination immunotherapy vs					
			Ipilimumab		Dabrafenib		Vemurafenib	
			ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)
[redacted]								
Parametric curves based on indirect comparison								

Parameter	Base case	Scenario analysis	PAS scenario: combination immunotherapy vs					
			Ipilimumab		Dabrafenib		Vemurafenib	
			ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-term survival								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	PAS scenario: combination immunotherapy vs					
			Ipilimumab		Dabrafenib		Vemurafenib	
			ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)	ICER (£/QALY)	INB[a] (£)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratios for BRAF inhibitors (dabrafenib vs vemurafenib)								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dosing and drug cost								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General model settings								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								

5.6.2.3 Area under the curve model including pembrolizumab as comparator

As requested by the ERG during clarification stage, the company carried out an additional analysis to include pembrolizumab as a comparator in the economic analysis. The company provided details of the changes between the base case analysis and this scenario analysis in the responses to clarification questions:

- Pembrolizumab was included as an additional comparator in both $BRAF^-$ and $BRAF^+$ subgroups;

- It was assumed that, similar to nivolumab in the nivolumab plus ipilimumab arm (combination immunotherapy), patients would be treated with pembrolizumab for a maximum of 2 years;

- Hazard ratios (HRs) were estimated for pembrolizumab versus ipilimumab and combination immunotherapy versus ipilimumab for overall survival (OS) and progression free survival (PFS) [redacted];

- The estimated HRs were applied to the reference ipilimumab OS/PFS curves as estimated in the base case economic model to calculate OS/PFS for pembrolizumab and combination immunotherapy;

- Area under the curve partitioned survival methods were used for combination immunotherapy and pembrolizumab.

The results of the analysis for $BRAF^-$ and $BRAF^+$ patients are presented in Table 105 and Table 106, respectively; Table 107 and Table 108 report the results using PAS prices. In the $BRAF^-$ subpopulation, ipilimumab was dominated by pembrolizumab and combination immunotherapy and therefore excluded from the analysis. Combination immunotherapy was expected to extend the lives of patients by 2 discounted years on average and to increase 1.63 additional QALYs compared to pembrolizumab. The resulting ICER for combination immunotherapy compared to pembrolizumab estimated by the company was £29,923 per QALY gained.

In the $BRAF^+$ subpopulation, both ipilimumab and BRAF inhibitors were excluded from the incremental analysis because of dominance. Combination immunotherapy was estimated to extend the lives of patients by 2.8 discounted years and to produce 1.64 additional QALYs compared to pembrolizumab. The ICER for the comparison was £27,859 per QALY gained.

The company also carried out a probabilistic sensitivity analysis as part of this scenario. The results of the PSA showed that the probability of combination immunotherapy being cost-effective at a willingness-to-pay threshold of £30,000 to be 52.5% and 55.55% for $BRAF^-$ and $BRAF^+$ patients, respectively, when list prices were used. The probability of combination immunotherapy being cost-

effective at a willingness-to-pay threshold of £30,000 when PAS prices were used is 65.1% and 69% for BRAF^{-} and BRAF^{+} patients, respectively.

Table 105. Base case results for BRAF^{-} patients (including pembrolizumab)

Technology	Total			Incremental			ICER (£/QALY) vs baseline	ICER (£/QALYs) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Pembrolizumab	[redacted]	4.86	3.79					
Ipilimumab	[redacted]	3.77	2.90	£25,460	-1.10	-0.89	-£28,555	Absolutely dominated
Combination immunotherapy	[redacted]	6.93	5.42	£48,804	2.07	1.63	£29,923	£29,923
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Notes: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.								

Table 106. Base case results for BRAF^{+} patients (including pembrolizumab)

Technology	Total			Incremental			ICER (£/QALY) vs baseline	ICER (£/QALYs) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Pembrolizumab	[redacted]	4.55	3.53					
Dabrafenib	[redacted]	2.24	1.74	£10,045	-2.30	-1.79	-£5,607	
Vemurafenib	[redacted]	2.24	1.74	£29,115	-2.30	-1.79	-£16,253	Absolutely dominated
Ipilimumab	[redacted]	3.38	2.59	£35,206	-1.17	-0.94	-£37,403	Absolutely dominated
Combination immunotherapy	[redacted]	6.63	5.17	£45,611	2.08	1.64	£27,859	£27,859
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Notes: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.								

Table 107. Pembrolizumab scenario analysis, BRAF^{-} sub population (PAS scenario)

Technology	Total			Incremental			ICER (£/QALY) vs baseline	ICER (£/QALYs) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
[redacted]								
[redacted]								
[redacted]								
[redacted]								

Table 108. Pembrolizumab scenario analysis, BRAF^{+} subpopulation (PAS scenario)

Technology	Total			Incremental			ICER (£/QALY) vs baseline	ICER (£/QALYs) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
[redacted]								

The ERG does not consider the comparison carried out by the company to be adequate for the comparison between combination immunotherapy and pembrolizumab. This is because of the following reasons:

- The model outcomes were based on the results of the ipilimumab arm in the company's base case. However, the ERG found a fundamental unreasonable modelling assumption around the integration of short- and long-term post-progression mortality which resulted in implausible intermediate outcomes;

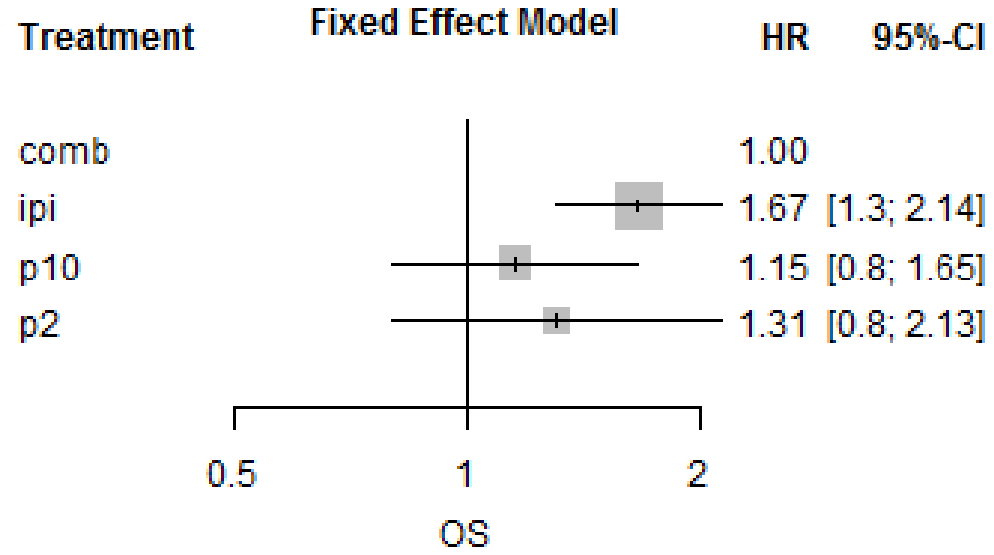
- The model assumed constant proportionality of the hazards over the entire time horizon for PFS and OS between ipilimumab and combination immunotherapy and ipilimumab and pembrolizumab. The HRs were estimated based on relatively short-term follow-up, with no evidence supporting the assumption for the entire time horizon;

- Assuming HRs for the OS in the model assumed that, in addition to melanoma-specific mortality, pembrolizumab and combination immunotherapy would also reduce the portion of mortality determined by age- and gender-match general population mortality compared to ipilimumab, over the entire time horizon. This translates in assuming that the mortality rates for patients in the PFS health states beyond 3 years in the combination immunotherapy and pembrolizumab arms would have death rates lower than the rates of the English general population. This is considered an unreasonable assumption by the ERG;

- The assumption of a different OS derives from a naïve comparison of the HRs between ipilimumab, combination immunotherapy and pembrolizumab. However [redacted] the network meta-analysis (NMA) performed by the company and replicated by the ERG between pembrolizumab and combination immunotherapy, as showed in Figure 50;

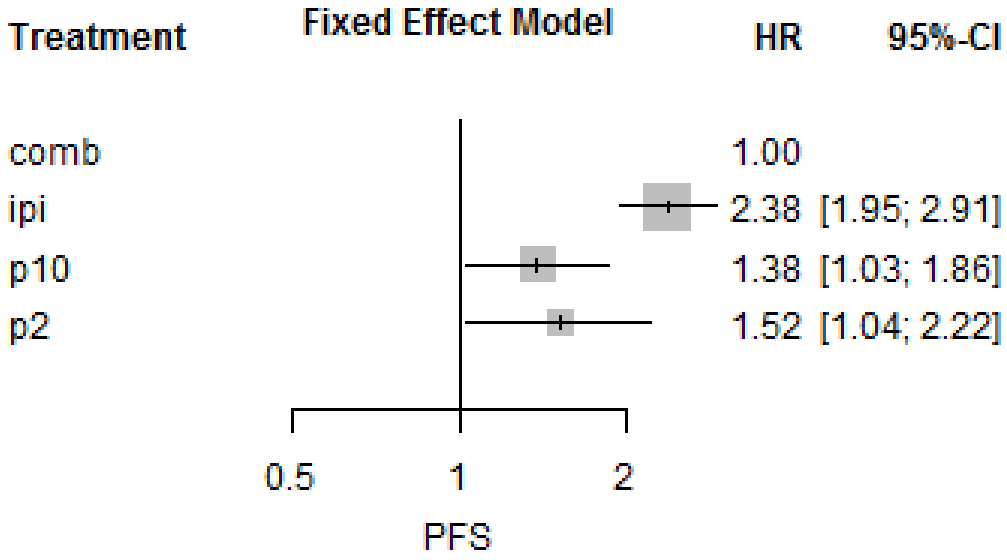
- The ERG agrees with the company that, as showed in Figure 51, the exploratory NMA [redacted]. However, the analysis is not probative of a treatment difference, and as such the results should be considered with extreme caution.

Figure 50. Forest plot of the exploratory NMA for OS performed by the ERG



Abbreviations in figure: CI, confidence interval; comb, combination immunotherapy; HR, hazard ratio; ipi, ipilimumab; OS, overall survival; p2, pembrolizumab 2mg/kg q3w; p10, pembrolizumab 10mg/kg q3w.

Figure 51. Forest plot for the exploratory NMA for PFS performed by the ERG



Abbreviations in figure: CI, confidence interval; comb, combination immunotherapy; HR, hazard ratio; ipi, ipilimumab; p2, pembrolizumab 2mg/kg q3w; p10, pembrolizumab 10mg/kg q3w; PFS, progression-free survival.

In conclusion, based on the results of the NMA and the underlying assumptions in the ipilimumab arm determining the comparative outcomes, the ERG does not deem the analysis performed to be sufficient to provide indications on the comparative cost-effectiveness profile between combination immunotherapy and pembrolizumab.

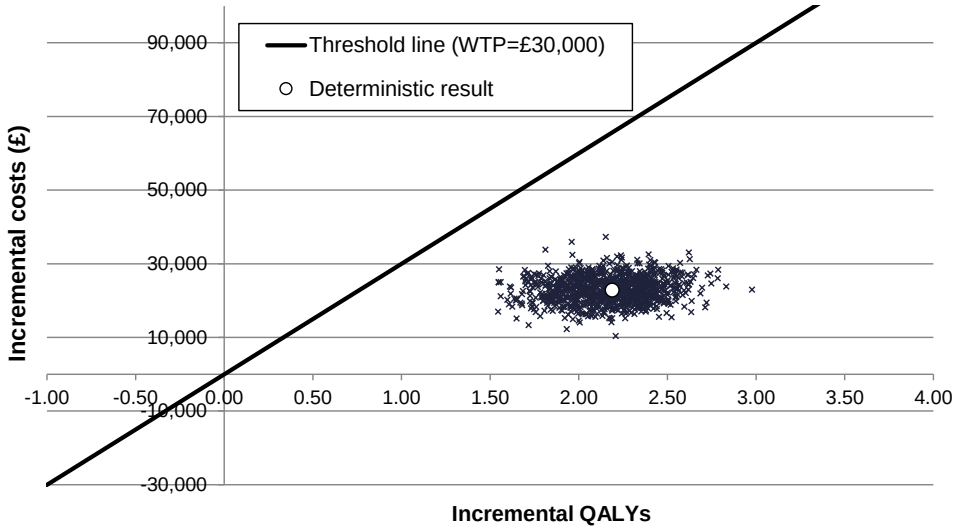
5.6.2.4 Probabilistic sensitivity analyses

The company performed a probabilistic sensitivity analysis (PSA) to assess the amount of parameter uncertainty around the base case scenario results. The results of the PSA across a 1,000 simulations were presented in the CS, however no details were provide regarding the parameters that were varied for the analysis. The scatter plots can be seen in Figure 52 and Figure 54 for $BRAF^-$ and $BRAF^+$ patients, respectively and show that at a willingness-to pay threshold of £30,000 per QALY, combination therapy remains the cost-effective option. The cost-effectiveness acceptability curves presented in Figure 56 and Figure 57 show that a willingness-to-pay threshold of £30,000 per QALY, the probability of combination immunotherapy being cost-effective is 100% in both populations.

The mean result of the PSA for $BRAF^-$ patients was an ICER of £10,654 per QALY for combination immunotherapy compared to ipilimumab. For $BRAF^+$ patients, ipilimumab and vemurafenib were dominated, therefore the mean results of the PSA of combination immunotherapy compared to dabrafenib was £10,909 per QALY. These results are in line with the results of the deterministic base case analysis.

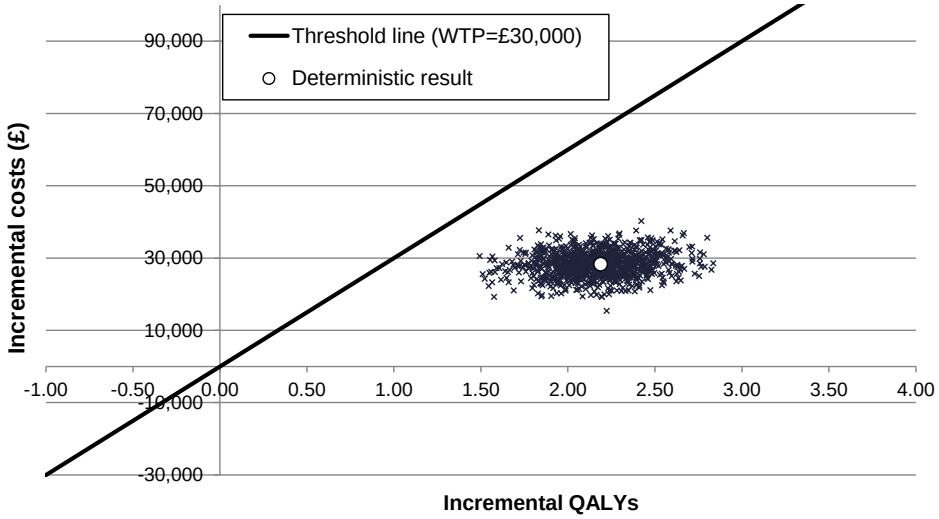
The company also carried out a PSA using discounted prices for comparators for the assumed PAS. The results were in line with the list price analysis, with the probability of combination immunotherapy being cost-effective being 100% at a willingness-to pay threshold of £30,000 per QALY in both $BRAF^-$ and $BRAF^+$ populations. The scatter plots when using PAS prices are presented for $BRAF^-$ and $BRAF^+$ patients in Figure 54 and Figure 55, respectively.

Figure 52. Distribution of cost-effectiveness simulations on the cost-effectiveness plane for combination immunotherapy versus ipilimumab in BRAF$^-$ patients: list prices (CS, pg 196, Figure 67)



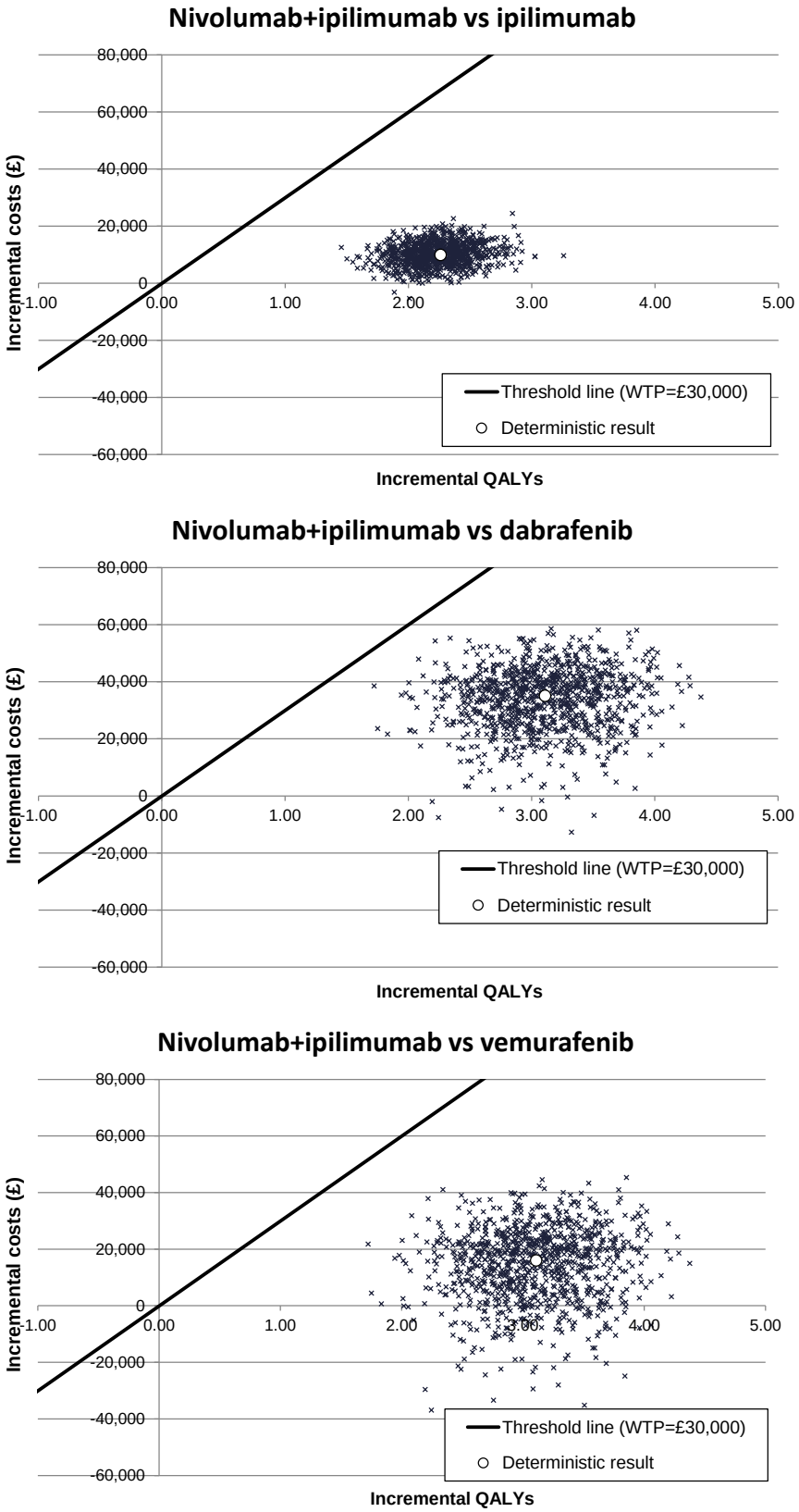
Abbreviations in figure: QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 53. Distribution of cost-effectiveness simulations on the cost-effectiveness plane for combination immunotherapy versus ipilimumab in BRAF$^-$ patients: PAS prices (CS, pg 198, Figure 69)



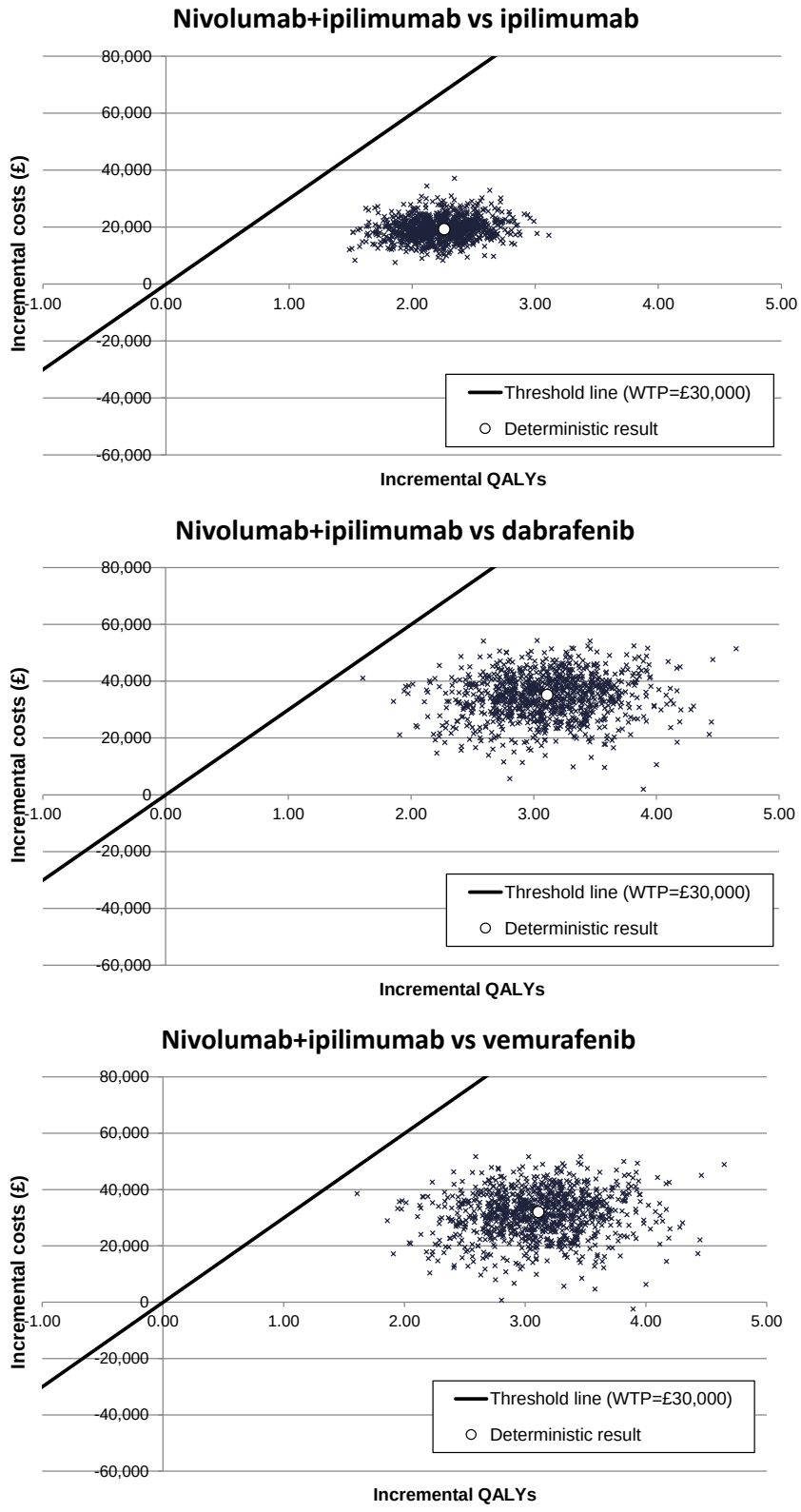
Abbreviations in figure: QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 54. Distribution of cost-effectiveness simulations on the cost-effectiveness planes for $BRAF^{+}$ patients, list prices (CS, pg 197, Figure 68)



Abbreviations in figure: QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 55. Distribution of cost-effectiveness simulations on the cost-effectiveness planes for $BRAF^{+}$ patients, PAS prices (CS, pg 199, Figure 70)



Abbreviations in figure: QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 56. Cost-effectiveness acceptability curve for BRAF^{-} patients (CS, pg 193, Figure 63)

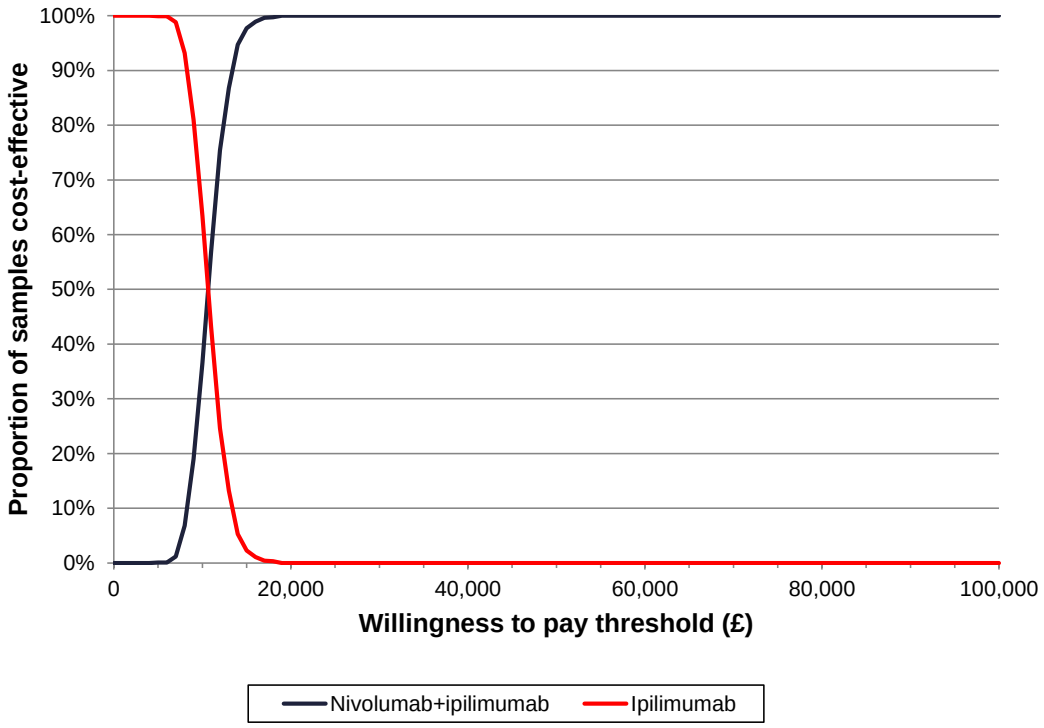
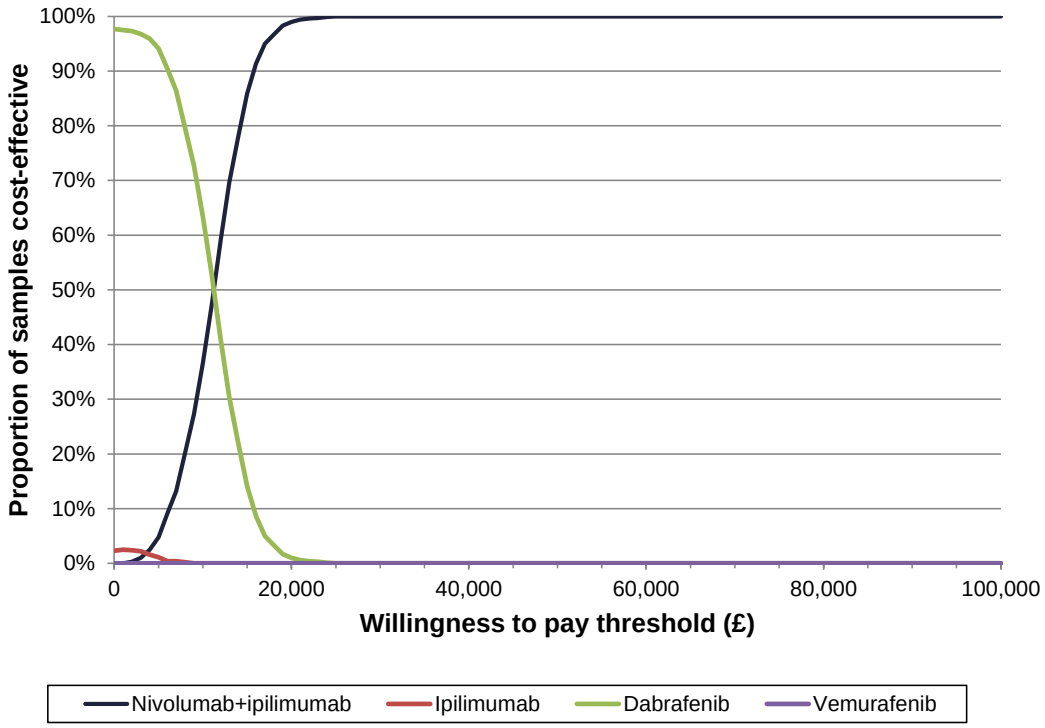


Figure 57. Cost-effectiveness acceptability curve for BRAF^{+} patients (CS, pg 193, Figure 64)



6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG identified two minor data entry errors in the model, as described in Section 5.5.6 and 5.5.8.1. The company's model was corrected to include the proportion of patients receiving ipilimumab after BRAF inhibitors reported by McArthur *et al.*, i.e. 18% and not 22% as included in the company's model.[3] Additionally, the ERG found the values associated with the proportion of patients experiencing endocrine treatment-related adverse events (TRAEs) in the ipilimumab arm not to correspond between the CS and the CheckMate 067 CSR, as the value was 11.3% in the former while the second reported a proportion equal to [redacted].[80] In all other aspects, the ERG considers that company's model to work as intended and described, consistent with the company's assumptions.

The revised base case results including the two minor ERG's corrections for the two BRAF subpopulations are presented from Table 109 to Table 112, under the list price and patient access scheme (PAS) scenario. The modifications did not have any impact on the BRAF$^-$ analysis results (as the variation in patients moving to second-line ipilimumab after BRAF inhibitors did not apply). The reduction in the proportion of patients receiving ipilimumab as second-line after vemurafenib or dabrafenib resulted in reduced discounted total per-patient cost estimates for both dabrafenib and vemurafenib by about £2,500 in the list prices base case scenario [redacted]. This resulted in an increase of the ICER for the incremental analysis between combination immunotherapy and the less expensive non-dominated intervention, i.e. dabrafenib, from £11.284 to £12,119 per QALY gained and [redacted] using list and PAS prices, respectively.

Table 109. Revised company's base case results for BRAF^{-} patients, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
Ipilimumab	[redacted]	3.77	2.90				
Combination immunotherapy	[redacted]	6.55	5.09	£22,826	2.79	2.19	£10,433
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 110. Revised company's base case results for BRAF^{-} patients, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

Table 111. Revised company's base case results for BRAF^{+} patients, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)

Dabrafenib	[redacted]	2.24	1.74						
Vemurafenib	[redacted]	2.24	1.74	£19,070	0.00	0.00	Same QALYs	Dominated	Excluded due to dominance
Ipilimumab	[redacted]	3.38	2.59	£27,758	1.13	0.85	£32,651	Extendedly dominated	Excluded due to dominance
Combination immunotherapy	[redacted]	6.26	4.85	£37,682	4.02	3.11	£12,119		£12,119

Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Note: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

Table 112. Revised company's base case results for BRAF^{+} patients, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

6.2 ERG scenario analysis

The ERG explored the impact of selected company's assumptions to assess the impact they produced on the model results and assess the plausibility of the model intermediate and final outputs. The key areas of uncertainty identified by the ERG granting exploration through scenario analyses were:

- Dependency on time of progression of post-progression mortality rates for immunotherapies;
- Treatment effect on pre-progression mortality for immunotherapies;
- Treatment dosage assumptions for combination immunotherapy;
- Second-line treatments received in post progression.

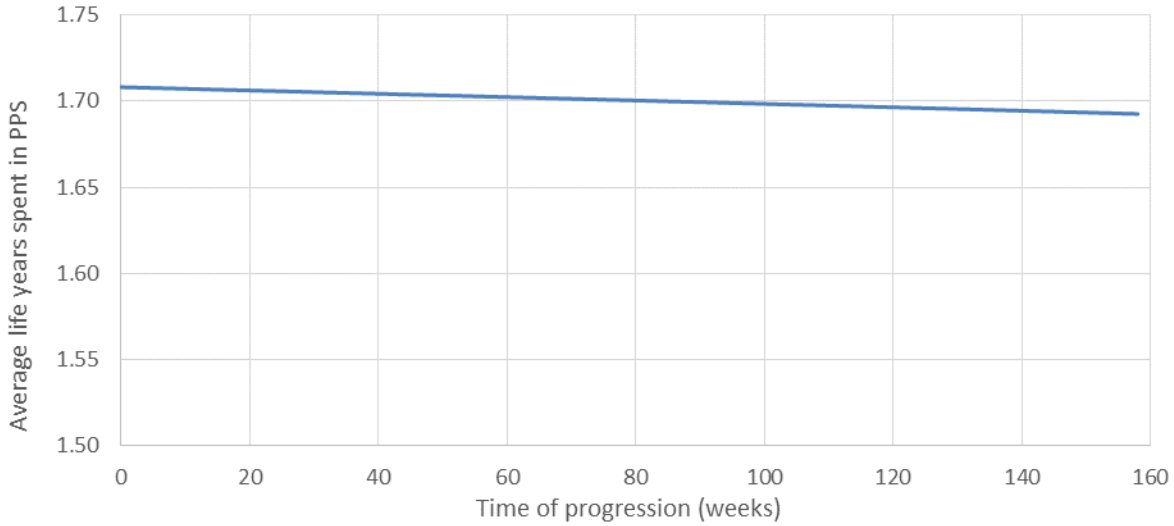
6.2.1 Dependency on time of progression of post-progression mortality rates

The integration of short- and long-term post-progression mortality rates is discussed in Section 5.5.5.2. The ERG finds implausible that post-progression expected survival over the model time horizon would increase from about 3 to about 16 years for patients who would progress in the first weeks of the model compared to patients who progress 3 or more years from model initiation. This effect was found to depend on the integration of the two mortality rate data sources, i.e. the analysis of CheckMate 066 and MDX010-20 for short-term survival (0-3 years) and the pooled ipilimumab analysis results reported by Schadendorf *et al.* for the long-term survival (3-40 years, with results rebased at 3 years).[4, 26, 86]

To obviate this issue, the ERG leveraged an undocumented functionality included in the company's model. The ERG increased the time point at which the long-term mortality rates nesting was implemented in the model to more than 40 years, so that the entire PPS was determined by extrapolation of data from the Checkmate 066 and MDX010-20 RCTs. [26, 86] Even though the ERG agrees with the company's that long-term data would produce a more robust estimate, this is likely to be the only option that would not require rebuilding the PPS model engine to remove the increased PPS by time of progression. This change in the model resulted in attributing an approximately constant average time alive in the PPS health state to all progressed patients. This survival time, with the exception of the effect of age-specific mortality based on the matched general population data increasing with the average patients' age, was almost independent of time of progression and of model time and approximately equal to 1.7 average undiscounted life years. The average life years spent in PPS over 40 years by week of progression are shown in Figure 58 for patients progressing between model week 1 and 159 (i.e. over 3 years). While Figure 58 refers specifically to $BRAF^-$ patients, the same approximately constant life years over time were associated to $BRAF^+$ patients as

well, even though it differed slightly because of the difference in baseline age assumed by the company.

Figure 58. Average life years spent in PPS by time of progression, BRAF$^-$ subpopulation



Using this alternative approach had a significant impact on the model results. This is mainly because of two effects:

- The total per-patient life years associated to the immunotherapies was substantially reduced. This is because the long-term mortality rates were almost null over time, as they were based on a curve which remained basically flat over almost the entire time horizon, as shown in Figure 31;

- The (discounted) life years gained with combination immunotherapy compared to ipilimumab were reduced by half in the explorative analysis. The ERG attributes this variation to the combined effect of the longer TTP of combination immunotherapy and the PPS time implausibly increasing with time of progression in the company's base case.

The results of the scenario analysis, based on the revised company's base case, are reported from Table 113 to Table 116. The ICERs for the incremental analysis between combination immunotherapy and the most efficient comparator in the BRAF$^-$ and BRAF$^+$ analysis were £18,324 and £42,539 per QALY gained using list prices, [redacted].

Table 113. Removal of nested long-term PPS mortality: BRAF^{-} patients, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
Ipilimumab	[redacted]	2.23	1.72				
Combination immunotherapy	[redacted]	3.67	2.86	£20,810	1.44	1.14	£18,324
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 114. Removal of nested long-term PPS mortality: BRAF^{-} patients, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

Table 115. Removal of nested long-term PPS mortality: BRAF^{+} patients, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)

Dabrafenib	[redacted]	2.24	1.74						
Vemurafenib	[redacted]	2.24	1.74	£19,070	0.00	0.00	Same QALYs	Absolutely dominated	Excluded due to dominance
Ipilimumab	[redacted]	1.91	1.47	£25,941	-0.33	-0.27	-£95,079	Absolutely dominated	Excluded due to dominance
Combination immunotherapy	[redacted]	3.26	2.53	£33,567	1.01	0.79	£42,539		£42,539
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Note: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.									

Table 116. Removal of nested long-term PPS mortality: BRAF^{+} patients, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

6.2.2 Treatment effect on pre-progression mortality for immunotherapies

The company assumed that the difference between the pre-progression survival (PrePS) Kaplan Meier curves observed in the CheckMate 067 trial for combination immunotherapy and ipilimumab was maintained over the entire time horizon, based on the tails of the curves although they contained very little information. The company's modelling approach is described in more detail in Section 5.4.2.3 and Section 5.5.5.

The ERG does not consider the company's approach to PrePS modelling plausible for various reasons, as also described in Section 5.5.5.2:

- No difference in PrePS was demonstrated between treatments. On the contrary, no difference emerged when tested within a Cox proportional hazards model (Table 50), albeit not an entirely appropriate method to test for treatment differences; additionally, a graphical analysis does not seem to support treatment difference, and particularly a constant treatment difference between the end of the CheckMate 067 PrePS follow-up (about 1.5 years) and the end of the 40-year lifetime model horizon[31];

- The beginning of the application of mean patient-matched general population mortality in two different time points was not appropriate and favoured combination therapy without justification, as a no-event period between day 271 and day 553 was assumed (as observed in the trial, based on a steeply decreasing number of patients at risk and thus extremely weakly informative), while the general population mortality was applied at day 511 in the ipilimumab arm, which was associated with increased mortality for more than one model month compared to combination immunotherapy;

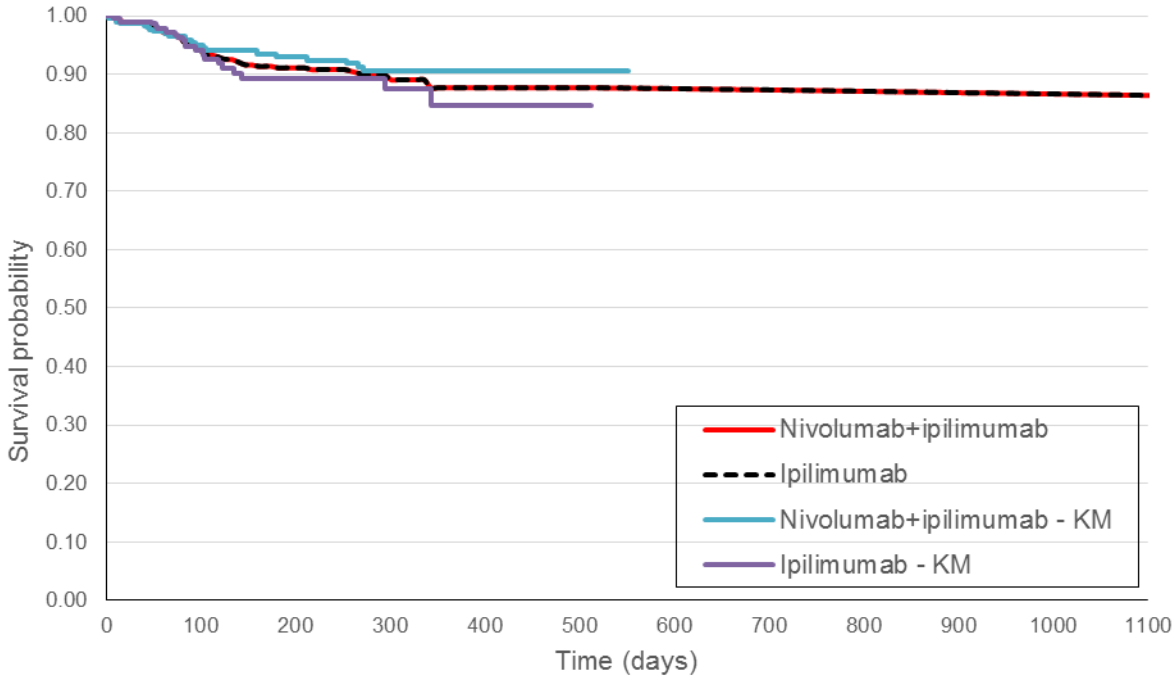
- Not limiting PrePS mortality with age- and gender-matched general population mortality, especially in correspondence of the flat tails of the curves (likely driven by an insufficient number of patients at risk) might have underestimated mortality;

- Assuming that patients with advanced, unresectable melanoma, even though free from progression, have the same mortality as the age- and gender-matched general population is likely to produce an overestimation of the expected survival.

To address these points, the ERG constructed an alternative PrePS scenario. In the scenario, the ERG averaged together the Kaplan Meier curves observed in the two trial arms. Half of the general population mortality rates were applied between day 511 and 553 (as they were applied in the ipilimumab Kaplan Meier curve), and applied fully from the end of the longest follow-up time between the two arms (i.e. 553 days in the combination immunotherapy arm) until the end of the time

horizon, as no other robust alternative data sources were identified. The resulting curve is shown in Figure 59 for the BRAF$^-$ subpopulation. The same methodology was applied to the BRAF$^+$ subpopulation, with analogous results.

Figure 59. Averaged Kaplan Meier curve used in the PrePS alternative scenario, BRAF$^-$ analysis



The model modification resulted in a substantial impact on the ICER, as it had a direct impact on the differential life years associated with ipilimumab and combination immunotherapy, with the quantity increasing in the former and decreasing in the latter. The scenario results are summarised from Table 117 to Table 120.

In the BRAF$^+$ analysis, the ICERs between combination immunotherapy and the most efficient comparator increased by about £800 and [redacted] per QALY gained in the list price and PAS scenarios, respectively. The ICERs for the BRAF$^+$ subpopulation increased by £500 per QALY in the list price scenario [redacted].

Table 117. PrePS Kaplan Meier curves averaging: BRAF^{-} patients, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
Ipilimumab	[redacted]	3.84	2.96				
Combination immunotherapy	[redacted]	6.38	4.95	£22,444	2.54	1.99	£11,260
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 118. PrePS Kaplan Meier curves averaging: BRAF^{-} patients, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

Table 119. PrePS Kaplan Meier curves averaging: BRAF^{+} patients, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)

Dabrafenib	[redacted]	2.24	1.74						
Vemurafenib	[redacted]	2.24	1.74	£19,070	0.00	0.00	Same QALYs	Absolutely dominated	Excluded due to dominance
Ipilimumab	[redacted]	3.45	2.65	£27,837	1.20	0.90	£30,804	Extendedly dominated	Excluded due to dominance
Combination immunotherapy	[redacted]	6.07	4.70	£37,377	3.83	2.96	£12,627		£12,627
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Note: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.									

Table 120. PrePS Kaplan Meier curves averaging: BRAF^{+} patients, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

6.2.3 Treatment dosage assumptions for combination immunotherapy

The company based the calculation of the amount of nivolumab and ipilimumab drugs received by patients in the combination immunotherapy arm based on the data collected in the CheckMate 067 trial.[80] In addition to a parametric model determining the proportion of patients who would remain on treatment over time (described in Section 5.4.5.3), the company also assumed a flat dose reduction for nivolumab. Patients were assumed to receive only 90.16% of the total quantity of the planned dose for the entire time horizon (with 2 years of maximum treatment time in the base case scenario). The company did not sufficiently justify this assumption and did not prove the reasonableness of a flat dose reduction constant over time. To test the robustness of the model to this assumption the ERG carried out a sensitivity analysis to assess the variation of the results when negating the dose reduction.

The results were found to be sensitive to the presence of the reduction, with the ICERs incrementing by about £1,900 and £1,200 per QALY in the $BRAF^-$ and $BRAF^+$ analyses using list prices, respectively.

[redacted]. The results of the scenario analyses are summarised in Table 121, Table 122, Table 123 and Table 124.

Table 121. Removal of flat dose reduction of nivolumab: BRAF^{-} patients, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
Ipilimumab	[redacted]	3.77	2.90				
Combination immunotherapy	[redacted]	6.55	5.09	£26,916	2.79	2.19	£12,302
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 122. Removal of flat dose reduction of nivolumab: BRAF^{-} patients, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

Table 123. Removal of flat dose reduction of nivolumab: BRAF^{+} patients, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)

Dabrafenib	[redacted]	2.24	1.74						
Vemurafenib	[redacted]	2.24	1.74	£19,070	0.00	0.00	Same QALYs	Dominated	Excluded due to dominance
Ipilimumab	[redacted]	3.38	2.59	£27,758	1.13	0.85	£32,651	Extendedly dominated	Excluded due to dominance
Combination immunotherapy	[redacted]	6.26	4.85	£41,169	4.02	3.11	£13,241		£13,241

Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Note: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

Table 124. Removal of flat dose reduction of nivolumab: BRAF^{+} patients, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

6.2.4 Second-line treatments received in post-progression

The company assumed that patients would receive second-line therapies according to the data collected in the CheckMate 067 and BRIM-3 RCTs, respectively for the immunotherapies and BRAF inhibitors.[3, 80] However, the ERG disagrees with how the data were used in the model and found inconsistencies between the data in the model and data reported in the CheckMate 067 CSR.[80]

The ERG conducted a scenario analysis to assess the robustness of the model results to the proportion of patients receiving subsequent therapies. As the ERG did not have access to the same data for the BRIM-3 trial, the analysis only compares combination immunotherapy and ipilimumab. As no difference in efficacy was assumed for the two treatments by the company, the analysis is performed for the entire population, irrespective of the BRAF status, using the model setting for the analysis of the $BRAF^-$ subpopulation.

The ERG used the data from the CheckMate 067 to estimate the probability of receiving one of the 4 subsequent treatments considered by the company (i.e. pembrolizumab, ipilimumab, dabrafenib and vemurafenib), as reported in Table 125.

Table 125. Probabilities of receiving subsequent therapy after progression by treatment arm

Subsequent therapies	Combination immunotherapy	Ipilimumab
Pembrolizumab	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]
[redacted]		

The differences in the probabilities of patients not receiving any subsequent treatment between the company's base case model and the ERG's scenario analysis are reported in Table 126.

Table 126. Comparison between proportions of patients not receiving any subsequent therapy

Value set	Combination immunotherapy	Ipilimumab
Company's base case model, $BRAF^-$ subpopulation	[redacted]	[redacted]
Company's base case model, $BRAF^+$ subpopulation	[redacted]	[redacted]
Company's base case model, average of subpopulations	[redacted]	[redacted]
ERG's scenario analysis	[redacted]	[redacted]
[redacted]		

The results for the whole population are reported in Table 127 and Table 128, respectively using list and PAS prices. [redacted] The resulting ICER was considerably lower than the base case estimate for list price scenario, when compared to the BRAF- analysis results. [redacted].

Table 127. Alternative probabilities of receiving subsequent treatments, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
Ipilimumab	[redacted]	3.77	2.90				
Combination immunotherapy	[redacted]	6.55	5.09	£18,256	2.79	2.19	£8,344
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 128. Alternative probabilities of receiving subsequent treatments, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ / QALY)
[redacted]							
[redacted]							
[redacted]							

6.2.5 Summary of the ERG scenario analyses

The scenario analyses based on the company's economic model are summarised in this section. Table 129 and Table 130 show the results for the analyses conducted in the BRAF- subpopulation, respectively using list prices and PAS prices. The results for the $BRAF^{+}$ subpopulation are summarised, for the list prices and PAS scenarios, in Table 131 and Table 132, respectively.

Table 129. Results of the ERG's scenario analyses: $BRAF^{-}$ subpopulation: list prices

	Results per patient	Combination immunotherapy (1)	Ipilimumab (2)	Incremental value (1-2)
0	**Revised base case**			
	Total costs (£)	[redacted]	[redacted]	£22,826
	QALYs	5.09	2.90	2.19
	ICER			£10,433
1	**Removal of nested long-term PPS mortality**			
	Total costs (£)	[redacted]	[redacted]	£20,810
	QALYs	2.86	1.72	1.44
	ICER			£18,324
2	**PrePS Kaplan Meier curves averaging**			
	Total costs (£)	[redacted]	[redacted]	£22,444
	QALYs	4.95	2.96	1.99
	ICER			£11,260
3	**Removal of flat dose reduction of nivolumab**			
	Total costs (£)	[redacted]	[redacted]	£26,916
	QALYs	5.09	2.90	2.19
	ICER			£12,302
4	**Alternative probabilities of receiving subsequent treatments (independent of BRAF status)**			
	Total costs (£)	[redacted]	[redacted]	£18,256
	QALYs	5.09	2.90	2.19
	ICER			£8,344

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; PPS, post-progression survival; PrePS, pre-progression survival; QALY, quality-adjusted life year.

Table 130. Results of the ERG's scenario analyses: $BRAF^{-}$ subpopulation: PAS prices

	Results per patient	Combination immunotherapy (1)	Ipilimumab (2)	Incremental value (1-2)
[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]		[redacted]
[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]		[redacted]
[redacted]				

	Results per patient	Combination immunotherapy (1)	Ipilimumab (2)	Incremental value (1-2)
[redacted]				

Table 131. Results of the ERG's scenario analyses: BRAF^{+} subpopulation: list prices

	Results per patient	Combination immunotherapy (1)	Ipilimumab (2)	Dabrafenib (3)	Vemurafenib (4)	Incremental value (1-2)	Incremental value (1-3)	Incremental value (1-4)
0	**Revised base case**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	£9,924	£37,682	£18,612
	QALYs	6.26	3.38	2.24	2.24	2.26	3.11	3.11
	ICER					£4,391	£12,116	£5,985
1	**Removal of nested long-term PPS mortality**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	£7,627	£33,568	£14,498
	QALYs	3.26	1.91	2.24	2.24	1.06	0.79	0.79
	ICER					£7,195	£42,491	£18,352
2	**PrePS Kaplan Meier curves averaging**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	£9,540	£37,377	£18,307
	QALYs	6.07	3.45	2.24	2.24	2.05	2.96	2.96
	ICER					£4,654	£12,627	£6,185
3	**Removal of flat dose reduction of nivolumab**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	£13,411	£41,169	£22,099
	QALYs	6.26	3.38	2.24	2.24	2.26	3.11	3.11
	ICER					£5,934	£13,238	£7,106

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; PPS, post-progression survival; PrePS, pre-progression survival; QALY, quality-adjusted life year.

Table 132. Results of the ERG's scenario analyses: BRAF^{+} subpopulation: PAS prices

	Results per patient	Combination immunotherapy (1)	Ipilimumab (2)	Dabrafenib (3)	Vemurafenib (4)	Incremental value (1-2)	Incremental value (1-3)	Incremental value (1-4)

	Results per patient	Combination immunotherapy (1)	Ipilimumab (2)	Dabrafenib (3)	Vemurafenib (4)	Incremental value		
						(1-2)	(1-3)	(1-4)
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
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[redacted]								

6.3 ERG base case ICER

6.3.1 Considerations on comparability with BRAF inhibitors

The ERG does not consider the comparative analysis between combination immunotherapy and BRAF inhibitors to be sufficiently robust evidence to base an assessment of cost-effectiveness. The analysis should be interpreted with extreme caution and the comparative results should be considered exploratory and not probative, as described in Section 6.3.3. Due to these considerations, the ERG does not present a preferred base case ICER for the comparison between combination immunotherapy and BRAF inhibitors. This comparison is presented in Section 6.3.4, under specific exploratory assumptions.

6.3.2 ERG base case scenario

The ERG presents a single preferred base case scenario including both $BRAF^{+}$ and $BRAF^{-}$ patients considering the same case mix observed in CheckMate 067. According to the company's assumptions and analyses, BRAF status does not influence the outcomes associated with immunotherapy treatment, and as the ERG base case makes use of the subsequent therapy data observed directly from the CheckMate 067 CSR, the model results are deemed to be relevant for both subpopulations.

The ERG identified four areas which were considered to be founded on implausible assumptions in the company's model, i.e. the integration of long-term PPS mortality, the assumption on treatment effect on PrePS, the constant flat reduction of the dosage of nivolumab, and finally the proportion of patients accessing to second-line treatments in post-progression. These scenarios have been analysed separately in Section 6.2, and considered altogether form the underlying assumptions differing between the company's and the ERG's base case.

The different assumptions or data used by the ERG compared to the company's base case scenario are:

- Data amendments as reported in Section 6.1: proportion of patients with endocrine events in the ipilimumab arm; proportion of patients who receive ipilimumab after BRAF inhibitors (not influential in the ERG base case);
- Alternative probabilities of receiving subsequent treatments, using data from the CheckMate 067 trial as detailed in Section 6.2.4. This modification allowed for not separating $BRAF^{+}$ and $BRAF^{-}$ patients in the analysis, as no other differences were assumed between the immunotherapies other than subsequent treatment received;
- Removal of nested long-term PPS mortality to avoid the implausible survival conditional on time of progression described in Section 5.5.5;
- Averaging of the PrePS Kaplan Meier curves for combination immunotherapy and ipilimumab from the CheckMate 067 RCT as no significant difference was observed;
- Removal of the constant flat dose reduction for nivolumab.

Details of the modifications to the economic model are reported in Appendix 9.1.

Table 133. ERG base case ICER, list prices

Results per patient	Combination immunotherapy	Ipilimumab	Incremental value
Company's amended base case ($BRAF^{-}$ subpopulation)			
Total costs (£)	[redacted]	[redacted]	£22,826
QALYs	5.09	2.90	2.19
ICER			**£10,433**
Alternative probabilities of receiving subsequent treatments			
Total costs (£)	[redacted]	[redacted]	£18,256
QALYs	5.09	2.90	2.19
ICER (compared with base case)			£8,344
ICER with all changes incorporated			**£8,344**
Removal of nested long-term PPS mortality			

Results per patient	Combination immunotherapy	Ipilimumab	Incremental value
Total costs (£)	[redacted]	[redacted]	£16,110
QALYs	2.86	1.72	1.14
ICER (compared with base case)			£18,324
ICER with all changes incorporated			**£14,185**
PrePS Kaplan Meier curves averaging			
Total costs (£)	[redacted]	[redacted]	£15,905
QALYs	2.79	1.75	1.03
ICER (compared with base case)			£11,260
ICER with all changes incorporated			**£26,028**
Removal of flat dose reduction of nivolumab			
Total costs (£)	[redacted]	[redacted]	£19,996
QALYs	2.79	1.75	1.03
ICER (compared with base case)			£12,302
ICER with all changes incorporated			**£19,322**
ERG preferred base case ICER			**£19,322**

Abbreviation used in the table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PPS, post-progression survival; PrePS, pre-progression survival; QALY, quality-adjusted life year.

Table 134. ERG base case ICER, PAS prices

Results per patient	Combination immunotherapy	Ipilimumab	Incremental value
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			[redacted]
[redacted]			

Results per patient	Combination immunotherapy	Ipilimumab	Incremental value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]			

6.3.3 Considerations on the ERG preferred base case ICER

The ERG estimates an ICER for the comparison between combination immunotherapy and ipilimumab in advanced (unresectable, metastatic) adult patients equal to £19,322 per QALY gained using list prices and [redacted]. However, the ERG notes the presence of a substantial degree of uncertainty associated with these results. That is, the survival benefit of combination immunotherapy over ipilimumab in the model relies completely on the surrogacy assumption between time to progression (TTP) and overall survival (OS).

6.3.4 Explorative results for the comparison to BRAF inhibitors in the BRAF^{+} subpopulation

As already stated throughout the report, the ERG does not consider the comparison between the immunotherapies and the BRAF inhibitors to be appropriate because of the different modelling approaches taken. The main differences between the partitioned survival and the semi-Markov approaches are the assumptions on the determinants of the mortality benefit. In the partitioned survival model the OS is assumed independent on PFS (and TTP), while in the semi-Markov approach differences in TTP (and PFS) determine differences in OS.

As an exploratory analysis, the ERG reports the economic results of the BRAF^{+} subpopulation analysis assuming a relatively short time horizon, equal to 5 years. Given the amount of uncertainty associated to long-term extrapolations and projections of mortality and concerns regarding the comparability of the two approaches, longer time horizons are not considered. The ERG expects that, based on the assumptions adopted in the preferred base case scenario, longer time horizons would underestimate the survival associated to immunotherapies compared to BRAF inhibitors. The following data and assumptions differed from the company's base case:

- Model corrections as described in Section 6.1;
- Removal of nested long-term PPS mortality for immunotherapies;
- Averaging of the PrePS Kaplan Meier curves for immunotherapies;
- Removal of flat dose reduction of nivolumab;
- Model time horizon of 5 years.

Table 135. Exploratory results for the BRAF^{+} subpopulation for a 5-year time horizon, list prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
Dabrafenib	[redacted]	1.62	1.27						
Vemurafenib	[redacted]	1.62	1.27	£17,041	0.00	0.00	Same QALYs	Absolutely dominated	Excluded due to dominance
Ipilimumab	[redacted]	1.54	1.19	£33,669	-0.08	-0.08	-£420,190	Absolutely dominated	Excluded due to dominance
Combination immunotherapy	[redacted]	2.20	1.70	£44,357	0.57	0.44	£101,779		£101,779

Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

Table 136. Exploratory results for the BRAF^{+} subpopulation for a 5-year time horizon, PAS prices scenario

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	Dominance	ICER (£) incremental (QALYs)
[redacted]									

7 OVERALL CONCLUSIONS

The company submitted clinical and economic evidence in support of the effectiveness of nivolumab and ipilimumab combination immunotherapy for the treatment of advanced melanoma. The evidence presented for the comparison of combination immunotherapy versus ipilimumab was based on data from CheckMate 067 and CheckMate 069, two well-designed, multicentre, double-blind, parallel-group randomised controlled trials. However, as the OS data from both CheckMate 067 and CheckMate 069 were immature at the time of submission, the company performed an "indirect" comparison using covariate adjusted data from CheckMate 066 and MDX010-20, in addition to data from CheckMate 067. An indirect comparison was also performed to compare combination immunotherapy to the BRAF inhibitor vemurafenib, as no direct evidence was identified for the comparison against either BRAF inhibitor (vemurafenib or dabrafenib). The ERG has concerns around the transparency of the choice of trials to inform the indirect comparisons of combination immunotherapy versus ipilimumab and BRAF inhibitors. The ERG also has concerns that the indirect comparison approach presented by the company requires several assumptions which may not be justified. The evidence presented by the company, in support of some of these assumptions does not definitively demonstrate their validity (e.g. the effect of line of treatment and the equivalence of BRAF inhibitor efficacy). The effect of previous treatments is likely a conservative estimate of OS for combination immunotherapy and ipilimumab, though the effect on PPS is unknown. Also, if the efficacy of the BRAF inhibitors is not equivalent, no estimate of combination immunotherapy versus dabrafenib is available. Although the company adjust the data for several prognostic factors and other covariates, the company did not present any validation of the covariate adjusted approach in the CS. It is unclear if all relevant covariates were captured and adjusted for in the indirect comparisons, and if the adjustments of the included covariates were sufficient. Importantly, by using the covariate adjusted approach, the intrinsic advantages of using results from randomised controlled trials are lost.

Additionally, no reliable long-term survival data were available for either of the BRAF inhibitors and no evidence for the comparison of combination immunotherapy and pembrolizumab presented in the CS, as the company did not consider pembrolizumab to be a relevant comparator to combination immunotherapy.

The company presented an economic analysis comparing combination immunotherapy to ipilimumab monotherapy in the $BRAF^-$ subpopulation, and to ipilimumab monotherapy, dabrafenib and vemurafenib in the $BRAF^+$ subpopulation. The company did not include pembrolizumab as a comparator in the submitted evidence as part of the company's submission (CS) while the technology was included in the NICE Final Scope.[1] Overall, the company's submission was clear and well-presented. The economic model was well-implemented and the results were in line with the

company's assumptions. However, the ERG notes that sensitivity analyses and alternative scenarios were scarcely documented and described.

The ERG considers the evidence presented was sufficient for the comparison between combination immunotherapy and ipilimumab in adult patients with advanced (unresectable or metastatic) melanoma. The results emerging from the ERG analysis of the company's comparison between combination immunotherapy and ipilimumab identified an estimated ICER of £19,322 per QALY gained in the list price scenario [redacted].

However, the ERG deems the economic evidence submitted for the comparisons between combination immunotherapy and the BRAF inhibitors (dabrafenib and vemurafenib) and between combination immunotherapy and pembrolizumab to be insufficient to produce reliable estimates of cost-effectiveness.

The ERG restricted the time horizon of the analysis in the $BRAF^+$ subpopulation to 5 years because of concerns regarding the comparability of the evidence submitted for BRAF inhibitors and combination immunotherapy. Due to the use of two different modelling approaches based on different assumptions and because of the impact these would have on deriving long-term extrapolations of the health outcomes, the ERG does not deem the comparison between combination immunotherapy and BRAF inhibitors to provide sufficient information on the comparative cost-effectiveness profile. In the analysis using list prices, the results of the ERG incremental exploratory analysis indicate that the most efficient comparator in the $BRAF^+$ subpopulation is dabrafenib. The ICER for the comparison between dabrafenib and combination immunotherapy is £101,779 per QALY gained. [redacted]. It is expected that a longer time horizon would result in a lower ICER, as combination immunotherapy is associated with higher treatment costs but also with increased PFS and OS times compared to dabrafenib.

The comparison between combination immunotherapy and pembrolizumab indicates that pembrolizumab seems to be associated with lower total costs per patient. The exploratory naïve network meta-analysis carried out by the ERG, based on the HRs reported in the main trials for combination immunotherapy and pembrolizumab when compared to ipilimumab, [redacted] This might be indicative of a similar cost-effectiveness profile, if the differences in costs are balanced by the potential difference in PFS time (determining a difference in terms of quality-adjusted life years), or else a favourable cost-effectiveness profile for pembrolizumab when compared to combination immunotherapy. However,

the ERG considers the evidence provided by the company to be insufficient to support any conclusion for this comparison.

7.1 Implications for research

From the clinical evidence presented in the CS it is clear that a substantial proportion of patients treated with combination immunotherapy, had a continued response despite discontinuation of study drug. Other patients were treated beyond RECIST defined progression as they continued to experience clinical benefit. This highlights the uncertainty around the optimal duration of treatment, which could be assessed in future trials.

Additional health economics evidence is needed in the disease area to inform the comparative cost-effectiveness profile of the available treatments. Robust, comparative evidence (either direct or indirect) is needed to compare the novel technologies for treatment of advanced melanoma, i.e. pembrolizumab, nivolumab monotherapy and nivolumab in combination with ipilimumab, with treatment alternatives such as dabrafenib, vemurafenib and ipilimumab monotherapy. The treatment pathway should also take into account the combination of BRAF and MEK inhibitors, and assess the patients who would benefit the most from each treatment strategy.

Given the increasing availability of treatment choices and the lack of clinical and economic comparative data, a full health economic evaluation which would take into account all the available technologies should be conducted. The ERG considers the Multiple Technology Appraisal (MTA) process the most suitable form of analysis to inform an evidence-based treatment pathway in advanced melanoma.

8 REFERENCES

1. National Institute for Health and Care Excellence (NICE). Final scope for the appraisal of nivolumab in combination with ipilimumab for advanced, unresectable melanoma. 2015.
2. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358-65.
3. McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. The Lancet Oncology. 2014;15(3):323-32.
4. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(17):1889-94.
5. Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Spatz A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline--Update 2012. European journal of cancer (Oxford, England : 1990). 2012;48(15):2375-90.
6. Society AC. Melanoma skin cancer Available at: http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-what-is-melanoma2014 [cited 2015 9 February].
7. UK CR. Skin Cancer Statistics Report. 2013.
8. Erdmann F, Lortet-Tieulent J, Schuz J, Zeeb H, Greinert R, Breitbart EW, et al. International trends in the incidence of malignant melanoma 1953-2008--are recent generations at higher or lower risk? International journal of cancer Journal international du cancer. 2013;132(2):385-400.
9. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. British journal of cancer. 2011;105 Suppl 2:S77-81.
10. Arnold M, Holterhues C, Hollestein LM, Coebergh JW, Nijsten T, Pukkala E, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. Journal of the European Academy of Dermatology and Venereology : JEADV. 2014;28(9):1170-8.
11. Foundation SC. Skin Cancer Facts Available at: http://www.skincancer.org/skin-cancer-information/skin-cancer-facts2014 [cited 2016 3 March].
12. Cancer AJCo. Melanoma of the Skin Staging Available at: http://www.cancer.org/cancer/skincancer-

melanoma/detailedguide/melanoma-skin-cancer-what-is-melanoma2009 [cited 2015 9 February].
13. Cancer Research UK. Melanoma skin cancer Available at: http://www.cancerresearchuk.org/about-cancer/type/melanoma/2015 [cited 2015 2 February].
14. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(36):6199-206.
15. UK CR. Skin cancer incidence statistics. Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/skin/incidence/uk-skin-cancer-incidence-statistics2013 [cited 2015 26 Jan].
16. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1998;83(8):1664-78.
17. Institute NC. SEER Stat Fact Sheets: Melanoma of the Skin. Available at: http://seer.cancer.gov/statfacts/html/melan.html [cited 2015 26 January].
18. (NCCN) NCCN. NCCN Guidelines for Patients: Melanoma. Available at: http://www.nccn.org/patients/guidelines/melanoma/: 2013.
19. Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(4):527-34.
20. UK M. About melanoma: Statistics. Available at: http://www.melanomauk.org.uk/about_melanoma/statistics/2015 [cited 2015 2 February].
21. Bedikian AY, Johnson MM, Warneke CL, Papadopoulos NE, Kim K, Hwu WJ, et al. Prognostic factors that determine the long-term survival of patients with unresectable metastatic melanoma. Cancer Invest. 2008;26(6):624-33.
22. J. E. Gershenwald DLM, J. F. Thompson, J. M. Kirkwood, S. Soong, C. M., Balch AME, V. K. Sondak, M. M. Johnson, C. Warneke Collaborators of, Force tAUMT, editors. Staging and prognostic factors for stage IV melanoma: Initial results of an American Joint Committee on Cancer (AJCC) international evidencebased assessment of 4,895 melanoma patients. The American Society of Clinical Oncology Annual Meeting; 2008; Chicago, IL, USA.
23. Ascierto PA, Kirkwood JM, Grob JJ, Simeone E, Grimaldi AM, Maio M, et al. The role of BRAF V600 mutation in melanoma. J Transl Med. 2012;10:85.

24. Long GV, Menzies AM, Nagrial AM, Haydu LE, Hamilton AL, Mann GJ, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(10):1239-46.
25. (NCCN) NCCN. NCCN Clinical Practice Guidelines on Oncology. Melanoma. version 3.2015. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf: 2015.
26. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. The New England journal of medicine. 2010;363(8):711-23.
27. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. The New England journal of medicine. 2011;364(26):2507-16.
28. National Institute for Health and Care Excellence (NICE). Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (TA357). 2015.
29. (NICE) NIfHaCE. Nivolumab for treating advanced (unresectable or metastatic) melanoma. Available at: https://www.nice.org.uk/guidance/TA384/documents/html-content2016.
30. Bristol-Myers Squibb. Nivolumab-Ipilimumab combination in Melanoma Advisory Board. 2015.
31. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. The New England journal of medicine. 2015;373(1):23-34.
32. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. The New England journal of medicine. 2015;372(21):2006-17.
33. Squibb B-M. A Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma. (Clinical Study Report: CA209067 v1.0). 2015.
34. Squibb B-M. A Phase 2, randomized, double blinded study of nivolumab (BMS-936558) in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma. (Clinical Study Report: CA209069 v1.0). 2015.
35. FDA. FDA approves Opdivo to treat advanced form of kidney cancer 2015. Available from: Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473971.htm.
36. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. The New England journal of medicine. 2015;372(4):320-30.

37. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. Journal of the National Cancer Institute. 2000;92(3):205-16.
38. Squibb B-M. A phase 1B, open-label, multicenter, multidose, dose-escalation study of MDX-1106 (BMS-936558) in combination with ipilimumab (BMS-734016) in subjects with unresectable stage III or stage IV malignant melanoma. Final Clinical Study Report for Study MDX1106-04 (CA209004). 2014.
39. (CRD) CfRaD. CRD's guidance for undertaking reviews in health care. 2008.
40. Hamid O, Schmidt H, Nissan A, Ridolfi L, Aamdal S, Hansson J, et al. A prospective phase II trial exploring the association between tumor microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. J Transl Med. 2011;9:204.
41. Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. The Lancet Oncology. 2010;11(2):155-64.
42. Hersh EM, O'Day SJ, Powderly J, Khan KD, Pavlick AC, Cranmer LD, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naive patients with advanced melanoma. Invest New Drugs. 2011;29(3):489-98.
43. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. New England Journal of Medicine. 2015;372(26):2521-32.
44. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. The New England journal of medicine. 2014;371(20):1877-88.
45. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. The New England journal of medicine. 2012;367(18):1694-703.
46. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. The New England journal of medicine. 2015;372(1):30-9.
47. Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. The New England journal of medicine. 2014;371(20):1867-76.
48. Grippo JF, Zhang W, Heinzmann D, Yang KH, Wong J, Joe AK, et al. A phase I, randomized, open-label study of the multiple-dose pharmacokinetics of vemurafenib in patients with BRAF V600E

mutation-positive metastatic melanoma. Cancer Chemother Pharmacol. 2014;73(1):103-11.
49. (NICE) NIfHaCE. Methodology checklist: randomised controlled trials. 2016.
50. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Protocol for: Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. The New England journal of medicine. 2015;373(1):23-34.
51. Sznol M, Callahan MK, Kluger H, Postow MA, Gordon RA, Segal NH, et al. Updated survival, response and safety data in a phase 1 dose-finding study (CA209-004) of concurrent nivolumab (NIVO) and ipilimumab (IPI) in advanced melanoma. Society for Melanoma Research (SMR) 2015 International Congress; November 18–21, 2015; San Francisco, California, USA2015.
52. Larkin J, Chiarion-Sileni V, Gonzalez R, al. e. Efficacy and safety in key patient subgroups of nivolumab alone or combined with ipilimumab versus ipilimumab alone in treatment-naïve patients with advanced melanoma (Checkmate 067). European Cancer Congress; 25-29 September 2015; Vienna, Austria2015.
53. Schadendorf D, Long GV, Larkin J, al. e. Patient reported outcomes from a Phase 3 study of nivolumab alone or combined with ipilimumab vs ipilimumab in patients with advanced melanoma: CheckMate 067. Society for Melanoma Research International Congress; 18-21 November 2015; San Francisco, CA, USA2015.
54. Wolchok J, Chiarion SV, Gonzalez R, al. e. Efficacy and safety results from a Phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment naive patients (pts) with advanced melanoma (MEL) (CheckMate 067). The American Society of Clinical Oncology Annual Meeting; 29 May - 2 June 2015; Chicago, IL, USA2015.
55. Abernethy AP, Postow MA, Chesney J. Effect of nivolumab (NIVO) in combination with ipilimumab (IPI) versus IPI alone on quality of life (QoL) in patients (pts) with treatment-naive advanced melanoma (MEL): Results of a Phase II study (CheckMate 069). The American Society of Clinical Oncology Annual Meeting; Chicago, Illinois, USA.2015.
56. Hodi FS, Postow MA, Chesney JA, al. e. Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study. The American Society of Clinical Oncology Annual Meeting; 29 May - 2 June 2015; Chicago, IL, USA2015.
57. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369(2):122-33.
58. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Protocol: Nivolumab and ipilimumab versus

ipilimumab in untreated melanoma. The New England journal of medicine. 2015;372(21):2006-17.
59. Bristol-Myers Squibb. A Phase 3, Randomized, Double-blind Study of BMS-936558 (Nivolumab) Versus Dacarbazine in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma. Final Clinical Study Report for Study CA209066. 2014.
60. Bristol-Myers Squibb. Nivolumab (BMS-936558) Study CA209067 OS Efficacy Update Report. 2015.
61. (NICE) NIfHaCE. Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID845]. 2016.
62. National Institute for Health and Care Excellence (NICE). TA319: Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. 2014.
63. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside trials - extrapolation with patient-level data. ScHARR, University of Sheffield, 2011.
64. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. ScHARR, University of Sheffield, 2014.
65. Latimer N. Handling treatment crossover (switching) in cancer trials. Presented at the InterTASC Survival Analysis Workshop, University of York, October 2014.
66. Shahabi V, Whitney G, Hamid O, Schmidt H, Chasalow SD, Alaparthy S, et al. Assessment of association between BRAF-V600E mutation status in melanomas and clinical response to ipilimumab. Cancer immunology, immunotherapy : CII. 2012;61(5):733-7.
67. Feng Y, Berman D, Chen T-T, al. e. Ipilimumab exposure-response and meta-analysis of overall survival of advanced melanoma patients. The European Society for Medical Oncology (ESMO) Congress; 26-30 September 2014; Madrid, Spain2014.
68. Won Kim D, Chakravarti N, Trinh VA, al. e. Predictive markers for programmed death1 (PD1)/programmed deathligand 1(PD-L1) axis blockade therapy in patients with metastatic melanoma (MM). The American Society of Clinical Oncology Annual Meeting; 29 May - 2 June 2015; Chicago, IL, USA2015.
69. National Institute for Health and Care Excellence (NICE). Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). 2012.
70. Pocock SJ. Clinical Trials: A Practical Approach. New York: Wiley; 1996.
71. National Institute for Health and Care Excellence (NICE). Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA321). 2014.
72. Hauschild A, Grob JJ, Demidov LV, al. e, editors. An update on overall survival (OS) and follow-on therapies in BREAK-3, a Phase III, randomized trial: Dabrafenib (D) vs. dacarbazine (DTIC) in patients (pts)

with BRAF V600E mutation-positive metastatic melanoma (MM). The European Society for Medical Oncology (ESMO) Congress Poster 1092PD; 2014 26-30 September 2014; Madrid, Spain.
73. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444-51.
74. Hauschild A, McArthur G, Robert C, al. e. Vemurafenib improves overall survival compared with dacarbazine in advanced BRAF V600-mutated melanoma: updated results from a Phase III randomized, multicenter trial. 10th International Meeting of the Society for Melanoma Research; 17-20 November 2013; Philadelphia, PA, USA2013.
75. Hauschild A. Response to a costly revolution for a subgroup of patients with metastatic melanoma. British Journal of Dermatology. 2013;168(3):470-1.
76. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology. 2012;12:9.
77. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. The Lancet Oncology.16(8):908-18.
78. Scottish Intercollegiate Guidelines Network (SIGN). Scottish Intercollegiate Guidelines Network (SIGN). Search Filters http://www.sign.ac.uk/methodology/filters.htmlLast modified 16/05/14 [13/04/2015].
79. Daud A. Recent Advances in Melanoma Therapy. Journal of Managed care Medicine. 2014;17(1):33.
80. Bristol-Myers Squibb. A Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma. (Clinical Study Report: CA209067 v1.0). 2015 19 June 2015. Report No.
81. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Available at https://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf, 2013.
82. Jackson C. flexsurv: Flexible Parametric Survival and Multi-State Models. CRAN, Comprehensive R Archive Network2015.
83. R Core Team. R: A language and enviromnment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2014.
84. Balch CM, Buzaid AC, Soong SJ, Atkins MB, Cascinelli N, Coit DG, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. Journal of clinical oncology : official

journal of the American Society of Clinical Oncology. 2001;19(16):3635-48.
85. Oxford Outcomes. Advanced melanoma resource use and costs in Europe: Final report. Data on File. 2011 16 May 2011. Report No.
86. Long GV, Atkinson V, Ascierto PA, Robert C, Hassel JC, Rutkowski P, et al. Effect of nivolumab (NIVO) on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): Results of a phase III study (CheckMate 066). Journal of Clinical Oncology. 2015;33(15).
87. Askew RL, Swartz RJ, Xing Y, Cantor SB, Ross MI, Gershenwald JE, et al. Mapping FACT-Melanoma Quality-of-Life Scores to EQ-5D Health Utility Weights. Value in Health. 2011;14(6):900-6.
88. Barzey V, Atkins MB, Garrison LP, Asukai Y, Kotapati S, Penrod JR. Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis. J Med Econ. 2013;16(2):202-12.
89. Batty A, Lee D, Winn B. Estimating quality of life in advanced melanoma; a comparison of standard gamble, SF-36 mapped, and EORTC QLQ-C30 mapped utilities. ISPOR 14th Annual European Congress; Madrid, Spain.2011.
90. Batty A, Winn B, Pericleous L. A comparison of general population and patient utility values for advanced melanoma. The European Society for Medical Oncology (ESMO) Congress; Vienna, Austria.2012.
91. Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. British journal of cancer. 2009;101(3):387-9.
92. Cormier JN, Xing Y, Ding M, Cantor SB, Salter KJ, Lee JE, et al. Cost Effectiveness of Adjuvant Interferon in Node-Positive Melanoma. Journal of Clinical Oncology. 2007;25(17):2442-8.
93. Dixon S, Walters SJ, Turner L, Hancock BW. Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial. British journal of cancer. 2006;94(4):492-8.
94. Hirst NG, Gordon LG, Scuffham PA, Green AC. Lifetime cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(2):261-8.
95. King S, Bonaccorsi P, Bendeck S, et al. Melanoma quality of life: Pilot study using utility measurements. Archives of Dermatology. 2011;147(3):353-4.
96. Lee D, Pennington B, Lebmeier M, Batty AJ. Modelling the cost effectiveness of ipilimumab for previously-treated, metastatic melanoma. ISPOR 15th Annual European Congress; 3-7 November 2012.; Berlin, Germany.2012.
97. Losina E, Walensky RP, Geller A, Beddingfield FC, Wolf LL, Gilchrest BA, et al. Visual Screening for Malignant Melanoma: A Cost-effectiveness Analysis. Archives of dermatology. 2007;143(1):21-8.

98. Mooney MM, Mettlin C, Michalek AM, Petrelli NJ, Kraybill WG. Life-long screening of patients with intermediate-thickness cutaneous melanoma for asymptomatic pulmonary recurrences: a cost-effectiveness analysis. Cancer. 1997;80(6):1052-64.
99. Hatswell AJ, Pennington B, Pericleous L, Rowen D, Lebmeier M, Lee D. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health and quality of life outcomes. 2014;12(1):1-9.
100. Porter J, Lee D, Hertel N, Hatswell AJ. Patient reported utilities in first-line advanced or metastatic melanoma: Analysis of trial CA 184-024. ISPOR 17th Annual European Congress; Amsterdam, The Netherlands.2014.
101. Delea TE, Amdahl J, Wang A, Amonkar MM, Thabane M. Cost Effectiveness of Dabrafenib as a First-Line Treatment in Patients with BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma in Canada. PharmacoEconomics. 2015;33:367-80.
102. Li Y, Bare LA, Bender RA, Sninsky JJ, Wilson LS, Devlin JJ, et al. Cost Effectiveness of Sequencing 34 Cancer-Associated Genes as an Aid for Treatment Selection in Patients with Metastatic Melanoma. Molecular Diagnosis & Therapy. 2015;19(3):169-77.
103. Matter-Walstra K, Braun R, Kolb C, Ademi Z, Dummer R, Pestalozzi BC, et al. A cost-effectiveness analysis of trametinib plus dabrafenib as first-line therapy for metastatic BRAF V600-mutated melanoma in the Swiss setting. British Journal of Dermatology. 2015;173(6):1462-70.
104. Shih V, ten Ham RM, Bui CT, Tran DN, Ting J, Wilson L. Targeted Therapies Compared to Dacarbazine for Treatment of BRAF(V600E) Metastatic Melanoma: A Cost-Effectiveness Analysis. Journal of Skin Cancer. 2015;2015:505302.
105. Amdahl J, Wang A, Thabane M, Amonkar M, Delea TE. Cost Effectiveness of Trametinib as First-Line (1l) Treatment for Braf V600 Positive Advanced or Metastatic Melanoma — A Canadian Societal Perspective. Value in Health. 2014;17(3):A83.
106. Rowen D, Brazier J, Young T, Gaugris S, King MT, Craig B, et al. Deriving a Preference-Based Measure for Cancer Using the EORTC QLQ-C30. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(5):721-31.
107. Hatswell AJ, Pennington B, Pericleous L, Rowen D, Lebmeier M, Lee D. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health Qual Life Outcomes. 2014;12:140.
108. Askew RL, Swartz RJ, Xing Y, Cantor SB, Ross MI, Gershenwald JE, et al. Mapping FACT-melanoma quality-of-life scores to EQ-5D health utility weights. Value Health. 2011;14(6):900-6.
109. Cormier JN, Xing Y, Ding M, Cantor SB, Salter KJ, Lee JE, et al. Cost effectiveness of adjuvant interferon in node-positive melanoma. Journal

of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(17):2442-8.
110. Kilbridge KL, Weeks JC, Sober AJ, Haluska FG, Slingluff CL, Atkins MB, et al. Patient Preferences for Adjuvant Interferon Alfa-2b Treatment. Journal of Clinical Oncology. 2001;19(3):812-23.
111. Hillner BE, Smith TJ, Desch CE. Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer: Estimates using decision analysis while awaiting clinical trial results. JAMA. 1992;267(15):2055-61.
112. Morton RL, Howard K, Thompson JF. The cost-effectiveness of sentinel node biopsy in patients with intermediate thickness primary cutaneous melanoma. Annals of Surgical Oncology. 2009;16(4):929-40.
113. Chen SC, Bendeck S, Hadley JC. Can melanoma patients predict the quality of life of an alternate melanoma stage? 26th Annual Meeting of the Society for Medical Decision Making; 17-20 October 2014; Atlanta, GA, USA.2004.
114. Beusterien KM, Ackerman SJ, Plante K, Glaspy J, Naredi P, Wood D, et al. The health-related quality-of-life impact of histamine dihydrochloride plus interleukin-2 compared with interleukin-2 alone in patients with metastatic melanoma. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2003;11(5):304-12.
115. King SM, Bonaccorsi P, Bendeck S, Hadley J, Puttgen K, Kolm PG, et al. Melanoma quality of life: pilot study using utility measurements. Archives of dermatology. 2011;147(3):353-4.
116. Lee D, Pennington B, Lebmeier M, Batty AJ. Modelling the cost effectiveness of ipilimumab for previously-treated, metastatic melanoma. ISPOR 15th Annual European Congress. Berlin: Germany; 2012.
117. Wong JB, Koff RS, Tine F, Pauker SG. Cost-effectiveness of Interferon-α2b Treatment for Hepatitis B e Antigen-Positive Chronic Hepatitis B. Annals of internal medicine. 1995;122(9):664-75.
118. National Institute for Health Research (NIHR) Horizon Scanning Centre (HSC). MEK162 for NRAS mutation positive advanced malignant melanoma - first and second line. 2013.
119. National Institute for Health Research (NIHR) Horizon Scanning Centre (HSC). MK-3475 for advanced melanoma - first or second line, in patients naïve to ipilimumab. 2013.
120. Johnston K, Levy AR, Lorigan P, Maio M, Lebbe C, Middleton M, et al. Economic impact of healthcare resource utilisation patterns among patients diagnosed with advanced melanoma in the United Kingdom, Italy, and France: results from a retrospective, longitudinal survey (MELODY study). European journal of cancer (Oxford, England : 1990). 2012;48(14):2175-82.
121. Lorigan P, Marples M, Harries M, Wagstaff J, Dalgleish AG, Osborne R, et al. Treatment patterns, outcomes, and resource utilization of patients

with metastatic melanoma in the U.K.: the MELODY study. The British journal of dermatology. 2014;170(1):87-95.
122. Morris S, Cox B, Bosanquet N. Cost of skin cancer in England. The European journal of health economics : HEPAC : health economics in prevention and care. 2009;10(3):267-73.
123. MIMS. 2015. Available from: http://www.mims.co.uk/.
124. Department of Health. NHS National Schedule of Reference costs 2014-2015. 2015.
125. National Institute for Health and Care Excellence (NICE). Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). 2012.
126. Oxford Outcomes. MELODY study resource use data analysis: UK results – final draft. Data on File. 2010 December 2010. Report No.
127. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care 2014. 2014.
128. Addicott R, Dewar S. Improving choice at end of life. A descriptive analysis of the impact and costs of The Marie Curie Delivering Choice Programme in Lincolnshire. The King's Fund., 2008.
129. Personal Social Services Research Unit (PSSRU). Unit Costs for Health and Social Care 2015. 2015.
130. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health technology assessment. 2004;8(36):iii-iv, ix-xi, 1-158.
131. Korn EL, Freidlin B, Abrams JS. Overall survival as the outcome for randomized clinical trials with effective subsequent therapies. Journal of Clinical Oncology. 2011;29(17):2439-42.
132. Bristol-Myers Squibb. CheckMate 067: HRQL output tables. Data on file. 2015.
133. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Protocol for: Nivolumab in previously untreated melanoma without BRAF mutation. The New England journal of medicine. 2015;372(4):320-30.
134. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Protocol for: Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. The New England journal of medicine. 2010;363(8):711-23.
135. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Protocol for: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. The New England journal of medicine. 2011;364(26):2507-16.

9 APPENDICES

9.1 Quality assessment

Table 137 Quality assessment of CheckMate 066 (Adapted from CS, Appendix 6, Table 7)

Question	Company's assessment	ERG's assessment
Was randomisation carried out appropriately?	Yes, randomisation performed by IVRS and stratified by PD-L1 status and M stage.	Yes, quote: "Randomization was stratified according to tumor PD-L1 status (positive versus negative or indeterminate) and metastasis stage (M0, M1a, or M1b versus M1c, defined according to the tumor–node–metastasis system of the American Joint Committee on Cancer and the International Union against Cancer)."
Was the concealment of treatment allocation adequate?	Yes	Yes; quote: "PD-L1 status was prospectively determined, and the results were used to stratify randomization, which was performed by means of a fully automated interactive voice-response system."
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, baseline demographics were well balanced; prognostic factors such as disease staging and LDH levels were comparable between groups.	Yes, age, sex, geographic location, metastasis stage, lactate dehydrogenase, history of brain metastases, PDL-1 status, BRAF status and prior systemic therapy were balanced. However, there were slighte more participants with an ECOG 1 status in the dacarbazine group (40.4%) compared to the nivolumab group (28.6%).
Did the comparison groups receive the same care apart from the intervention(s) studied?	Not assessed	Yes; quote: "Patients were randomly assigned in a 1:1 ratio to receive by means of intravenous infusion either 3 mg of nivolumab per kilogram of body weight every 2 weeks, plus a dacarbazine-matched placebo every 3 weeks, or 1000 mg of dacarbazine per square meter of body-surface area every 3 weeks, plus a nivolumab-matched placebo every 2 weeks."
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, the sponsor, subjects, investigators and site staff were blinded to study drug administration.	Yes; quote protocol: "The Sponsor, subjects, investigator and site staff will be blinded to the study drug administered (BMS-936558 or Dacarbazine)."
Were all groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)?	Not assessed	Yes, quote: "The median follow-up for overall survival was 8.9 months in the nivolumab group and 6.8 months in the dacarbazine group."
Were there any unexpected imbalances in drop-outs between groups?	No	No, quotes: "The most frequent reason for discontinuation was disease progression, in 96 of 206 patients (46.6%) in the nivolumab group and 175 of 205 (85.4%) in the dacarbazine group." "The percentage of patients who discontinued the study treatment owing to adverse events was 6.8% in the nivolumab group and 11.7% in the dacarbazine group."
Were the groups comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)?	Not assessed	Yes, best overall response could not be determined in 10.5% of particpants in the nivolumab arm versus 15.4% in the dacarbazine arm.
Is there any evidence to	No	No

Question	Company's assessment	ERG's assessment
suggest that the authors measured more outcomes than they reported?		
Did the study have an appropriate length of follow-up?	Not assessed	Yes, quote: "All the patients who underwent randomization were followed for up to 16.7 months at the time of database lock on August 5, 2014, which was 5.2 months after the first visit of the last patient who had undergone randomization."
Did the study use a precise definition of outcome?	Not assessed	Yes, quote: "The primary end point was overall survival. Secondary end points included investigator-assessed progression-free survival, objective response rate, and PD-L1 expression in the tumor as a predictive biomarker of overall survival."
Was a valid and reliable method used to determine the outcome?	Not assessed	Yes; quote: "Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,19 at 9 weeks after randomization, every 6 weeks thereafter for the first year, and then every 12 weeks until disease progression or treatment discontinuation. Assessments for survival were performed every 3 months. Safety evaluations were performed for patients who received at least one dose of the study treatment, and the severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.20."
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, all efficacy analyses were performed according to the intention-to-treat principle.	Yes; quote: "The efficacy analyses were performed in the population of patients who underwent randomization (the intention-to-treat population)."
Was statistical powering such to detect a significant difference between treatment groups?	Yes	Yes; quote protocol: "The study requires at least 312 deaths to ensure approximately 90% power to detect a hazard ratio of 0.69 with an overall type I error of 0.05 (two-sided)."
Abbreviations in table: ITT, intention-to-treat; IVRS, interactive voice response system; RCT, randomised controlled trial. Quotes are from Robert *et al.* 2015[36] unless stated otherwise (Protocol for Robert *et al.* 2015[133]).		

Table 138 Quality assessment of MDX010-20 (Adapted from CS, Appendix 6, Table 8)

Question	Company's assessment	ERG's assessment
Was randomisation carried out appropriately?	Adequate: patients were randomly assigned to one of three study groups using centralised scheme with stratification according to baseline metastases stage (M0, M1a or M1b).	Yes; quote: "patients were randomly assigned to one of three study groups, with stratification according to baseline metastasis stage (M0, M1a, or M1b versus M1c, classified according to the tumor–node–metastasis [TNM] categorization for melanoma of the American Joint Committee on Cancer), and receipt or nonreceipt of previous interleukin-2 therapy."
Was the concealment of treatment allocation adequate?	Adequate: placebo for both ipilimumab and vaccine were used; the pharmacist at each study site was unblinded to study medication; other study site personnel and	Yes; quote protocol: "The Biostatistics group in Medarex will provide a centralized randomization list to Clinical Operations using SAS procedure PROC PLAN."

Question	Company's assessment	ERG's assessment
	patients were blinded to patient assignment.	
Were the groups similar at the outset of the study in terms of prognostic factors?	Adequate: metastases stages among the three arms were comparable; previous systemic therapy (including IL-2 therapy) was similar.	Yes, age, sex, geographic location, ECOG performance status, M stage, lactate dehydrogenase level, central nervous system metastases at baseline, previous treatment for metastatic disease and previous interleukin-2 therapy were balanced."
Did the comparison groups receive the same care apart from the intervention(s) studied?	Not assessed	Yes; quote: "Patients were randomly assigned, in a 3:1:1 ratio, to treatment with an induction course of ipilimumab, at a dose of 3 mg per kilogram of body weight, plus a gp100 peptide vaccine; ipilimumab plus gp100 placebo; or gp100 plus ipilimumab placebo — all administered once every 3 weeks for four treatments. In the vaccine groups, patients received two modified HLAA*0201–restricted peptides, injected subcutaneously as an emulsion with incomplete Freund's adjuvant (Montanide ISA-51): a gp100:209-217(210M) peptide, 1 mg injected in the right anterior thigh, and a gp100:280-288(288V) peptide, 1 mg injected in the left anterior thigh. Peptide injections were given immediately after a 90-minute intravenous infusion of ipilimumab or placebo. Treatment began on day 1 of week 1, and if there were no toxic effects that could not be tolerated, no rapidly progressive disease, and no significant decline in performance status, patients received an additional treatment during weeks 4, 7, and 10. Patients in whom new lesions developed or baseline lesions grew were allowed to receive additional treatments to complete induction. Patients with stable disease for 3 months' duration after week 12 or a confirmed partial or complete response were offered additional courses of therapy (reinduction) with their assigned treatment regimen if they had disease progression."
Were the care providers, participants and outcome assessors blind to treatment allocation?	Adequate: all site personnel including clinicians, data management, statisticians and patients were blinded (except pharmacists who were unblinded to the study medication).	Yes; quote protocol: "Placebo will be provided for both MDX-010 and vaccine. The placebo vaccine will be delivered in a masked syringe by s.c. injection. To facilitate monitoring of patient safety, Medarex, Inc. will be unblinded to patient assignment. The pharmacist at each study site will be unblinded to study medication; other study site personnel and patients will be blinded to patient assignment."
Were all groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)?	Not assessed	Yes, quote: "Patients were followed for up to 55 months, with median follow-up times for survival of 21.0 months in the ipilimumab-plus-gp100 group, 27.8 months in the ipilimumab-alone group, and 17.2 months in the gp100-alone group."
Were there any unexpected imbalances in drop-outs between groups?	Adequate: drop-out rates among the groups were similar.	No, quotes: "A total of 242 of 403 patients in the ipilimumab-plusgp100 group (60.0%), 88 of 137 in the ipilimumab-alone group (64.2%), and 78 of 136 in the gp100-alone group (57.4%) received all four ipilimumab doses or placebo infusions."
Were the groups comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms	Not assessed	Yes, best overall response was not evaluated in 20.6% of participants in the ipilimumab plus gp 100 arm versus 20.4% in the ipilimumab arm and 23.5% in the gp 100 alone arm.

Question	Company's assessment	ERG's assessment
of those for whom outcome data were not available)?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all mentioned outcomes presented in the primary publication.	No
Did the study have an appropriate length of follow-up?	Not assessed	Yes, quote: "A total of 481 events were required in all three groups (assuming that the events were distributed in a 3:1:1 ratio in the ipilimumab-plus-gp100, ipilimumab-alone, and gp100-alone groups, respectively). Therefore, all patients who were randomly assigned in the study were to be followed until at least 481 events had occurred in the study."
Did the study use a precise definition of outcome?	Not assessed	Yes, quote: "The primary comparison in overall survival was between the ipilimumab-plus-gp100 group and the gp100-alone group. Prespecified secondary end points included a comparison of overall survival between the ipilimumab-alone and the gp100-alone groups and between the two ipilimumab groups, the best overall response rate, the duration of response, and progression-free survival.."
Was a valid and reliable method used to determine the outcome?	Not assessed	Yes; quote: "Tumor assessments were performed at baseline, and all patients who did not have documented early disease progression and who had stable disease or better at week 12 had confirmatory scans at weeks 16 and 24 and every 3 months thereafter. Tumor responses were determined by the investigators with the use of modified WHO criteria to evaluate bidimensionally measurable lesions.26 Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. An immune-related adverse event was defined as an adverse event that was associated with exposure to the study drug and that was consistent with an immune phenomenon."
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: all efficacy analyses were performed according to the intention-to-treat principle with standard censoring used to account for missing data.	Yes; quote: "Efficacy analyses were performed on the intention-to-treat population, which included all patients who had undergone randomization (676 patients)."
Was statistical powering such to detect a significant difference between treatment groups?	Yes	Yes; quote: "We estimated that with 385 events (deaths) among a total of 500 patients randomly assigned to the ipilimumab-plus-gp100 and the gp100-alone groups, the study would have at least 90% power to detect a difference in overall survival, at a two-sided alpha level of 0.05, with the use of a log-rank test."
Abbreviations in table: ITT, intention-to-treat; RCT, randomised controlled trial. Quotes are from Hodi *et al*. 2010[26] unless stated otherwise (Protocol for Hodi *et al*. 2010[134])		

Table 139 Quality assessment of BRIM-3 (Adapted from CS, Appendix 6, Table 10)

Question	Company's assessment	ERG's assessment
Was randomisation carried out appropriately?	Adequate: randomisation scheme utilised with stratification according to baseline M stage; ECOG; location; serum LDH.	Yes randomly assigned in a 1:1 ratio; quote: "Study patients were stratified according to American Joint Committee on Cancer stage (IIIC, M1a, M1b, or M1c), ECOG performance status (0 or 1), geographic region (North America, Western Europe, Australia or New Zealand, or other region), and serum lactate dehydrogenase level (normal or elevated)."
Was the concealment of treatment allocation adequate?	Open-label study Adequate: no likely impact on the risk of bias for primary outcome analysis as they are not patient reported outcomes	Unclear, no mention of how patients were assigned to treatment groups.
Were the groups similar at the outset of the study in terms of prognostic factors?	Adequate: patient characteristics between treatment arms well balanced; prognostic factors: M stage, ECOG, baseline LDH similarly distributed	Yes, age, sex, race, geographic location, ECOG performance status, extent of metastatic melanoma and lactate dehydrogenase were balanced."
Did the comparison groups receive the same care apart from the intervention(s) studied?	Not assessed	Yes; quote: "Dose reductions for both vemurafenib and dacarbazine were prespecified for intolerable grade 2 toxic effects or worse. The development of cutaneous squamous-cell carcinoma did not require dose modification. The administration of vemurafenib was interrupted until the resolution of the toxic effect to at least grade 1 and restarted at 720 mg twice daily (480 mg twice daily for grade 4 events), with a dose reduction to 480 mg twice daily if the toxic effects recurred. If the toxic effect did not improve to grade 1 or lower or recurred at the 480-mg twice-daily dose, treatment was discontinued permanently. The administration of dacarbazine was interrupted for grade 3 or 4 toxic effects and could be restarted on recovery within 1 week to grade 1 (at full dose) or grade 2 (at 75% dose) or at 75% dose for grade 4 neutropenia or febrile neutropenia. A second dose reduction was allowed, if needed. Antiemetics and granulocyte colony-stimulating factor were administered according to standards at each study center. Treatment was discontinued on disease progression unless continued treatment was in the best interest of the patient in the judgment of the investigator and the sponsor."
Were the care providers, participants and outcome assessors blind to treatment allocation?	Open-label study. Adequate: no likely impact on the risk of bias for primary outcome analysis as they are not patient reported outcomes	No; quote protocol: "Patients, investigators, study site monitor, site pharmacist or designee, and sponsors will not be blinded to the study treatment assignment."
Were all groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)?	Not assessed	Yes, quote: "Median follow-up for the interim analysis was 3.8 months for patients in the vemurafenib group and 2.3 months for those in the dacarbazine group."
Were there any unexpected imbalances in drop-outs between	Unclear: overall discontinuations comparable; in	No, quotes: "A total of 242 of 403 patients in the ipilimumab-plusgp100 group (60.0%), 88 of 137 in the ipilimumab-alone group (64.2%), and 78 of 136 in the

Question	Company's assessment	ERG's assessment
groups?	accordance with the pre-defined study protocol, cross-over to vemurafenib was reported.	gp100-alone group (57.4%) received all four ipilimumab doses or placebo infusions."
Were the groups comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)?	Not assessed	Yes; quote: "At the time of the interim analysis, there were an inadequate number of patients in follow-up beyond 7 months in either study group to provide reliable Kaplan–Meier estimates of the survival curves.17."
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for primary outcomes and secondary response outcomes presented in primary publication (duration of response not reported).	No
Did the study have an appropriate length of follow-up?	Not assessed	Yes; quote: "In order to ensure adequate follow-up for each efficacy end point, patients could be evaluated for the analysis of overall survival, progression-free survival, and confirmed response if they had undergone randomization at least 2, 9, and 14 weeks, respectively, before the cutoff date."
Did the study use a precise definition of outcome?	Not assessed	Yes; quote: "The original primary end point was the rate of overall survival. The statistical plan was revised in October 2010 on the basis of phase 1 and 2 efficacy and safety results and after consultation with global regulatory authorities. Under the revised plan, the rates of overall survival and progression-free survival were co-primary end points."
Was a valid and reliable method used to determine the outcome?	Not assessed	Yes; quote: "Patients were examined every 3 weeks; tumor assessments were performed at baseline, at weeks 6 and 12, and every 9 weeks thereafter. Tumor responses were determined by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Electrocardiograms were repeated every other cycle. Blood counts, biochemical analyses, and measurements of lactate dehydrogenase levels were performed at each visit. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0."
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear: whilst all efficacy outcomes were analysed according to the intention-to-treat principle with standard censoring used to account for missing data, high cross-over rates limits interpretation of PFS and OS analysis.	Yes; quote: "Efficacy analyses were performed in the intention-to-treat population."
Was statistical powering such to detect a significant difference	Yes	Yes; quote: "The trial had a power of 80% to detect a hazard ratio of 0.65 for overall survival with an alpha level of 0.045 (an increase in median survival from 8 months

Question	Company's assessment	ERG's assessment
between treatment groups?		for dacarbazine to 12.3 months for vemurafenib) and a power of 90% to detect a hazard ratio of 0.55 for progression-free survival with an alpha level of 0.005 (an increase in median survival from 2.5 months for dacarbazine to 4.5 months for vemurafenib)..”
Abbreviations in table: ITT, intention-to-treat; RCT, randomised controlled trial. Quotes are from Chapman *et al.* 2011[27] unless stated otherwise (Protocol for Chapman *et al.* 2011[135]).		

Table 140 Quality assessment of BREAK-3 (Adapted from CS, Appendix 6, Table 9)

Question	Company's assessment	ERG's assessment
Was randomisation carried out appropriately?	Adequate: centralised, computerised, interactive voice activated randomisation scheme utilised with stratification according to baseline M stage.	Yes; quote: "We stratified patients according to American Joint Committee on Cancer stage (unresectable III+IVM1a+IVM1b versus IVM1c)."
Was the concealment of treatment allocation adequate?	Open-label study Adequate: no likely impact on the risk of bias for primary outcome analysis as they are not patient reported outcomes.	No; quote: "A centrally located, computerised, interactive, voice activated response system controlled assignment of patient treatment."
Were the groups similar at the outset of the study in terms of prognostic factors?	Adequate: patient characteristics between treatment arms well balanced; prognostic factors: M stage, ECOG, baseline LDH similarly distributed.	Yes, age, sex, ethnic origin, ECOG performance status, M-status at screening, lactate dehydrogenase level, and previous treatment were balanced."
Did the comparison groups receive the same care apart from the intervention(s) studied?	Not assessed	Yes; quote: "Dose reductions for both dabrafenib and dacarbazine were pre-specified for adverse events of grade 2 or higher. Treatment with dabrafenib was interrupted until the adverse event resolved or reduced to grade 1. Treatment was restarted at the current dose for an adverse event of grade 2 or reduced by one dose level for an adverse event of grade 3 unless the adverse event was deemed unrelated to dabrafenib by the investigator. Dabrafenib was discontinued for drug-related grade 4 toxic effects and the patient was monitored and supportive care provided; if in the investigator's opinion, the event was not likely to be treatment-related and was therefore unlikely to recur, dabrafenib was restarted at one dose level lower. For fevers of grade 3 or higher, or of any grade with signs and symptoms including rigors, dehydration, hypotension, dizziness, or weakness, dabrafenib treatment was interrupted until fever resolved to less than 38°C and symptoms resolved; treatment was restarted at one dose level lower. For fevers of grade 2 or lower, treatment was interrupted until fever resolved to less than 38°C and then restarted at the original dose level."
Were the care providers, participants and outcome assessors blind to treatment allocation?	Open-label study. Adequate: no likely impact on the risk of bias for primary outcome analysis as they are not patient reported outcomes	No, open-label trial; quote: "Although investigators were aware of treatment group when assessing progression-free survival, a masked independent review committee (IRC) reviewed all scans and, per protocol, had to confirm progression before patients crossed over from dacarbazine to dabrafenib."
Were all groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)?	Not assessed	No, quotes: "Patients randomly assigned to dacarbazine who progressed during the study were permitted to enter a crossover group to receive dabrafenib. We followed up these patients for response, progression, survival, and additional anticancer therapy." "Further interpretation of overall survival data is limited because the median duration of follow-up for patients receiving dabrafenib was 5 months at the time of the primary analysis, and because patients given

Question	Company's assessment	ERG's assessment
		dacarbazine could cross over to dabrafenib in cases of disease progression."
Were there any unexpected imbalances in drop-outs between groups?	Unclear: overall discontinuations comparable; in accordance with the pre-defined study protocol, cross-over to dabrafenib was reported..	Unclear, imbalance in drop-out; higher proportion of discontinuation in dacarbazine arm (46/59) compared to dabrafenib arm (80/187), but unclear whether this was unexpected.
Were the groups comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)?	Not assessed	Yes; quote: "At the time of the interim analysis, there were an inadequate number of patients in follow-up beyond 7 months in either study group to provide reliable Kaplan–Meier estimates of the survival curves.17."
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes presented in primary or secondary publications.	No
Did the study have an appropriate length of follow-up?	Not assessed	Unclear; quote: "We enrolled patients in this open-label phase 3 trial between Dec 23, 2010, and Sept 1, 2011. This report is based on a data cutoff date of Dec 19, 2011."
Did the study use a precise definition of outcome?	Not assessed	Yes; quote: "The primary endpoint was progression-free survival as assessed by the individual investigator from randomisation. Secondary endpoints included progression-free survival as assessed by an IRC, overall survival, objective response rate according to Response Evaluation Criteria in Solid Tumors, version 1.19 assessed by the investigator and the IRC, progression-free survival after crossover, duration of response, quality of life, safety and tolerability, and support of a BRAF mutation assay validation."
Was a valid and reliable method used to determine the outcome?	Not assessed	Yes; quote: "We defined progression-free survival as the time from randomisation to the earliest date of radiographic or photographic disease progression or death due to any cause. We estimated the HR using the Pike method with a two-sided 95% CI. We also used the Pike estimate of the HR for overall survival. We compared overall survival and overall response rate between treatment groups. We reported all secondary efficacy endpoints with two-sided, 95% CIs."
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear: whilst all efficacy outcomes were analysed according to the intention-to-treat principle with standard censoring used to account for missing data, high cross-over rates limits interpretation of PFS and OS analysis	Yes; quote: "All randomised patients were included in efficacy analyses; safety analyses included all randomised patients who received at least one dose of study medication."
Was statistical powering such to detect a significant difference	Yes	Yes; quote: "The trial was designed to enrol 200 patients to observe 102 progression-free survival events with statistical power of 99.7% to detect a HR of 0.33 (median

Question	Company's assessment	ERG's assessment
between treatment groups?		progression-free survival of 2 months in patients who received dacarbazine and 6 months in patients who received dabrafenib). The trial design used a one-sided log-rank test with α=0.02."
Abbreviations in table: ITT, intention-to-treat; RCT, randomised controlled trial. Quotes are from Hauschild *et al.* 2012[2].		

Table 141 Quality assessment results for CheckMate 004[51, 59] (Adapted from CS, Section 4.11, pg 106-107)

Type of bias and study questions	How is the question addressed in the study?	
	Company	**ERG**
Selection bias		
Were attempts made to minimise selection bias? (Were attempts made within the design or analysis to balance the comparison groups for potential confounders?)	Yes, patients assigned to a dose cohort in the order they entered the study	Yes; quote: "This was a Phase 1b, open-label, multi-center, multi-dose, dose-escalation study of nivolumab in combination with ipilimumab. Study drugs were administered either concurrently (Cohorts 1 through 5 and Cohort 8) or in a sequenced regimen (Cohorts 6 and 7)."
Was the method of allocation to treatment groups unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)?	Not assessed	Unclear.
Were the groups comparable at baseline, including all major confounding and prognostic factors?	Not assessed	Yes, baseline characteristics for Cohorts 1-3 and Cohorts 6-8 are shown and overall similar between the groups.
Performance bias		
Did the comparison groups receive the same care apart from the intervention(s) studied?	Not assessed	Unclear.
Were participants receiving care kept 'blind' to treatment allocation?	Not assessed	No, open-label.
Were individuals administering care kept 'blind' to treatment allocation?	Not assessed	No, open-label.
Attrition bias		
Were all groups followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)?	Not assessed	No, planned follow-up seems similar but cohort 8 had insufficient follow-up; quotes: "Cohorts 1-3: [Starting at Week 0] 4 doses of nivolumab and 4 doses of ipilimumab on the same day Q3 weeks (ending at Week 9), 3 week interval, then 4 doses of nivolumab monotherapy Q3 weeks (ending Week 21), 3 week interval, followed by 8 doses of nivolumab and 8 doses of ipilimumab on the same day Q12 weeks (ending at Week 108). Cohorts 6 and 7: Up to 96 weeks of nivolumab (with a follow-up period of a minimum of 12 weeks). Cohort 8: [Starting at Week 0] 4 doses of nivolumab and 4 doses of ipilimumab on the same day Q3W (ending at Week 9), 3 week interval, followed by 48 doses of nivolumab Q2W (ending at Week

		108).” “there was insufficient follow-up in Cohort 8).”
Were the groups comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)?	Not assessed	No, treatment completion was lower in cochort 8 (53.7%) compared to cohort 1-3 (79.3%) and cohort 6-7 (84.8%).
Were the groups comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)?	Not assessed	No, insufficienct follow-up in cohort 8 for assessment of OS and PFS.
Detection bias		
Did the study have an appropriate length of follow-up?	Not assessed	Yes; quote: “For subjects enrolled in the concurrent dose cohorts, or dose-escalation cohorts (Cohorts 1 through 5), the study consisted of Screening (up to 4 weeks), Treatment (induction for up to 24 weeks and maintenance for up to 96 weeks), Follow-up (minimum of 12 weeks), and Survival Follow up (up to 3 years). During the treatment period, subjects were scheduled to receive nivolumab and ipilimumab in combination for 4 doses, then nivolumab for 4 additional doses, followed by nivolumab and ipilimumab in combination for 8 doses. The Cohort 3 dose regimen exceeded the maximum tolerated dose, thus no subjects were enrolled in Cohorts 4 and 5. For subjects enrolled in the sequenced regimen cohorts (Cohorts 6 and 7), the study consisted of 4 periods: Screening (up to 4 weeks), Study Treatment (up to 96 weeks), Follow-up (minimum of 12 weeks), and Survival Follow up (up to 3 years). For subjects enrolled in the nivolumab/ipilimumab combination expansion cohort (Cohort 8), the study consisted of the screening period (up to 4 weeks), Treatment period (combination treatment for 12 weeks then nivolumab monotherapy for 96 weeks), Follow-up (minimum of 12 weeks), and Survival Follow up (up to 3 years). During the treatment period, subjects were scheduled to receive nivolumab and ipilimumab in combination for 4 doses Q3W, followed by nivolumab alone Q2W.”
Did the study use a precise definition of outcome?	Not assessed	Yes; quote: “Primary Endpoint: Safety was evaluated for all treated subjects using NCI CTCAE v3.0. The assessment of safety was based on frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, select AEs (of special importance for immuno-oncology agents), clinical laboratory assessments (hematology, serum chemistry, and liver and thyroid function tests), ECG evaluation, and vital sign measurements. Secondary Endpoints: Efficacy, Immunogenicity, Pharmacokinetics Although the primary efficacy endpoint was based on immune-related response criteria, a response assessment by conventional criteria (mWHO) was also conducted. In order to compare to historical data, this report focuses on efficacy results using conventional criteria based on all treated subjects. The efficacy endpoints included best overall response (BOR) by mWHO,

		duration of response (DOR), time to response, progression-free survival (PFS) rates, overall survival (OS) rates, and immune-related BOR. Response evaluation for BOR was assessed by the sponsor. Efficacy was also assessed by PD-L1 and BRAF mutation status. Evaluation of immunogenicity included incidence rates of persistent positive anti-drug antibodies (ADA) as well as neutralizing positive ADA postbaseline. ADA for both nivolumab and ipilimumab were assayed from immunogenicity samples. For Cohorts 1-3 and Cohort 8, the pharmacokinetics (PK) endpoints included peak and trough concentrations of nivolumab after the 1st and 4th dose and peak and trough concentrations of ipilimumab after the 1st dose. For Cohort 6 and 7, the pharmacokineetic endpoints included peak and trough concentrations at Week 16."
Were outcome measures reliable? And were all clinically relevant outcome measures assessed? (Was a valid and reliable method used to determine the outcome?)	Yes, efficacy assessed in terms of response and survival. These are clinically relevant outcomes named in the decision problem. Response was assessed according to mWHO and irRC criteria and survival curves were estimated according to the KM method. These are well-established and validated methods of assessment	Yes; quote: "Efficacy: Although the primary efficacy endpoint was based on immune-related response criteria, a response assessment by conventional criteria (mWHO) was also conducted. Overall response (ie, CR, PR, SD, PD) at each tumor assessment timepoint and a BOR before a subject experienced progression based on the mWHO criteria was derived by the sponsor. The objective response rate (ORR) was estimated as the total number of subjects whose BOR was either a CR or PR divided by the total number of treated subjects, and its corresponding two-sided 95% exact confidence interval (CI) was calculated using Clopper-Pearson method. Immunogenicity: Analyses were conducted on immunogenicity-evaluable subjects. Numbers and percentages of subjects who were ADA+ at baseline and during post-baseline period were summarized."
Were investigators kept 'blind' to participants' exposure to the intervention?	Not assessed	No, open-label.
Were investigators kept 'blind' to other important confounding and prognostic factors?	Not assessed	No, open-label.
Other		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No, but analysis conducted on all treated patients with the conservative principle used for data imputation	No.
Were all participants accounted for at study conclusion?	Yes.	Yes, 150 patients enrolled of who 127 were treated for who data is presented.
Applicability of study results to the decision problem		
Do the selected patients represent the eligible population for the intervention?	Yes, adult patients with advanced (unresectable or metastatic) melanoma, directly	Yes, patients with unresectable stage III or stage IV malignant melanoma; quote: "In Cohorts 1-5 and 8, subjects may have been treated with up to 3 prior systemic standard treatments for melanoma, but prior ipilimumab treatment was not allowed. Subjects in Cohorts 6 and 7 may also have been treated with

	reflecting the population in the decision problem	up to 3 prior systemic standard treatments and must have achieved either stable disease (SD), a partial response (PR) to treatment, or PD (provided there was no evidence of clinical deterioration) with ipilimumab."
Did the setting reflect UK practice?	Yes, baseline demographics and disease characteristics representative of typical patients presenting with advanced melanoma in UK clinical practice. Nivolumab plus ipilimumab administered by IV in the hospital setting as would be the case in UK practice. A proportion of patients were treated with the licensed regimen (cohort 8)	Unclear, patients were treated in four study centers in the United States.
Are the study results internally valid?	Yes, analyses conducted in accordance with approved statistical methods	Yes.
Are the findings externally valid?	Yes, clinical analyses of direct relevance to the decision problem and reflective of evidence on which treatment decisions will be made in clinical practice	Unclear.
Abbreviations in table: irRC, immune-related response criteria; IV, intravenous; KM, Kaplan–Meier; mWHO, modified World Health Organization.		

9.2 Baseline characteristics of trials in indirect comparison

At the clarification stage, the company supplied baseline characteristics of patients in CheckMate 066 and MDX010-20, to complement CS Table 29 with baseline characteristics of patients in CheckMate 067, BRIM-3 and BREAK-3 (Table 142).

Table 142: Baseline characteristics of trials in indirect comparison

	CheckMate 066		**MDX010-20**		**CheckMate 067**		**BRIM-3**		**BREAK-3**	
Characteristic	dacarbazine (n=208) n/N (%)	Nivolumab (n=210) n/N (%)	gp100 (n=136) n/N (%)	Ipilimumab (n=137) n/N (%)	Ipilimumab (n=315)	Nivolumab plus ipilimumab (n=314)	dacarbazine (n=338)	Vemurafenib (n=337)	dacarbazine (n=63)	Dabrafenib (n=187)
ECOG = 0	121/208 (58.2)	148/210 (70.5)	70/136 (51.5)	72/137 (52.6)	71.1%	73.3% (unknown= 0.3%)	68%	68%	70%	66%
LDH (>ULN)	74/208 (35.6)	79/210 (37.6)	52/136 (38.2)	53/137 (38.7)	36.5% (1.9% not reported)	36.3% (0.3% not reported)	58%	58%	30% (2% unknown)	36% (<1% unknown)
M stage = M1c	127/208 (61.1)	128/210 (61.0)	98/136 (72.1)	100/137 (73.0)	58.1%	57.6%	65%	66%	63%	66%
History of brain metastases	8/208 (3.8)	7/210 (3.3)	21/136 (15.4)	15/137 (10.9)	4.8%	3.5%	NR	NR	NR	NR
Age (under 65)	94/208 (45.2)	106/210 (50.5)	94/136 (69.1)	95/137 (69.3)	57.8% Median=62 years	58.9% Median=61 years	100% Median=52 years	100% Median=56 years	NR% Median=50 years	78.6% Median=53 years
Gender (males)	125/208 (60.1)	121/210 (57.6)	73/136 (54.0)	81/137 (59.1)	64.1%	65.6%	54%	59%	59%	60%

9.3 Trial design indirect comparison

At the clarification stage, the company supplied a summary of the trial designs of the trials in the network (CheckMate 066, MDX010-20, BRIM-3 and BREAK-3, Table 143) to complement CS Table 11 (RCT methodology of CheckMate 067 and CheckMate 069).

Table 143. Trial design of CheckMate 066, MDX010-20, BRIM-3 and BREAK-3

	CheckMate 066	MDX010-20	BRIM-3	BREAK-3
Location	Patients were treated across 76 sites in Argentina, Australia, Canada, Chile, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, Norway, Poland, Spain and Sweden.	Patients were enrolled at 125 centres in Argentina, Belgium, Brazil, Canada, Chile, France, Germany, Hungary, the Netherlands, South Africa, Switzerland, the United Kingdom and the United States	Patients were screened at 104 centres in Australia, Canada, France, Germany, Israel, Italy, the Netherlands, New Zealand, Sweden, Switzerland, the United Kingdom and the United States.	Patients were screened at 70 institutions in Australia, Canada, France, Germany, Hungary, Ireland, Italy, the Netherlands, Poland, Russian Federation, Spain and the United States.
Trial design	Phase III, randomised, double-blind, placebo-controlled, parallel assignment, multi-centre clinical trial. Patients were randomised in a 1:1 ratio through an IVRS. Randomisation was stratified by PD-L1 status and metastatic stage. The sponsor, patients, investigator and site staff were blinded to treatment assignment.	Phase III, randomised, double-blind, active-controlled, multi-centre clinical trial. Patients were randomised in a 3:1:1 ratio through a centralised randomisation scheme. Randomisation was stratified by baseline metastatic stage and previous IL-2 therapy. The sponsor, patients, investigator and site staff were blinded to treatment assignment.	Phase III, randomised, active-controlled, multi-centre clinical trial. Patients were randomised in a 1:1 ratio.	Phase III, randomised, open-label, active-controlled, multi-centre clinical trial. Patients were randomised in a 3:1 ratio through an IVRS. Randomisation was stratified by AJCC staging. The study was open-label.
Eligibility criteria for participants	Men and women aged ≥18 years with previously untreated, unresectable or metastatic melanoma who signed informed consent and met the following key target disease and other criteria were enrolled: untreated, histologically confirmed unresectable Stage III or Stage IV melanoma as per	Men and women aged ≥18 years with previously treated, unresectable or metastatic melanoma who signed informed consent and met the following key target disease and other criteria were enrolled: untreated, histologically confirmed unresectable Stage III or Stage IV melanoma	Men and women aged ≥18 years with previously untreated, unresectable or metastatic melanoma who signed informed consent and met the following key target disease and other criteria were enrolled: untreated, histologically confirmed unresectable Stage	Men and women aged ≥18 years with previously untreated, unresectable or metastatic melanoma who signed informed consent and met the following key target disease and other criteria were enrolled: untreated, histologically confirmed unresectable Stage III or Stage IV melanoma

	CheckMate 066	MDX010-20	BRIM-3	BREAK-3
	AJCC staging BRAF mutation-negative (wild-type) as per regionally acceptable V600 mutational status testing PD-L1-positive, PD-L1-negative or PD-L1-intermediate classification according to recent biopsy from an unresectable or metastatic site measurable disease by RECIST v1.1 criteria ECOG PS of 0 or 1 Patients who met any of the following key criteria were excluded from the study eligibility criteria: active brain metastases or leptomeningeal metastases ocular melanoma prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured active, known or suspected autoimmune disease conditions requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibody or any antibody or drug specifically targeting T-cell co-stimulation or checkpoint	prior treatment with regimen containing dacarbazine, temozolomide, fotemustine, carboplatin or IL-2 positive for HLA-A*0201 ECOG PS 0 or 1 Patients who met any of the following key criteria were excluded from study eligibility: Active, untreated brain metastases ocular melanoma any other cancer from which the patient had been disease-free for less than 5 years active autoimmune disease concomitant treatment with any non-study anticancer therapy or immunosuppressive agent or long term corticosteroid use prior treatment with anti-CTLA-4 antibody or cancer vaccine	III or Stage IV melanoma BRAF mutation positive as per regionally acceptable V600 mutational status testing ECOG PS 0 or 1 Patients who met any of the following key criteria were excluded from study eligibility: Active, untreated brain metastases History of cancer within the past 5 years	BRAF mutation positive as per regionally acceptable V600 mutational status testing ECOG PS of 0 or 1 Patients who met any of the following key criteria were excluded from study eligibility: Active brain metastases Previous malignancy within the last 5 years Surgery, radiotherapy or immunotherapy within 4 weeks History of HIV infection or glucose-6-dehydrogenase deficiency

	CheckMate 066	MDX010-20	BRIM-3	BREAK-3
	pathways			
Settings and locations where the data were collected	Local laboratory assessments were arranged by site. ICON Laboratories were responsible for management of local laboratory results from the site. ICON entered, reviewed, queried, and transferred the results, from the local laboratory reports received from sites to the BMS Oracle Clinical Database. An independent DMC was established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio.	Laboratory analysis was performed at a central laboratory. A DMC was established to provide advice on accumulating safety data from the study.	An independent data and safety monitoring board provided oversight and evaluated interim results on efficacy data.	An in dependent data monitoring committee assessed benefit risk and monitored safety measures.
Trial drugs	Nivolumab group (n=210): nivolumab 3mg/kg q2w by IV infusion plus a dacarbazine - matched placebo q3w by IV infusion. dacarbazine group (n=208): dacarbazine 1000mg/m2 q3w by IV infusion plus a nivolumab-matched placebo q2w by IV infusion. Treatment continued until there was disease progression or an unacceptable level of toxic effects. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial AE with the study drug, as determined by the investigator. Patients who received dacarbazine were permitted to cross-over to nivolumab therapy	gp100 group (n=136): gp100 2mg Peptide A and 2mg Peptide B q3w for up to 4 doses plus placebo q3W for up to 4 doses. Ipilimumab group (n=137): ipilimumab 3mg/kg q3w for up to 4 doses plus vaccine placebo q3w for up to 4 doses. Treatment began on day 1 of week 1, and if there were no toxic effects that could not be tolerated, no rapidly progressive disease, and no significant decline in performance status, patients received an additional treatment during weeks 4, 7, and 10. Patients with stable disease for 3 months' duration after week 12 or a confirmed partial or complete response were offered additional courses of therapy (reinduction) with their assigned treatment regimen if they had disease	Vemurafenib group (n=337): 960mg twice daily, orally. dacarbazine group (n=338): 1000 mg/m^2 BSA, q3w by IV infusion. Dose reductions for both vemurafenib and dacarbazine were pre-specified for intolerable grade 2 toxic effects or worse. The development of cutaneous squamous-cell carcinoma did not require dose modification. The administration of vemurafenib was interrupted until the resolution of the toxic effect to at least grade 1 and restarted at 720 mg twice daily (480 mg twice daily for grade 4 events), with a dose reduction to 480 mg twice daily if the toxic effects recurred.	Dabrafenib group (n=187): 150mg twice daily, orally dacarbazine group (n=63): 1000mg/m^2 q3w Treatment continued until disease progression, death, study treatment discontinuation, or withdrawal. Patients in the dacarbazine group were allowed to cross over to receive dabrafenib after progression was confirmed by independent review. Patients who permanently discontinued dacarbazine because of an adverse event, withdrawal of consent, or for any reason other than progression of disease, were not eligible for crossover. Dose reductions for both dabrafenib and dacarbazine

	CheckMate 066	MDX010-20	BRIM-3	BREAK-3
	post progression in accordance with a DMC-recommended protocol amendment. Dose escalations were not permitted. Dose reductions were permitted for dacarbazine only in accordance with a pre-determined schedule. Dose delays were permitted for all AEs related to trial drugs (regardless of which treatment was attributed to the event).	progression.	If the toxic effect did not improve to grade 1 or lower or recurred at the 480-mg twice-daily dose, treatment was discontinued permanently. The administration of dacarbazine was interrupted for grade 3 or 4 toxic effects and could be restarted on recovery within 1 week to grade 1 (at full dose) or grade 2 (at 75% dose) or at 75% dose for grade 4 neutropaenia or febrile neutropaenia. A second dose reduction was allowed, if needed. Antiemetics and granulocyte colony-stimulating factor were administered according to standards at each study centre. Treatment was discontinued on disease progression unless continued treatment was in the best interest of the patient in the judgment of the investigator and the sponsor.	were pre-specified for adverse events of grade 2 or higher. Treatment with dabrafenib was interrupted until the adverse event resolved or reduced to grade 1. Treatment was restarted at the current dose for an adverse event of grade 2 or reduced by one dose level for an adverse event of grade 3 unless the adverse event was deemed unrelated to dabrafenib by the investigator. Dabrafenib was discontinued for drug-related grade 4 toxic effects and the patient was monitored and supportive care provided; if in the investigator's opinion, the event was not likely to be treatment-related and was therefore unlikely to recur, dabrafenib was restarted at one dose level lower. For dacarbazine-related toxic effects of grades 3 or 4, treatment was interrupted until the adverse event returned to grade 1 or lower, and then restarted with a dose reduction of 20%. Treatment with dacarbazine was discontinued if the adverse event did not resolve to grade 2 or lower within 4 weeks, or if a haematological adverse event of grade 4 recurred after dose reduction.
Permitted and disallowed concomitant medication	Antiemetic premedications were administered prior to dosing of dacarbazine or dacarbazine - matched placebo.	Patients could not use chemotherapy, biochemotherapy, surgery, radiation or immunotherapy, within 28 days of	Concomitant treatment with any other anticancer therapy was not allowed.	Not reported

	CheckMate 066	MDX010-20	BRIM-3	BREAK-3
	Immunosuppressive agents, systemic corticosteroids >10mg daily prednisone equivalent or any concurrent antineoplastic therapy were prohibited during the study (unless utilised to treat a drug-related AE). Palliative radiotherapy and surgical resection were permitted if the lesion being considered for such treatment was not a target lesion, the patient was considered to have progressed at the time of palliative therapy, and the case was discussed with the medical monitors. Patients could continue to receive HRT if initiated prior to randomisation. Bisphosphonates and RANK-L inhibitors were allowed for bone metastases if initiated prior to randomisation.	the first dose of study drug and gamma knife treatment within 14 days of the first dose of study drug. Patients could not use any of the following therapies during the course of the study: IL-2; IFN or any other non-study anti-melanoma immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigational therapies; chronic use of systemic corticosteroids. Patients with progressive disease who were not eligible for continued treatment or for re-introduction were permitted to receive non-study anti-melanoma medications at the discretion of the investigator.		

Abbreviations in table: AEs, adverse events; AJCC, American Joint Committee on Cancer; BMS, Bristol-Myers Squibb; BSA, body surface area; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DMC, data monitoring committee; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; HRT, hormone replacement therapy; IFN, interferon; IL-2, interleukin-2; IV, intravenous; IVRS, interactive voice response system; PD-L1, programmed death receptor ligand 1; PS, performance status; q2w, every 2 weeks; q3w, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumours

9.4 Crossover and subsequent therapy indirect comparison

At the clarification stage, the company kindly supplied Table 144 giving an overview of the proportion of patients who had crossover and/or subsequent therapies in the trials in the proposed network.

For CheckMate 067, the ERG is uncertain why in CS Table 18 the company states, "Post progression subsequent therapies included anti-PD1s, ipilimumab and BRAF inhibitors", though in the company clarification response post-progression response was stated as "not applicable". Also the ERG notes that there are inconsistencies in the number of patients who crossed-over in CheckMate 069 when comparing the number of patients who crossed over that are reported in the CS (CS Figure 9) and company clarification response (Table 144), which may have been caused by different data cut-off points.

Table 144. Crossover and subsequent therapy in trials evaluated for a mixed treatment comparison

Trial	Treatment	No subsequent therapy post progression	Crossover pre-progression	Crossover post-progression	Crossover total	Subsequent ipilimumab therapy	Subsequent systemic anti-cancer therapy (including crossover)
		n/N* (%)	n/N** (%)	n/N** (%)	n/N** (%)	n/N** (%)	n/N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 069 (August 2015 datacut)	Combination immunotherapy	11/35 (31.4%)	N/A	N/A	N/A	0	27/94 (28.7%)
	Ipilimumab	10/40 (25%)	0	26/26 (100%)	26/46 (56.5%)	0	30/46 (65.2%)
CheckMate 066 (18 month datacut)	Nivolumab	47/122 (38.5%)	N/A	N/A	N/A	57/206 (27.7)	79/206 (38.3)
	Dacarbazine	70/187 (37.4%)	N/A	N/A	N/A	89/205 (43.4)	122/205 (59.5)
MDX010-20 (19th June 2009 datacut)	Ipilimumab 3mg/kg	14/23 (60.9)	0	0	0	0	23/24 (95.8)
	gp-100	2/16 (12.5)	0	0	0	0	16/16 (100)
	Ipilimumab 3mg/kg + gp-100	15/51 (29.4)	0	0	0	0	51/54 (94.4)

Trial	Treatment	No subsequent therapy post progression	Crossover pre-progression	Crossover post-progression	Crossover total	Subsequent ipilimumab therapy	Subsequent systemic anti-cancer therapy (including crossover)
		n/N* (%)	n/N** (%)	n/N** (%)	n/N** (%)	n/N** (%)	n/N (%)
BRIM-3 (20^{th} Dec 2012 datacut)	Vemurafenib	192/337 (56.9)	0	0	0	74/337 (22.0)	145/337 (43.0)
	Dacarbazine	175/338 (51.8)	Not reported	Not reported	84/338 (24.9)	81/338 (24.0)	163/338 (48.2)
BREAK-3 (Jan 2014 datacut)	Dabrafenib	71/187 (38.0)	0	0	0	27/187 (14.4)	116/187 (62)
	Dacarbazine	12/63 (19.0)	0	37/63 (58.7)	37/63 (58.7)	3/63 (4.8)	51/63 (81)

* all treated patients that had disease progression
** all treated patients

9.5 Company's search strategy

9.6 Rationale for protocol Amendment 2 in CheckMate 069 (CSR, pg 5666)

[redacted]

[redacted]

9.7 Detailed modifications to the company's model implemented by the ERG

Table 145. Detailed modifications to the company's model implemented by the ERG

Sheet	Cell	Company's value	ERG value
Proportion of patients receiving ipilimumab after BRAF inhibitors			
Drug Dose Costs	D73:D74	22%	18%
Proportion of patients experiencing endocrine TRAEs in the ipilimumab arm			
Adverse Events	E11	34	[redacted]
Removal of nested long-term PPS mortality			
Controls	H133	3	100
PrePS Kaplan Meier curves averaging			
PrePS Parameters	D47:D2134	Blank	=AVERAGE(AE47:AF47) … =AVERAGE(AE2134:AF2134)
	E47:E2134	Blank	=AVERAGE(O47:P47) … =AVERAGE(O2134:P2134)

	I44:J2134	{=IF(ctrl_PrePScurve_TTPPPS="KM data",O44:P2134,
		IF(ctrl_PrePScurve_TTPPPS="Exponential",Q44:R2134,
		IF(ctrl_PrePScurve_TTPPPS="Weibull",S44:T2134,
		IF(ctrl_PrePScurve_TTPPPS="Gompertz",U44:V2134,
		IF(ctrl_PrePScurve_TTPPPS="Log-logistic",W44:X2134,
		IF(ctrl_PrePScurve_TTPPPS="Log-normal",Y44:Z2134,
		IF(ctrl_PrePScurve_TTPPPS="generalised gamma",AA44:AB2134,"Error")))))))}
			{=IF(ctrl_PrePScurve_TTPPPS="ERG",E44:E1234, IF(ctrl_PrePScurve_TTPPPS="KM data",O44:P2134,
			IF(ctrl_PrePScurve_TTPPPS="Exponential",Q44:R2134,
			IF(ctrl_PrePScurve_TTPPPS="Weibull",S44:T2134,
			IF(ctrl_PrePScurve_TTPPPS="Gompertz",U44:V2134,
			IF(ctrl_PrePScurve_TTPPPS="Log-logistic",W44:X2134,
			IF(ctrl_PrePScurve_TTPPPS="Log-normal",Y44:Z2134,
			IF(ctrl_PrePScurve_TTPPPS="generalised gamma",AA44:AB2134,"Error")))))))}

	K44:L2134	{=IF(ctrl_PrePScurve_TTPPPS="KM data",AE44:AF2134,
		IF(ctrl_PrePScurve_TTPPPS="Exponential",AG44:AH2134,
		IF(ctrl_PrePScurve_TTPPPS="Weibull",AI44:AJ2134,
		IF(ctrl_PrePScurve_TTPPPS="Gompertz",AK44:AL2134,
		IF(ctrl_PrePScurve_TTPPPS="Log-
			{=IF(ctrl_PrePScurve_TTPPPS="ERG",D44:D2134, IF(ctrl_PrePScurve_TTPPPS="KM data",AE44:AF2134,
			IF(ctrl_PrePScurve_TTPPPS="Exponential",AG44:AH2134,
			IF(ctrl_PrePScurve_TTPPPS="Weibull",AI44:AJ2134,
			IF(ctrl_PrePScurve_TTPPPS="Gompertz",AK44:AL2134,

Sheet	Cell	Company's value	ERG value
		logistic",AM44:AN2134, IF(ctrl_PrePScurve_TTPPPS="Log-normal",AO44:AP2134, IF(ctrl_PrePScurve_TTPPPS="generalised gamma",AQ44:AR2134,"Error"))))))}	IF(ctrl_PrePScurve_TTPPPS="Log-logistic",AM44:AN2134, IF(ctrl_PrePScurve_TTPPPS="Log-normal",AO44:AP2134, IF(ctrl_PrePScurve_TTPPPS="generalised gamma",AQ44:AR2134,"Error"))))))}
Controls	H95:I95	Data validation range: =list_survival_curves_PrePS	Data validation range: ='Selected Values'!B37:B44
Selected Values	B44	Blank	ERG
Removal of flat dose reduction of nivolumab			
Drug Dose Costs	H22	90.16%	100%
Alternative probabilities of receiving subsequent treatments			
Drug Dose Costs	D69	4.7%	[redacted]
	D70	1.8%	[redacted]
	E69	0.9%	[redacted]
	E70	0.9%	[redacted]
	F69	0.0%	[redacted]
	F70	0.9%	[redacted]
	G69	4.7%	[redacted]
	G70	34.4%	[redacted]
Abbreviations in table: ERG, Evidence Review Group; PrePS, pre-progression survival; TRAE, treatment-related adverse event.			

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 15/06/13

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
2	Amended "Objective response rate (ORR) was defined as the number of patients with a best objective response of complete or partial remission " to, "Objective response rate (ORR) was defined as the number of patients with a best overall response of complete or partial"
5	Amended "PrePS from end of maximum follow-up in the CheckMate 067 trial to end of time horizon" to, "PrePS from end of maximum follow-up in the CheckMate 067 trial to year 3" Added the following text: "PrePS from year 3 to end of time horizon: Gompertz parametric model estimated based on the pooled ipilimumab data reported by Schadendorf *et al*.[4];"
6	Added the following text: "with UK age- and gender-matched general population mortality used as lower bound;". Removed the text, "in BREAK-3 for".
18	Amended "The company does not give an estimate of the proportion of this population who may be eligible to treatment with combination immunotherapy." To, "The company does not give an estimate of the proportion of this population who may be fit enough to tolerate treatment with combination immunotherapy."
23	Amended "(68-78%)" to, "(68-79%)
25	Amended" bi-weekly" to, "every two weeks"
62	Amended "approximately 80% of patients in CheckMate 69 have performance status 0 as opposed to 70% in CheckMate 67" to, "approximately 80% of patients in CheckMate 069 have performance status 0 as opposed to 70% in CheckMate 067"
71	Amended [redacted]
72	Amended "57.6% of patients versus 19.0% with partial response" to, "46.2% of patients versus 16.8% with partial response"
91	Amended "any grade TRAEs were similar in the combination immunotherapy arm (99.7% versus 91.5%, respectively) and ipilimumab arm (99.0% versus 93.5%, respectively)" to "any grade TRAEs were similar in the combination immunotherapy arm (95.5% versus 91.5%, respectively) and ipilimumab arm (86.2% versus 93.5%, respectively) Amended "Also the proportion of grade 3-4 AEs were similar" to, "Also the proportion of grade 3-4 TRAEs were similar" Amended "discontinuation due to any grade and grade 3-4 AEs" to, "discontinuation due to any grade and grade 3-4 TRAEs" Amended "discontinuation due to any grade AEs" to, "discontinuation due to any grade TRAEs" Amended "discontinuation due to grade 3-4 AEs" to, "discontinuation due to grade 3-4 TRAEs" Amended "(13.0% versus 13.2%, respectively)" to, "(13.2% versus 13.0%, respectively)"
96	Amended "the ipilimumab plus dacarbazine arm" to, "the ipilimumab plus gp100 arm"
102	Removed the text "[redacted]

Page No.	Change
	[redacted]"
106	Amended "9.5 months[3]" to, "12.5 months[3]"
108	Amended "The ERG notes that it is not specified which patient characteristics were adjusted for and how; though it seems reasonable to assume that they were the same as the covariates used in the combination immunotherapy versus ipilimumab comparison (ECOG, LDH, M stage, brain metastases, age and gender)." to, "The data for combination immunotherapy were adjusted for the observed patient characteristics in the BRIM-3 trial, for the same covariates used in the combination immunotherapy versus ipilimumab comparison (ECOG, LDH, M stage, brain metastases, age and gender)."
113	Amended "There is a lack of data in the CS to support the company claim that the response kinetics is similar for combination immunotherapy and BRAF inhibitors" to, "There is a lack of data showing potential differences in response kinetics between combination immunotherapy and ipilimumab and BRAF inhibitors"
183	Removed the text, "however details regarding the parameters that were varied in the analysis were not provided".
193	Removed the text, "Additionally, the age- and gender-matched general population mortality should have been set as a lower bound for the mortality rates".

1.1 Summary of clinical effectiveness evidence submitted by the company

CheckMate 067 and CheckMate 069 are multicentre, double-blind, parallel-group randomised controlled trials. CheckMate 067 is a phase III trial including 629 patients randomised 1:1 to combination immunotherapy and ipilimumab. In the phase II trial CheckMate 069, 142 patients were randomised 2:1 to combination immunotherapy and ipilimumab.

In both trials, patients in the combination immunotherapy arm received nivolumab 1mg/kg plus ipilimumab 3mg/kg every three weeks by intravenous (IV) infusion for four doses followed by nivolumab 3mg/kg every two weeks until disease progression, discontinuation due to toxicity or any other reason. Patients who had a clinical benefit and were tolerating treatment, as determined by the investigator, were allowed to be treated after disease progression. Patients in the ipilimumab group received ipilimumab 3mg/kg every three weeks by IV infusion for four doses and a nivolumab-matched placebo.

In CheckMate 067 and CheckMate 069, combination immunotherapy was associated with a statistically significant improvement in PFS (HR 0.42, 95% CI: 0.31 to 0.57, and HR 0.39, 95% CI: 0.25 to 0.63, respectively). PFS was defined as the time between the date of randomisation and the first date of documented progression or death due to any cause (investigator-assessed). OS (defined as time between the date of randomisation and the date of death) data were immature for both CheckMate 067 and CheckMate 069, with median survival not reached in either intervention or comparator arm in either trial. An interim analysis of CheckMate 069 showed no statistically significant difference in OS for combination immunotherapy versus ipilimumab (HR 0.73, 95% CI: 0.39 to 1.36). No OS data was presented for CheckMate 067 in the CS. [redacted]

Objective response rate (ORR) was defined as the number of patients with a best overall response of complete or partial response divided by the number of randomised patients (investigator-assessed). Combination immunotherapy was associated with a statistically significant ORR compared to ipilimumab in both CheckMate 067 (OR 6.11, 95% CI: 3.59 to 10.38) and CheckMate 069 (OR 12.19, 95% CI: 4.41 to 33.68). In both CheckMate 067 and CheckMate 069 time to response did not differ significantly between treatment arms, with the majority of all responses observed at the time of the first scan at 12 weeks.

comparing immunotherapies and BRAF inhibitors based on the indirect comparison carried out by the company.

The data sources used and the methodologies applied to model treatment effectiveness of immunotherapies for the three outcomes in the company's model were:

- TTP, modelled separately for the two time periods individuated before and after 84 days into the CheckMate 067 trial. This was because of an observed cluster of progression events occurring at the first scheduled assessment of progression:
    - TTP pre-84 days: Kaplan Meier curves from the CheckMate 067 trial, adjusted for the patients' baseline characteristics based on the estimates of a Cox proportional hazards model;
    - TTP post-84 days: log-normal parametric model estimated based on the post-84 days CheckMate 067 trial data. Treatment effect was based on the model estimate, assuming proportionality of the hazards;
- PrePS:
    - PrePS from model inception to end of observed follow-up in the CheckMate 067 trial: Kaplan Meier curves from the CheckMate 067 trial, adjusted for the patients' baseline characteristics based on the estimates of a Cox proportional hazards model. The treatment effect estimated in the Cox model was not considered in the adjustment, and it was accounted for by the difference in the area under the Kaplan Meier curves. The maximum follow-up periods differed between the two model arms and were equal to 551 days and 513 days for combination immunotherapy and ipilimumab, respectively;
    - PrePS from end of maximum follow-up in the CheckMate 067 trial to year 3: patients were assumed to die at the same rate of the general population. The age-specific mortality was based on the UK life tables;
    - PrePS from year 3 to end of time horizon: Gompertz parametric model estimated based on the pooled ipilimumab data reported by Schadendorf *et al.*[4]
- PPS:
    - PPS from model inception to year 3: log-logistic model estimated based on the nivolumab arm of the CheckMate 066 trial and the pooled ipilimumab and ipilimumab plus gp100 arms of the MDX010-20 trial.

- PPS from year 3 to end of time horizon: Gompertz parametric model estimated based on the pooled ipilimumab data reported by Schadendorf *et al.*[4] with UK age- and gender-matched general population mortality used as lower bound.

The effectiveness of BRAF inhibitors was modelled based on two outcomes:

- PFS, based on a generalised gamma parametric model estimated based on pseudo-PLD generated from the BRIM-3 trial. The OS was set as upper bound for the PFS;
- OS, based on the log-normal parametric model based on pseudo-PLD generated from the BRIM-3 trial results until model year 3. A Weibull parametric model fitted on pseudo-PLD extracted from the AJCC registry for melanoma-specific mortality, in addition to age- and gender-matched English general population mortality.

Pharmacological resource use for immunotherapies was based on the data collected from the CheckMate 067 RCT. Patients were assumed to receive nivolumab within combination immunotherapy based on the time on treatment (ToT) observed in the trial up to 2 years since initiation, at which point all patients were to discontinue treatment. The company also assumed that, based on the trial relative dose intensity, only 90.16% of the target dose of nivolumab would be received by patients at each treatment administration over the maximum treatment duration of 2 years. A separate parametric model, independent of PFS but limited by OS, was used because the clinical stopping rule of nivolumab within combination immunotherapy allowed for treatment following disease progression.

The proportion of patients that would receive each of the four planned doses of ipilimumab was also based on the CheckMate 067 trial. Simple proportions of patients were used to model ToT rather than survival analysis. The company assumed that patients on BRAF inhibitors would be treated while in the PFS health state.

In the company's model patients could receive subsequent therapies after progression and discontinuation or failure of the model first-line treatment. Subsequent therapies were based on data collected in the CheckMate trial for combination immunotherapy and ipilimumab, in the BRIM-3 trial for vemurafenib and dabrafenib. The company assumed that different proportion of patients would receive subsequent therapies across treatment arms. In particular, ipilimumab was associated with the lowest proportion of patients who would not receive subsequent therapy. The cost of subsequent treatment was applied as a one-off quantity at treatment progression.

Follow-up resource use was based on time since treatment initiation and time to death. Resource use data were largely on the UK subset of patients from a longitudinal observational study on healthcare resource utilisation associated with the treatment of melanoma in Italy, France and UK. Resource use

checkpoint inhibitors do not have the delayed response kinetics observed with ipilimumab.[30] Hence, the first consideration would be whether the patient is likely to tolerate combination therapy, i.e. tolerate the side effects of the treatment. The company acknowledges eligibility for combination immunotherapy to be a subjective assessment. Clinicians may base this judgement on a combination of factors such as the presence of brain metastases, performance status, or disease volume. Patients who are not considered eligible for combination immunotherapy are likely to receive pembrolizumab or nivolumab monotherapy as first-line treatment, irrespective of BRAF status and risk of metastases. Subsequent lines of therapy will include ipilimumab and BRAF inhibitors based on BRAF status and risk, similar to current clinical practice. According to the company patients who receive combination immunotherapy as first-line treatment are unlikely to receive either nivolumab or ipilimumab in subsequent lines of treatment.[30]

Based on clinical expert advice the ERG notes that, combination immunotherapy may become the preferred choice for first-line treatment of advanced melanoma. However, the ERG clinical expert also points out that the group of patients that may benefit the most from combination immunotherapy as first-line treatment are those with high risk and/or large tumour burden disease. The preferred first-line treatment for some patients may be PD-1 inhibitor monotherapy (pembrolizumab or nivolumab) because of the better side effect profile compared to combination immunotherapy. Also, if either of the BRAF/MEK inhibitor combination therapies are recommended by NICE later this year (2016) they may become the preferred first-line treatment option for some $BRAF^+$ patients, as they also have a fast response time, but may have a better response rate and be better tolerated than combination immunotherapy.

The ERG recognises the importance for patients with advanced melanoma to have a wide range of effective treatment options. According to the company the two groups of patients likely to have the greatest need for combination immunotherapy are $BRAF^-$ patients and $BRAF^+$ patients who fail to respond to BRAF inhibitor therapy at first-line. The ERG notes that the latter group is expected to be small if most patients follow the suggested treatment pathway with combination immunotherapy as first-line treatment.

The company estimates the number of new cases of advanced (unresectable or metastatic) melanoma, which constitutes the patient group defined in the NICE final scope[1] for this STA, to 1,304 in 2016 (CS, Section 3.3). The company does not give an estimate of the proportion of this population who may be fit enough to tolerate treatment with combination immunotherapy. The ERG's clinical experts agree the importance of combination immunotherapy for a group of patients with advanced and unresectable melanoma. However, they also note that a substantial proportion of patients will not be able to tolerate the toxicity of combination therapy.

	CheckMate 067	CheckMate 069
	L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibody or any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways	pathways
Pre-planned subgroups	Subgroup analyses assessing the impact of age, gender, race, region, baseline ECOG PS, PD-L1 expression status, BRAF mutation status, M stage at study entry, history of brain metastases, smoking status, baseline LDH and AJCC stage on clinical efficacy outcomes were pre-planned.	Subgroup analyses assessing the impact of M stage at study entry, AJCC stage, age, gender, race, region, baseline ECOG performance status, history of brain metastases, smoking status, and baseline LDH on clinical efficacy outcomes were pre-planned for patients with BRAF mutation-negative and BRAF mutation-positive tumours.

Abbreviations in table: AJCC, American Joint Committee on Cancer; CD137, cluster of differentiation 137 (a member of the tumour necrosis factor family); CTLA-4, cytotoxic T-lymphocyte associated antigen 4; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand-1; PS, performance score; RECIST, Response Evaluation Criteria in Solid Tumors.
Source: CheckMate 067 CSR[33]; CheckMate 069 CSR[34]; Larkin *et al*. 2015[31]; Postow *et al*. 2015.[32]

In both trials there were several pre-planned subgroups, the results of which the company presents in CS Section 4.8. No subgroups were identified in the scope issued by NICE.[1] The ERG notes that the omission of subgroups from the final scope is in line with the anticipated clinical pathway if combination immunotherapy is recommended by NICE. The ERG also notes that the subgroups presented by the company include important prognostic factors and factors that may guide treatment choice.

CheckMate 069 was carried out at several sites in France and North America, and CheckMate 067 at sites in Australia, Israel, New Zealand, North America and Europe, including 66 patients (10.5%) from seven sites in the United Kingdom. In both trials randomisation was stratified by BRAF mutation status. However, the proportion of $BRAF^-$ patients in the trials was substantially higher (68-79%) than in the general patient population with advanced melanoma where around 50% are $BRAF^-$.

In summary, the ERG's clinical experts stated that the characteristics of the patient population enrolled in CheckMate 067 and 069 are representative of patients with metastatic or unresectable melanoma in England and Wales, however, an eligibility criteria for enrolment in these trials was an ECOG of 0 or 1, whereas in clinical practice the performance status of patients will be mixed, with some patients with ECOG 2.

1.2 Intervention

The company provides an overview of the technology (CS Section 2.1), the regulatory status (CS Section 2.2) and draft Summary of Product Characteristics (SmPC) of nivolumab, ipilimumab and the combination of the two.

Ipilimumab and nivolumab are both human monoclonal antibodies that act as inhibitors of T-cell receptors known as checkpoints, i.e. checkpoint inhibitors. Ipilimumab and nivolumab inhibit

2015 nivolumab also received marketing authorisation in the US for treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy.[35]

Nivolumab plus ipilimumab combination therapy is administered through intravenous infusion in a hospital or clinic setting. The recommended dose of nivolumab is 1mg/kg of body weight plus 3mg/kg of body weight of ipilimumab given every three weeks for four doses followed by nivolumab 3mg/kg of body weight every two weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated, for a maximum duration of two years. Hence, in the key clinical trials, CheckMate 067[31] and CheckMate 069[32], combination immunotherapy was given according to the draft SmPC recommendation and treatment after disease progression was permitted for patients who had a clinical benefit and were tolerating treatment, as determined by the investigator.

To summarise, the ERG considers the intervention in the CS to be consistent with the anticipated licence and the NICE final scope for this STA.[1]

1.3 Comparators

The final scope issued by NICE[1] lists comparators of interest as:

- ipilimumab;
- pembrolizumab;
- BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma.

The company does not include pembrolizumab as a comparator in the CS and gives the following reasons (Table 1):

- "[pembrolizumab] is not included in the current clinical pathway of care having only been recommended by NICE for use in NHS England after disease progression with ipilimumab in October 2015; and for use in patients not previously treated with ipilimumab in November 2015. Recent prescribing data indicate that there is virtually no pembrolizumab usage in a first-line setting and it is not in routine use in clinical practice. Pembrolizumab is not therefore established standard of care for advanced melanoma in NHS England and thus is not a relevant comparator to the Regimen [combination immunotherapy]." (CS, pg 14, Section 1.1)
- "at the time of systematic review initiation, pembrolizumab was not recommended for use in the NHS by NICE and was not included in either the draft or pre-invitation scope for this appraisal; therefore pembrolizumab was not included as an intervention of interest." (CS, pg 39, Section 4.1)

In addition, the ERG's clinical experts note that patients in CheckMate 069 are different from those in CheckMate 067 in terms of performance status and elevated LDH levels. Patients in CheckMate 069 have a better performance status than patients in CheckMate 069 (approximately 80% of patients in CheckMate 69 have performance status 0 as opposed to 70% in CheckMate 67). The performance status of patients in both trials is better than what is seen in clinical practice (in clinical practice there are generally more patients with ECOG performance status of 2). Also only 5% of patients in CheckMate 069[32] have two times the upper limit of LDH compared to 11% in CheckMate 067[31]. Prognosis of patients in CheckMate 067 is thus poorer than those in CheckMate 069.

In summary, the ERG's clinical experts stated that the characteristics of the patient population enrolled in both CheckMate 067 and 069 are representative of patients with metastatic or unresectable melanoma in England and Wales, however, in clinical practice the performance status of patients will include patients with ECOG 2, which were excluded from both trials.

CheckMate 004 started in December 2009 and enrolled 150 patients of which 127 were treated and 23 did not receive treatment, because they did not meet eligibility criteria or withdrew consent. Primary analysis was undertaken in June 2014 when 72.4% of all patients had discontinued treatment. In cohort 8, 53.7% of patients enrolled discontinued, with the most common reason (24.4% of patients) being study drug toxicity (Table 16).

Table 16. Patient disposition summary in CheckMate 004 (reproduced from CS, Table 35, Section 4.11)

	Cohorts 1-3 (n=53)	**Cohorts 6&7 (n=33)**	**Cohort 8 (n=41)**	**All cohorts (n=127)**
Patients discontinuing, n (%)	42 (79.3)	28 (84.8)	22 (53.7)	92 (72.4)
Reason for discontinuation, n (%)				
Death	1 (1.9)	2 (6.1)	3 (7.3)	6 (4.7)
Study drug toxicity	18 (34.0)	3 (9.1)	10 (24.4)	31 (24.4)
Disease progression	15 (28.3)	20 (60.6)	8 (19.5)	43 (33.9)
AE unrelated to study drug	1 (1.9)	0	0	1 (0.8)
Maximum clinical benefit	4 (7.5)	1 (3.0)	0	5 (3.9)
Other	3 (5.7)	2 (6.1)	1 (2.4)	6 (4.7)

Abbreviations in table: AE, adverse event.
Notes: no patients enrolled in cohorts 4 or 5.
Source: CheckMate 004 CSR[59]

The company described patient characteristics of patients in CheckMate 004 and the ERG agrees with this description (Box 9).

Box 9 Patient characteristics in CheckMate 004 (CS, pg 105, Section 4.11)

In cohort 8 there were slightly more females than males enrolled but across cohorts, the majority of

Figure 8. Kaplan-Meier curve for overall survival from 12 studies of ipilimumab in metastatic melanoma[4]

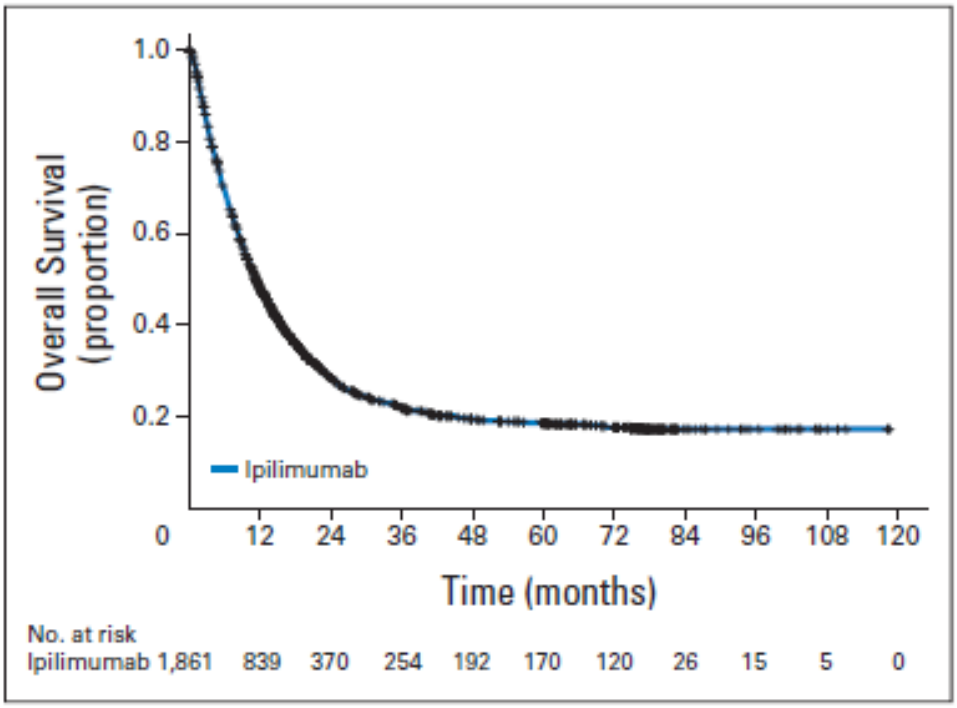


Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

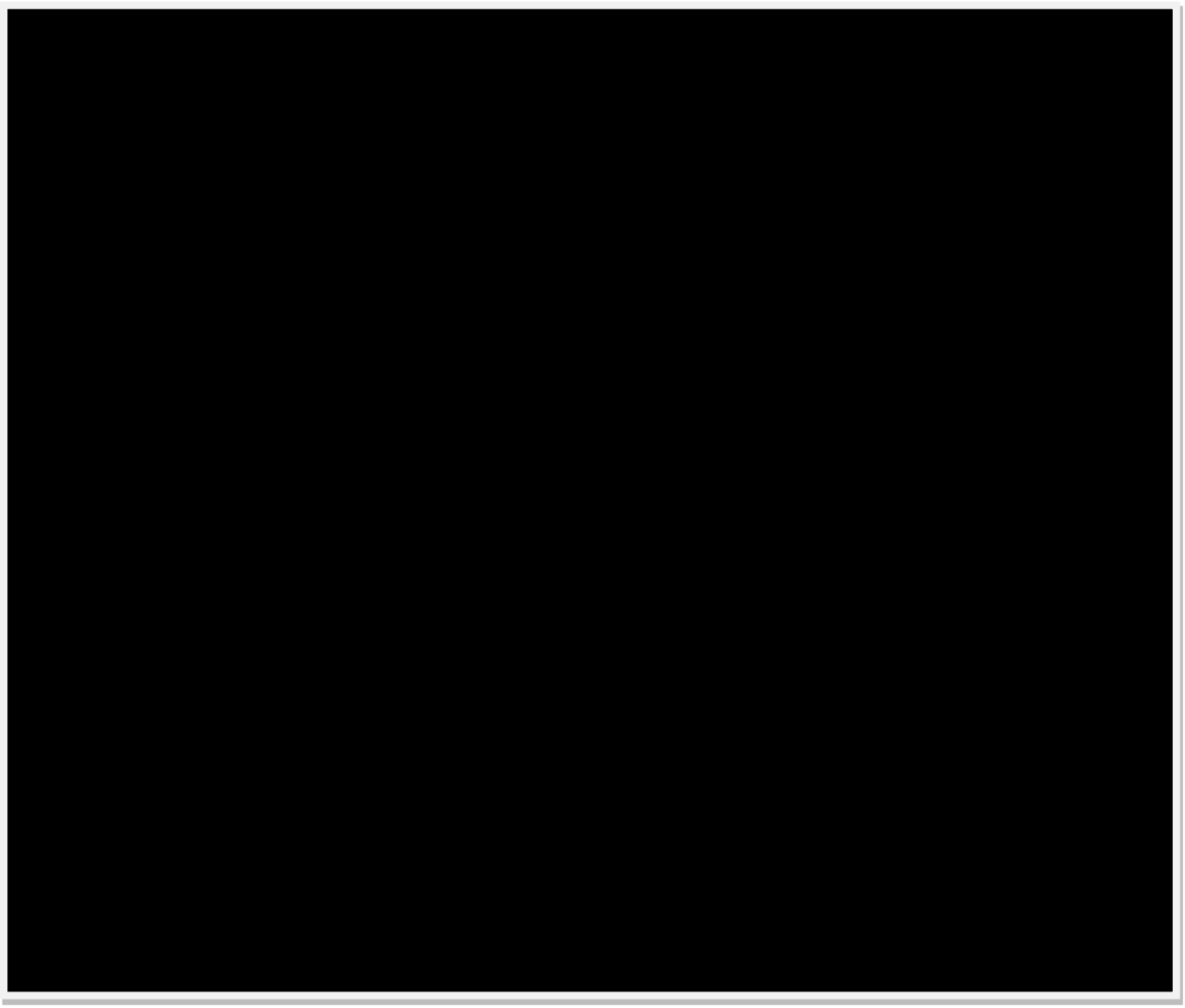
No OS data were presented for CheckMate 067 in the CS, [redacted] Table 20 [redacted] Figure 9.

[redacted]

Table 20 Interim OS analysis for CheckMate 067

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

Figure 9. Kaplan Meier curves[60]



1.3.1 Response analysis

The response analysis from CheckMate 067 is summarised in Table 21. In CheckMate 067 response to treatment was investigator-assessed. Both the proportion of patients with partial and complete response to treatment were higher in the combination immunotherapy arm than the ipilimumab arm; 46.2% of patients versus 16.8% with partial response and 11.5% versus 2.2% with complete response

Box 13. AEs in CheckMate 004 (CS, pg 120, Section 4.12)

As anticipated a priori, there were fewer Grade 3-4 AEs, SAEs (all causality and treatment related), Grade 3-4 SAEs and AEs leading to discontinuation in the lowest dose cohort of CheckMate 004 (cohort 1) compared with the higher dose escalation cohorts. This is because the higher dose escalation cohort (3mg/kg nivolumab plus 3mg/kg ipilimumab) exceeded the maximum tolerated dose (MTD).

The safety profile observed in cohort 8 was similar to that observed in RCTs; most patients experienced a TRAE but the nature of events was consistent with the mechanisms of action of nivolumab and ipilimumab.

Overall, the safety profile of combination immunotherapy in CheckMate 067 and 069 appeared to be similar. However, while no deaths due to study drug toxicity were reported in the combination immunotherapy in CheckMate 067, three deaths related to combination immunotherapy were reported in CheckMate 069. Given the limited information provided on CheckMate 004 in the CS, the ERG is unable to comment further on its safety profile compared to the other trials.

In CheckMate 067 and 069, most patients experienced a TRAE and the proportions of patients with any grade TRAEs were similar in the combination immunotherapy arm (95.5% versus 91.5%, respectively) and ipilimumab arm (86.2% versus 93.5%, respectively). Also the proportion of grade 3-4 TRAEs were similar in CheckMate 067 and 069 and higher in the combination immunotherapy arm (55.0% versus 54.3%, respectively) compared to the ipilimumab arm (27.3% versus 23.9% respectively). Additionally, the proportions of discontinuation due to any grade and grade 3-4 TRAEs were similar in both trials; the proportion of discontinuation due to any grade TRAEs was higher in the combination immunotherapy arm in CheckMate 067 and 069 (36.4% and 46.8%, respectively) compared to the ipilimumab arm (14.8% versus 17.4%, respectively) as well as the proportion of discontinuation due to grade 3-4 TRAEs in the combination immunotherapy arm (29.4% and 38.3%, respectively) versus the ipilimumab arm (13.2% versus 13.0%, respectively).

The proportions of the most common TRAEs, diarrhoea, fatigue, and pruritus, were similar in the combination immunotherapy and ipilimumab arms in CheckMate 067 and 069. In both trials, there were a higher proportion of all and grade 3-4 select AEs in the combination immunotherapy arm compared to the ipilimumab arm for the endocrine, gastrointestinal, hepatic, pulmonary, renal and skin categories.

1.3.1 Meta-analysis

At the clarification stage the company supplied the results of a meta-analysis of CheckMate 067 and CheckMate 069 for PFS and ORR (Table 30 and Table 31). The results of the meta-analyses are in

The two indirect comparisons are described and appraised separately below, including identification and selection of trial evidence, and statistical procedures used (methods, assumptions, covariate selection). Sections 5.4 and 5.5 of this report describe and critique the statistical procedures used to fit and extrapolate parametric survival curves from the trials to inform the comparisons made within the economic model.

1.3.1 Indirect comparison of combination immunotherapy and ipilimumab

Evidence base

For the comparison of combination immunotherapy versus ipilimumab, OS data from CheckMate 067 and CheckMate 069 were not used because they were immature. In addition, for CheckMate 069 the OS results were potentially confounded by substantial crossover from the ipilimumab arm to nivolumab monotherapy [redacted]. Instead the company used PFS data from CheckMate 067 (combination immunotherapy and ipilimumab arm) and data from CheckMate 066 (nivolumab arm) and MDX010-20 (ipilimumab and ipilimumab+gp100 arms) as a proxy for OS, assuming similar post-progression survival efficacy for ipilimumab, nivolumab and combination immunotherapy (assumption discussed later in this Section).

Among the trials included in the review (Table 4), five studies investigated ipilimumab monotherapy 3mg/kg (Table 32). The reason for the company's decision to use data from MDX010-20 as the basis for the long term survival data of combination immunotherapy and ipilimumab is not clearly stated in the CS. However, the ERG notes that of the five ipilimumab trials, MDX010-20 had the most mature OS data with a median follow-up for survival of 27.8 months in the ipilimumab monotherapy arm. MDX010-20 also had the largest sample size as a result of combining the ipilimumab arm and the ipilimumab plus gp100 arm (based on the company's assumption of equal efficacy of ipilimumab and ipilimumab plus chemotherapy [dacarbazine and gp100], this is discussed later in this Section).

Table 32 Included trials with an ipilimumab 3mg/kg monotherapy arm (adapted from CS, pg 42, Table 9)

Study	Ipilimumab treatment schedule	N randomised	median follow up	Other
CA184-004[40]	Q3W *4 + Q12W	Ipilimumab N = 40	8.9 months	Phase II
CA184-022[41]	Q3W *4 + Q12W	Ipilimumab N = 72	8.7 months	Phase II
MDX010-08[42]	Q3W *4	Ipilimumap N = 40	16.4 months	Phase II
		Ipilimumab + dacarbazine N = 36	20.9 months	

The ERG does not consider the evidence presented by the company to definitively demonstrate no impact of line of therapy on treatment effect. If previous treatments do affect the efficacy of immunotherapies, the impact may be an underestimation of PPS for combination immunotherapy and ipilimumab, as both are based on data from MDX010-20, which only enrolled previously treated patients.[53] However, the ERG notes that the company's arguments for the assumption around line of therapy is based on OS data, and may not hold for PPS.

- Ipilimumab plus gp100 and ipilimumab monotherapy were assumed to have equal efficacy in MDX010-20. This assumption was required to maximise the data used by including data from both these trial arms in MDX010-20 to estimate PPS of combination immunotherapy and ipilimumab. In MDX010-20 there was no marked difference in OS or PFS for ipilimumab plus gp100 and ipilimumab monotherapy.[26] In the previous NICE appraisal for ipilimumab in previously treated patients (NICE TA268) the committee agreed that gp100 was likely to be an acceptable proxy for best supportive care.[69] The ERG's clinical experts agree that this is a reasonable assumption.

The company states that, "using this approach [covariate-adjusted model], and in particular [using] PPS rather than OS, allows increased validity and robustness of survival extrapolations for long-term estimation of treatment effects when data are relatively immature (i.e. they do not reach the median survival point)" (CS, pg 85, Section 4.10). The ERG acknowledges the uncertainty introduced if extrapolating OS and PFS long-term from very immature data, and notes that with this approach the company could use data from MDX010-20, with a follow-up of up to 56 months (4.7 years) for OS, compared to the available data for the direct comparison from CheckMate 069 with a follow up of up to 18 months for OS. [redacted]

There are several issues with the covariate-adjusted model approach, which may affect the validity of and increase the uncertainty around the results:

The ERG notes that although LDH levels in BRIM-3 may be more reflective of patients seen in UK clinical practice, they differ quite substantially to the LDH levels in CheckMate 067,CheckMate 066 and MDX010-20 (Table 34and Table 38); the basis of the immunotherapy combination effectiveness. The ERG is concerned that no reasons were given in the CS for the exclusion of the other six BRAF inhibitor trials identified in the systematic search (Table 37). Of the seven included BRAF inhibitor trials, BRF113220 and Grippo *et al.* 2014 are phase I trials with small sample sizes. However, in addition to BRIM-3 there are four other phase III trials (BREAK-3, COMBI-d, COMBI-v and coBRIM) with relatively large sample sizes and median follow up of 10 to 20 months. The baseline characteristics appeared to be relatively similar between these five trials, apart from the higher LDH levels in BRIM-3 (Table 38). Limited time precluded the ERG from investigating the impact of trial selection on the subsequent analyses.

Table 37. Included trials with a BRAF inhibitor monotherapy arm (adapted from CS, pg 42, Table 9)

Study	**Design**	**N randomised to BRAF inhibitor**	**Outcome**	**Median length of follow up for which the most recent Kaplan Meier curve is reported**
Studies investigating dabrafenib 150 mg monotherapy				
BREAK-3	Phase III	187	OS	16.9 months[72]
			PFS	4.9 months[2]
COMBI-d	Phase III	212	OS	20 months[73]
			PFS	
BRF113220	Phase I	54	OS	Median overall survival not reached at time of analysis[45]
			PFS	14.1 months[45]
Studies investigating vemurafenib 960 mg monotherapy				
BRIM-3	Phase III	337	OS	13.4 months[74]
			PFS	12.5 months[3]
COMBI-v	Phase III	352	OS	10 months[46]
			PFS	
coBRIM	Phase III	248	OS	~14 months[47]
			PFS	
Grippo *et al.* 2014	Phase I	16	OS	15 days, no KM data reported[48]
			PFS	
Abbreviations in table: OS, overall survival; PFS, progression-free survival.				

Table 38. Baseline characteristics of BRAF inhibitor (dabrafenib or vemurafenib) monotherapy arm (adapted from CS, pg 97, Table 29)

Characteristic	**Dabrafenib trials**			**Vemurafenib trials**			
	BREAK-3	**Combi-d**	**BRF113220**	**BRIM-3**	**Combi-V**	**coBRIM**	**Grippo *et al.* 2014**

immunotherapy] in the BRAF mutation-positive patient population, keeping the efficacy observed for vemurafenib within BRIM-3 unaltered.

Similar to the indirect comparison of combination immunotherapy and ipilimumab, the company assumes that BRAF mutation status does not affect the treatment effect of immunotherapies, and that line of treatment is not independently prognostic and does not independently impact treatment effectiveness. These assumption were necessary as 100% of patients in BRIM-3 were $BRAF^{+}$, around 30% of patients in CheckMate 067 were $BRAF^{+}$, CheckMate 066 included only $BRAF^{-}$ patients and MDX010-20 did not report the BRAF mutation status of patients, and BRIM-3, CheckMate 067 and CheckMate 066 all enrolled treatment naive patients, whereas MDX010-20 enrolled previously treated patients. The rationales for these assumptions for the comparison of combination immunotherapy and BRAF inhibitors are the same as discussed previously (Section 4.4.1).

The data for combination immunotherapy were adjusted for the observed patient characteristics in the BRIM-3 trial, for the same covariates used in the combination immunotherapy versus ipilimumab comparison (ECOG, LDH, M stage, brain metastases, age and gender). However, there is no mention in the CS of adjusting for potential trial differences or subsequent ipilimumab therapy as was done in the analysis of PPS for CheckMate 066 and MDX010-20. Also, no adjustments have been made for pseudo progression, which would be expected to affect PFS in the comparison of combination immunotherapy and BRAF inhibitors. However, according to the ERG clinical experts, the impact of pseudo progression is expected to be low.

The ERG notes, the same limitations for the comparison of combination immunotherapy and BRAF inhibitors as for combination immunotherapy versus ipilimumab (Section 4.4.1): advantage of using data derived from RCTs is lost, it is unclear if all relevant prognostic factors have been adjusted for and if the adjustments were sufficient, and no validation of the covariate adjusted approach was provided in the CS. In addition, the selection of study data was inadequately described and unclear, no reliable long-term survival data were available for either of the BRAF inhibitors, and if the efficacy of the BRAF inhibitors is not equivalent, no estimate of combination immunotherapy versus dabrafenib is available.

1.3.1 Indirect comparison of combination immunotherapy and pembrolizumab

Evidence base

At the clarification stage the company performed an adjusted indirect comparison to enable a comparison of combination immunotherapy and pembrolizumab by including the trials: CheckMate 067, Keynote 006 (pembrolizumab 10m/kg Q3W versus ipilimumab) and Keynote 002

- Data from CheckMate 067 and 069 indicate that a substantial proportion of patient experience continued clinical response after discontinuation of treatment with combination immunotherapy.

- A substantial proportion of patients in both CheckMate 067 and 069 were treated beyond RECIST defined progression because they showed continued clinical benefit and could tolerate the treatment.

- There were no clinically meaningful differences in HRQoL between combination immunotherapy and ipilimumab in either trial.

- The rates of grade 3-4 AE were considerably higher among patients treated with combination immunotherapy compared to ipilimumab. The most common treatment-related serious adverse effects associated with combination immunotherapy were diarrhoea, colitis, pyrexia, increased transaminases, nausea and hypophysitis.

- The company used a covariate-adjusted approach to produce comparative efficacy estimates for combination immunotherapy, ipilimumab and BRAF inhibitors to extrapolate survival data that were used in the economic model.

    - Combination immunotherapy compared to ipilimumab was estimated using participant level data (PLD) from CheckMate 067 for PFS, and PLD from CheckMate 066 and MDX010-20 as proxy for OS (due to the immaturity of OS data from CheckMate 067 and 069).

    - Combination immunotherapy compared to BRAF inhibitors was similarly estimated using PLD from CheckMate 067, CheckMate 066 and MDX010-20, together with aggregate data from BRIM-3 (vemurafenib) to form an indirect comparison.

- [redacted]

1.3.2 Clinical issues

- There is a lack of data showing potential differences in response kinetics between combination immunotherapy and ipilimumab and BRAF inhibitors, and therefore the use of combination immunotherapy as first line therapy for all patients, including patients deemed to be at high risk.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D.
Benefit valuation	Time-trade off or standard gamble	Not reported.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Data were collected during the CheckMate 067 RCT. Valuation methodology was not reported in the CS.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	A probabilistic sensitivity analysis around the base case was performed.
Abbreviations used in the table: HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; RCT, randomised clinical trial.		

Table 84. Philips checklist[130]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2: Statement of scope/perspective	Stated correctly.
S3: Rationale for structure	The company stated clearly the rationale for the modelling structure chosen. A semi-Markov state-transition model was adopted because of the immaturity of the OS data from the CheckMate 067 trial. The company therefore modelled OS as a function of TTP, PrePS and PPS. PPS and the long-term extrapolation of PrePS were based on sources other than the phase III CheckMate 067 RCT.
S4: Structural assumptions	The company did not state clearly the structural assumptions. Under the modelling approach taken, the company implied surrogacy between TTP and OS over the entire time horizon.

The ERG notes that, had the cut-off date been different, the post-84 days parametric models might have been substantially different, and that even small differences in the effects would have influenced the extrapolated outcomes substantially.

In conclusion, the ERG is not satisfied with the TTP analysis carried out by the company, in particular given the lack of flexibility around the cut-off time assumption. The ERG considers that allowing for progression events to occur pre-cut off date is not consistent with the assumption of all patients having a first assessment at 84 days as described by the company.

Pre-progression survival

The company fitted a Cox PH model to the observed PrePS observed in the CheckMate 067 trial. The PH assumptions were not tested, but used in the covariate adjustment. Even though no difference was found between the treatment arms, the company assumed the existence of a difference between the curves during the follow-up period and then equal to the difference in the tails of the curves at the end of the maximum follow-up. Moreover, the general population mortality was not used as bound for the mortality rates during the CheckMate 067 follow-up period, even though there were very few patients at risk at later follow-up times. General population mortality rates were nested on the adjusted Kaplan Meier curves earlier on in the ipilimumab arm compared to the combination immunotherapy arm by about 1 month of model time, as described in Section 5.4.2.9.

The ERG disagrees with the company's approach for modelling PrePS. Very little information was contained in the Kaplan Meier curves and no difference between the two treatments emerged to both graphical analysis (Figure 27) and formal testing (via the Cox model, Table 50). A more reasonable approach would be to pool together the two curves and assume equal mortality between the treatments. This would remove the assumption of a PrePS survival benefit carried over along the entire time horizon which was not justified. In the ERG opinion the assumption of an extrapolated survival benefit equal to the difference in the tails of the curves is inappropriate.

The company assumed that long-term pre-progression survival would be equal to the general population mortality. This assumption implies that patients with advanced, metastatic melanoma, alive and not progressed after about 2 years, would have the same mortality rate as the age- and gender-matched general English population. The expected survival in PrePS projected in the company's base case model is reported in Table 87.

Table 87. Average progression-free survival time for immunotherapies compared to matched general population

Expected survival (years)	BRAF- subpopulation	BRAF+ subpopulation

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma [ID848]

You are asked to check the ERG report from BMJ Technology Assessment Group (BMJ-TAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 30th March 2016** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Commercial in confidence marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
[redacted]	[redacted]	[redacted]	The ERG does not consider the omission of confidential marking of the listed text to be a factual error nor a misrepresentation of the information presented in the company submission. Company submission page 12 states, “Median OS has not yet been reached in either Checkmate 067 or Checkmate 069 because the number of events (deaths) pre-specified in the statistical analysis plan has not yet been reached in either study.”, page 79 states, “Head to head trial data (CheckMate 067) has been used to inform treatment comparisons between the Regimen and ipilimumab. Overall survival is yet to be mature and available for this comparison.” Neither of these statements are marked as CIC in the company submission. The ERG considers this a matter for NICE to consider if this text warrants a retrospective consideration as commercial in confidence.

	[redacted] 		

Issue 2 Incomplete representation of exploratory ERG BRAF inhibitor analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 254: "The ERG expects that, based on the assumptions adopted in the preferred base case scenario, longer time horizons would underestimate the survival associated to immunotherapies compared to BRAF inhibitors" This statement is not provided in other sections discussing this analysis.	This statement should be carried forward to the summary on page 11 as it aids the Committee in understanding the direction of bias in the ERG's revised analysis. In addition it should also be made clear that the use of a 5 year time horizon is not in accordance with the NICE reference case as the time horizon should be "long enough to reflect all important differences in costs or outcomes between the technologies being compared". We note that a 40 year time horizon is confirmed as appropriate for this purpose earlier in the document (page 183).	In order to provide the Committee with information on the validity and direction of bias within the ERG scenario analysis.	The ERG does not consider the statement to be factually incorrect.

Issue 3 Old source of data used for BRIM-3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In page 106, Table 37 and page 201 the ERG reference an older datacut of BRIM-3. This means that incorrect conclusions are drawn relating to the proportion of patients receiving subsequent ipilimumab and the length of follow-up available for BRIM-3. Additionally this statement on page	Remove analysis altering the proportion of patients receiving subsequent ipilimumab within BRIM-3. Amend Table 37. Remove wording that BRIM-3 is not the longest follow-up available for BRAF inhibitors. Amend wording on page 197 in light of the data available for BRIM-3.	The Hauschild 2013 poster presented at SMR (ref 81 in the CS) represented the most relevant up-to-date source of information for BRIM-3 identified within the systematic literature. For information an additional cut of BRIM-3 has since been released at SMR 2015 which supplies additional information for 1 more year of follow-up for BRIM-3; conclusions remain the same as when the 3 year data is used. A copy of this additional data is supplied with this response. Incorrect assumptions are currently made by the ERG relating	The ERG thanks the company for highlighting the error on the incorrect follow up for PFS in BRIM-3. This has been amended. However, the references in Table 37 are correct. The ERG notes that the company did not cite the

197 is incorrect: “because no OS trial data exist for the BRAF inhibitors after 3 years”		to the validity of the analyses presented and rationale for selection of this study for use within the ITC based upon use of incorrect evidence.	source used to derive the proportion of patients treated with ipilimumab following vemurafenib in the BRIM-3 trial, and that the 22% value in Table 68 of the CS does not match the value in the Chapman *et al*. 2015 poster or in the McArthur *et al.* 2014 publication. The correct 18% proportion from the McArthur *et al*. 2014 paper was used for consistency with the sources used to derive the treatment efficacy of the BRAF inhibitors.

Issue 4 Misinterpretation of use of modelling approach for PPS and implications regarding surrogacy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 10 the ERG state that the use of TTP / PrePS and PPS separately (rather than using an area under the curve model) implies that BMS consider PFS a good surrogate for OS for immunotherapies Additionally page 10 the following is stated: • Differences in PPS are seen due	Clarify statements that the manufacturer considers progression to be a surrogate for OS. Clarify statement regarding assumption of equal PPS. It was not stated that equal PPS was assumed throughout the model time	We are aware of the issues relating to surrogacy between progression and OS for immunotherapies. As stated on page 23 of the CS: “varying patterns of response can be observed with immuno-oncology therapies such that patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment. This is due to increased T-cell activity making the tumour appear bigger	The ERG does not consider the statements to be factually incorrect. The company did not state the reliance of the model on the surrogacy assumption, nor did they provide evidence to support it. The equal conditional survival

to the use of Schadendorf data to model long-term survival • The company did not state or to explain this discrepancy to their assumption that the same post-progression mortality was applied to the two immunotherapies. • The ERG considers the survival benefit of combination immunotherapy over ipilimumab is likely to have been overestimated by an unknown quantity This is also stated on page 99 The ERG also state on page 195: "As already mentioned in Section 5.5.2, the ERG disagrees with the company's statement that, "It is conservatively assumed that PPS is the same for all immunotherapies" (CS, pg 143, Section 5.3.2). While the assumption would be conservative *per se*, it is not in the context of the sequentiality of the health states in the semi-Markov model. This is because survival depends on a combination of treatment-specific factors, specifically PrePS and TTP. An assumption of equal PPS among immunotherapies would imply an assumption of surrogacy between TTP and OS, i.e. an extension in TTP would	horizon only that equal PPS curves were applied to both model arms for the time period during which PPS was used to model OS. [redacted]	('pseudo-progression')" This means that some patients can be classed as progressed according to RECIST criteria when in fact what is being observed is response to treatment. [redacted], progression data were used as an imperfect proxy for OS. [redacted] The assumption of equal PPS only applied during the time period where PPS was used to model survival as stated within the CS (i.e., up to year 3 when Schadendorf long-term OS was applied to immunotherapies).. Outside of this time period the assumption of equal conditional survival for all immunotherapies based upon long-term data for ipilimumab was applied. The use of alternative sources of data to estimate survival projection in the long-term reduced the reliance of the model on the implicit assumption of surrogacy. [redacted]	assumption was not stated in the CS. The difference between the equal survival and equal conditional survival assumptions was not justified by the company. [redacted]

translate into an extension in OS. This assumption was not explicitly stated, justified or proved by the company, and is not considered a conservative assumption by the ERG."			

Issue 5 Scope addressed in company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state on Page 1: "According to the company pembrolizumab is not established standard of care for advanced melanoma in NHS England and thus it is not a relevant comparator to combination immunotherapy. The ERG considers that the CS does not fully address the scope issued by NICE based on the omission of the comparator pembrolizumab, and inclusion of dabrafenib only by making an assumption of equivalence with vemurafenib."	The statement regarding the BRAF inhibitors should be removed and that referring to pembrolizumab amended to reflect the fact that the committee for a recent nivolumab appraisal also recognised that pembrolizumab is not yet standard of care in NHS England.	Whilst it is true that the CS did not include pembrolizumab as a comparator, in the FAD for the recent nivolumab appraisal TA384, published very recently on 18th February 2016, it was confirmed within the FAD that "*pembrolizumab is not yet in routine clinical use"* The company is not alone in recognising that pembrolizumab is not established standard of care for advanced melanoma in NHS England. It was confirmed by clinical experts for appraisals TA321 and TA366 that vemurafenib and dabrafenib are not considered to have different effectiveness and "are broadly interchangeable" Therefore, the suggestion that dabrafenib was not included as a comparator is incorrect as clear justification of why the BRIM-3 study alone was used to estimate the relative effectiveness of both vemurafenib and dabrafenib is provided in the CS.	The ERG does not consider the statements to be factually incorrect.

Issue 6 Wrong direction of bias implied for assumption of equivalence of BRAF inhibitors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG note that comparison is presented assuming equal effectiveness for vemurafenib and dabrafenib (page 105) and appear to imply that if BREAK-3 had been used then dabrafenib would have been considered more effective Conclusions derived for this are mentioned on page 1	We would ask the ERG to include all relevant information from the TA321 Final Appraisal Determination and the direction of effect being considered by the Committee. In addition to the points raised: "The Committee also heard from the clinical specialist that the clinical effectiveness of dabrafenib and vemurafenib were not considered to differ in clinical practice and that the choice between the 2 treatments would be largely based on their adverse reaction profiles" "The Committee considered that BRIM-3 was a large trial and could show an overall survival benefit with vemurafenib, whereas BREAK-3 was a smaller trial and it would be more difficult to demonstrate a statistically significant overall survival benefit with dabrafenib. The Committee also noted that the progression free survival gains in the two trials were very similar, and concluded that there was no clear evidence that dabrafenib and vemurafenib differed in clinical effectiveness and that it would not be unreasonable to assume that they have similar effect" The same statement as issued recently in TA366: "The clinical experts indicated that in clinical practice dabrafenib and vemurafenib are not considered to have different effectiveness and are broadly interchangeable"	The Committee in TA321 was originally concerned that dabrafenib was less effective than vemurafenib (as opposed to the other way round).	The ERG does not consider the statements to be factually incorrect. The ERG considers the company choice of trial not to be transparent, but does not imply any change in size or direction of effect that this choice may cause.

Issue 7 Incorrect conclusion implied on availability of evidence to form a network

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

ERG state on page 93 “the same inclusion criteria to inform both the direct and indirect evidence, which were limited to the intervention and comparator in the scope (with the exception of pembrolizumab, which was excluded). Tailoring the inclusion criteria for the indirect comparison by, e.g. including nivolumab monotherapy as an intervention, would have identified CheckMate 066, and potentially other relevant trials, that could link the network, or inform an indirect comparison using covariate adjusted data as presented by the company.” Similar points regarding potential additional evidence for comparison to BRAF inhibitors are raised on page 106	Where these statements are raised, the ERG should clarify that despite lack of a formal systematic review no further trials are available in order to allow a traditional indirect comparison. This is stated in places within the document but not consistently.	Provide the Committee with the relevant information so it is understood what information is available and that inclusion of additional trials would not aid in this decision. A network diagram and table are provided as an Appendix to this document. The table includes all RCTs containing one of the following treatments: • Nivolumab plus ipilimumab • Nivolumab • Pembrolizumab • Ipilimumab • Dabrafenib • Vemurafenib As noted by the ERG later in the document no additional trials are available which would allow a network to be formed using a standard indirect comparison including all comparators within the NICE scope. As can be seen within the network diagram subsequent therapy pollution is likely to be a major issue for conducting any traditional indirect comparison.	The ERG does not consider the statements to be factually incorrect.

Issue 8 Incorrect recommendation that missed doses are included in effectiveness and not costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 11 "The ERG did not find the company's justification around the assumption of a constant reduction over time in the nivolumab resource use and cost to be sufficient to grant a reduction in costs equal to approximately 10% of the total costs associated with the drug acquisition costs of nivolumab" Similar statement is made on page 203	Provide additional information on the reason for this assumption.	As is the case for all drugs given intravenously, not all patients will be able to attend their planned appointment to receive their dose of therapy. The impact of missed doses on effectiveness is accounted for within the observed outcomes of patients within the CheckMate 067 trial. The impact of missed doses should therefore also be accounted for within cost calculations. As stated in the CS, the 90.16% (the ERG is correct 90.2% represents the same figure rounded to 1 decimal place) represents the proportion of patients who received their expected dose whilst on treatment with nivolumab within the CheckMate 067 trial. The proportion of patients receiving their planned dose was included (and accepted) within cost-effectiveness calculations for pembrolizumab for previously treated and previously untreated melanoma for this reason.	The company did not provide a clear definition of planned and missed doses, with particular reference to dose adjustments and their variations over time. The calculations used to determine the reduction were not detailed. The assumption of a constant reduction over time was not justified and accompanied by supporting evidence. The ERG does not consider the statement to be factually incorrect.

Issue 9 Incorrect statement regarding proportion of patients who may be eligible for combination immunotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 18 "The company does not give an estimate of the proportion of this	Remove statement	This information is provided within the market share assumptions	The ERG thanks the company for highlighting the error.

population who may be eligible to treatments with combination immunotherapy.		within Section 6 of the CS.	It has been amended.

Issue 10 Incorrect presentation of applicability of Schadendorf data to ipilimumab outcomes and confounding of CheckMate 067 ipilimumab arm

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 69 “The ERG notes that the OS curve for ipilimumab in CheckMate 069 is markedly different from the OS curve for ipilimumab in trials included in the pooled analysis; the 12 month survival rate for patients on ipilimumab is around 65% in CheckMate 069 and around 50% in the pooled analysis by Schadendorf et al. (Figure 7 and Figure 8). The ERG notes that, the pooled analysis by Schadendorf et al. included may early phase studies, which were run at a time when PD-1 inhibitor was not available for patients on progression following treatment with ipilimumab. Hence, their results are not polluted by crossover from ipilimumab to subsequent nivolumab as in CheckMate 069. Also, in many of the included trials ipilimumab was given as second-line treatment compared to CheckMate 069, where patients were treatment naive.” And on page 71 in relation to CheckMate 067 “However, the difference in survival curves for ipilimumab in this case cannot be explained by	Remove the statement on page 71 and replace with the statement that this can be explained by confounding from subsequent therapies (50% of patients receive an active subsequent therapy after ipilimumab; mainly anti-PD1 therapy). Remove similar statements throughout the document. Remove the statement on page 69 that an alternative rationale for difference between Schadendorf ipilimumab outcomes and CheckMate 067 / 069 may be line of therapy.	As shown in the Table 1 provided with this response there is substantial confounding from subsequent PD-1 inhibitor therapy (i.e,, 29% of patients in the ipilimumab arm receive subsequent PD-1 inhibitors) in CheckMate 067 despite formal crossover not being allowed. Additionally Schadendorf data from the curves for patients receiving first-line treatment shows similar outcomes for patients at first and subsequent lines treated with ipilimumab therefore the statement regarding Schadendorf including previously treated patients is not relevant. The overall OS reported by Schadendorf (regardless of lines of treatment) was used in the economic model (Figure 1 in the	The ERG does not consider the statements on page 69 to be factually incorrect. The ERG thanks the company for the additional information around the proportion of crossover in CheckMate 067 and for highlighting the error in conclusions on page 71. The text has been amended.

potential confounding from crossover therapies as these were not allowed in CheckMate 067.”		Schadendorf paper).	

Issue 11 Incorrect interpretation of dose analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 73 that the analysed supplied in relation to PFS and OS for patients receiving <=4 vs 4 doses of nivolumab indicate a consistent benefit for OS and PFS in patients receiving more than 4 doses.	Remove this statement	This interpretation is incorrect as within the trial protocol treatment was mandated to continue until either progression or unacceptable toxicity, patients were also allowed to continue treatment post progression if tolerated and the investigator considered the patient would benefit. As treatment beyond 4 doses was mandated for patients able to continue therapy it is unsurprising that patients had longer PFS and OS. The analyses presented are a measure of whether or not remaining on study for longer resulted in better patient outcomes.	The ERG does not consider the statement to be factually incorrect.

Issue 12 Incorrect statement on non RCT information available for the Regimen

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 30 “it is unclear if CheckMate 004 is the only non-RCT of combination immunotherapy or if there may be other observational trials not reported in the CS.”	Remove this statement	The ERG also state “Apart from those studies presented in Sections 4.2 and 4.11, no other studies investigate the Regimen [combination immunotherapy]; safety data are therefore only presented from CheckMate 067, CheckMate 069 and CheckMate 004” on page 81 For information Regimen only recently became available in some countries outside the EU, so there are no observational studies available. The only other study including the Regimen not reported in the CS is CA209-038, which is a biomarker study which does not report any relevant outcomes for this submission. Also 004 is a non-controlled study	The ERG does not consider the statement to be factually incorrect.

Issue 13 Reason for using MDX010-20 and CheckMate 066 for indirect comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 96 “The reason for	Amend statement on page 97 to	Statement is incorrect in relation to	The ERG thanks the company

the company's decision to use data from MDX010-20 as the basis for the long term survival data of combination immunotherapy and ipilimumab is not clearly stated in the CS. However, the ERG notes that of the five ipilimumab trials, MDX010-20 had the most mature OS data with a median follow-up for survival of 27.8 months in the ipilimumab monotherapy arm. MDX010-20 also had the largest sample size as a result of combining the ipilimumab arm and the ipilimumab plus dacarbazine arm (based on the company's assumption of equal efficacy of ipilimumab and ipilimumab plus chemotherapy [dacarbazine and gp100], this is discussed later in this Section).." and on page 97 "the ERG notes that nivolumab monotherapy trials were not included in the systematic review, and the reason for using data from the nivolumab trial CheckMate 066 was not clearly described in the CS." on page 97 "It is also unclear why the company used data from both CheckMate 066 and MDX010-20 rather than choosing one trial"	reflect the rationale provided for inclusion of CheckMate 066 Amend "the ipilimumab plus dacarbazine arm" to "the ipilimumab plus gp100 arm"	CheckMate 066. Details were provided on page 80 of the CS: "Although not formally identified as part of the systematic literature review, CheckMate 066 has been included in these analyses as relevant data to support and enhance overall survival (post-progression survival) evidence." For the ERG's information MDX010-20 was included for 2 reasons: • MDX010-20 has the most mature immunotherapy OS data from an RCT • MDX010-20 contains the licensed dose of ipilimumab and was the basis for ipilimumab recommendation by NICE at first line Both trials were included in order to use all available unpolluted information on immunotherapy long-term effectiveness within the analysis.	for highlighting the error that dacarbazine should have been gp100 on page 96. It has been amended. The ERG does not consider the statement regarding the reason to included CheckMate 066 being unclear to be factually incorrect. The ERG does not consider the statement regarding the reason to include both CheckMate 066 and MDX010-20 being unclear to be factually incorrect.

Issue 14 Issues with using a piecewise constant model for comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 95 "However, an alternative approach could have been to segment the survival curves into different sections within which the HRs are different but the proportional hazards assumptions holds. The company could then have used a piecewise constant model."	Clarify that this approach would not deal with the substantial issues of pollution from subsequent therapy within the BRAF inhibitor trials.	Whilst this approach would account for non PH there remains the issue of substantial pollution of the chemotherapy arms of both BRIM-3 and BREAK-3 with subsequent use of ipilimumab and BRAF inhibitors. The current statement in the ERG report does not make clear that the suggested approach would address this issue (and that this issue cannot be dealt with without access to the patient level data from either BRIM-3 or BREAK-3, which the company does not have).	The ERG does not consider the statement to be factually incorrect.

Issue 15 Issues formally adjusting for treatment switching

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 95 "The differences between the trials in terms of crossover and subsequent therapies may have a substantial impact on the comparability of the trials in the network.(64) However, the company could have used	Remove statements regarding ability to adjust formally for crossover and DSU guidance only advocating adjustment for subsequent therapy when switching affects more than 60% of	The key trials where adjustment for subsequent therapy pollution is required in order to provide a sensible comparison are BRIM-3 and BREAK-3. Within BRIM-3 59% of patients receive subsequent active treatment; 75% in BREAK-3. BMS does not have access to patient level data for either of these trials therefore cannot adjust for subsequent therapy pollution.	The ERG does not consider the statement to be factually incorrect.

an appropriate method to adjust for switching (64) or used the ITT method as more complicated methods advocated by the DSU for dealing with treatment switching are only substantially more reliable than using the ITT results when switching affects more than 60% of patients..”	patients.	DSU guidance states: “The ITT analysis represents a valid comparison of randomised groups, but in the presence of treatment switching this is unlikely to be what is required for an economic evaluation because the “true” survival benefit associated with the novel intervention will be diluted due to the switching of control group patients onto the novel therapy.” We cannot find any statement in the DSU guidance related to ITT analyses being appropriate when switching affects less than 60% of patients. If this is the ERG’s opinion, it should be presented as such. We note that recently NICE considered adjustment for crossover appropriate within the NICE appraisal for pembrolizumab in previously-treated patients (where 48% of patients switched treatment from ICC to pembrolizumab). We understand the ERG would have preferred to see an NMA comparing the Regimen to BRAF inhibitors, however, the problem of comparison to BRAF inhibitors given subsequent therapy pollution is a fundamental issue with the two trials available to form a network. These issues have not changed over the many NICE technology appraisals conducted recently within melanoma. In fact, in previous appraisals attempting to conduct such an NMA has been deemed inappropriate (TA319 and TA366 for example).	

Issue 16 Misunderstanding regarding statement on line of treatment not being prognostic

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

ERG state on page 102 "The ERG does not consider the evidence presented by the company to definitively demonstrate no impact of line of therapy on treatment effect. [redacted] compared to the pooled analysis of ipilimumab data by Schadendorf et al. in which a large proportion of patients were previously treated (Section 4.3.2)."	Remove statement relating to CheckMate 067 and Schadendorf evidence Amend to wording to make clear that the evidence presented was intended to demonstrate that line of treatment was not **independently** prognostic, rather than not prognostic.	As noted by the ERG earlier the assumption of line of treatment not being prognostic was only required, and intended, to relate to the MDX010-20 trial. This assumption therefore only relates to prior chemotherapy not having an independent impact (i.e., other things being equal) on outcomes with ipilimumab, which has previously been accepted by NICE TA384. [redacted]13[redacted] As noted by the ERG in the previous page the Schadendorf dataset itself does not show a significant impact of line of treatment on outcomes. The trials included in this paper are the most relevant to look at outcomes for ipilimumab without pollution from subsequent active therapies as these trials were all run prior to the availability of PD-1 inhibitors and BRAF inhibitors. Finally the statement made in the CS related to line of treatment not being **independently** prognostic when other prognostic covariates are taken into account. Presenting evidence from disparate trials without adjustment for prognostic covariates where outcomes differ does not demonstrate this statement to be incorrect.	The ERG thanks the company for the additional information around the proportion of crossover in CheckMate 067. The text has been removed.

Issue 17 Misunderstanding regarding loss of randomisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 103 "Loss of	Clarify how the covariate included	We understand the ERG would	The ERG does not consider

randomisation. The intrinsic advantage of randomisation is the minimisation of several types of bias, as all factors other than the effect of the intervention and comparator are considered balanced in the treatment arms as a result of the randomisation process.(70) In the company approach, only observed prognostic covariates could be adjusted for. Any unobserved prognostic covariates could not have been accounted for. This isn't a problem when using a method that preserves randomisation since the randomisation should provide balanced groups within each trial. As is discussed below, it is unclear if the covariate adjustments made in the company approach can capture and adequately adjust for all differences between the trials, which would be minimised in a direct RCT and would have been retained in an NMA." A similar statement is made on page 9	for trial accounts for unobserved prognostic factors. Clarify that the 'loss of randomisation' issue only refers to the indirect comparison of the Regimen with BRAF inhibitors, and that the alternative, a traditional indirect comparison or NMA, also has limitations.	have preferred to see an NMA comparing the Regimen to BRAF inhibitors, however, the problem of comparison to BRAF inhibitors given subsequent therapy pollution is a fundamental issue with the two trials available to form a network. These issues have not changed over the many appraisals conducted recently within melanoma. In fact in previous appraisals attempting to conduct such an NMA has been deemed inappropriate (TA319 and TA366 for example). It is our opinion, that although the 'loss of randomisation' issue present with the indirect comparison to BRAF inhibitors is not ideal, it is a preferable approach to the issues with construction of an NMA including these treatments.	the statement to be factually incorrect. The ERG is still unclear about what was included in the trial covariate and how it was adjusted for.

Issue 18 Misunderstanding regarding lack of validation of covariate adjustment approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 103 "Validation of covariate adjustment approach. At the clarification stage, the company was asked to examine the validity of their approach by comparing the relative treatment effect estimates	Validation of the covariate adjusted patient level indirect comparison against results from an adjusted indirect comparison using summary level study results was not performed for the CheckMate 066 and MDX010-20 data included in this submission, because an indirect comparison of nivolumab versus ipilimumab was not performed using dacarbazine/gp100 as a common comparator. This was not performed in this submission because where this data was used (post progression survival), ipilimumab and nivolumab were assumed to have equivalent	The ERG clarification request, question A4, was misunderstood, and therefore the required information was not previously provided in the response.	The ERG does not consider the statement to be factually incorrect.

using the covariate adjusted "indirect" comparison approach with relative treatment effect of nivolumab versus ipilimumab obtained in an adjusted indirect comparison using dacarbazine/gp100 as a common comparator. Instead the company provided more details around the methodology employed in the covariate adjusted approach, and provided a comparison of the results from their model with unadjusted, partially adjusted (study and treatment), and fully adjusted (all covariates) results, and results from CheckMate 067."

post progression survival, and the latest data for CheckMate 066 was polluted with crossover and subsequent therapy in the dacarbazine arm, therefore only data for ipilimumab and nivolumab was used. However, the validation exercise requested was actually included in the nivolumab monotherapy submission (NICE TA 384, Table 36, page 116), and is reproduced below for reference.

	Hazard ratio (95% confidence interval), nivolumab vs ipilimumab	
Outcome	**Adjusted indirect comparison using covariate adjusted Cox regression HRs from CheckMate 066 and MDX010-20, and dacarbazine/gp100 as a common comparator**	**Indirect comparison estimated as a treatment effect from a covariate adjusted Weibull parametric model, including PLD from both CheckMate 066 and MDX010-20, where the study main effect in the model forms the indirect comparison and maintains the randomisation**
TTP Post 100 days	0.37 (0.17, 0.81)	0.38 (0.18, 0.84)
PPS	0.92 (0.56, 1.53)	0.95 (0.58, 1.55)
OS	0.55 (0.36, 0.84)	0.62 (0.41, 0.94)
PFS	0.58 (0.42, 0.80)	0.59 (0.43, 0.80)

Key: DTIC, dacarbazine; gp100, gp100 melanoma peptide vaccine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PLD, patient level data; PPS, post-progression survival; TTP, time to progression.
Note: Covariates included in the Cox regressions and Weibull

	regressions included: Study (Weibull models only), Treatment, Sex, Age group, ECOG, Elevated LDH, M stage, History of brain metastases, subsequent ipilimumab (PPS and OS only)		

Issue 19 Reference for PFS data from CheckMate 067 and valuation method for HRQL analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 104 “For PFS, where information is more complete, the estimated HR of 0.536 (95% CI: 0.391 to 0.735, covariates for study and treatment) is similar to the observed HR of 0.55 (99.5% CI: 0.42 to 0.73; p<0.0001). The ERG notes that the observed PFS data has not been referenced and hence the ERG is unable to validate the data” ERG state on Page 7 – “the valuation method applied was not reported”	None - information provided by ERG for clarity.	[redacted] The valuation of EQ-5D data was performed using the Dolan 1997 time trade off valuation algorithm.	The ERG thanks the company for the additional information.

Issue 20 Misunderstanding regarding CS statement on response kinetics

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG state on page 113” that we claim that the response kinetics is similar for combination immunotherapy and BRAF inhibitors”	Remove this statement from throughout the report.	We do not believe that this statement best reflects the situation. We did not suggest that response kinetics are similar to BRAF inhibitors only that the Regimen does not suffer from the same delayed response kinetics as ipilimumab. As the ERG state earlier no firmer conclusion can be	The ERG thanks the company for highlighting this. The sentence has been rephrased.

		drawn than this because the first measurement of response in the relevant trials was at 12 weeks.	

Issue 21 Inappropriate assumption of comparative cost-effectiveness of the Regimen (combination immunotherapy) and pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state on page 257 "……. based on the HRs reported in the main trials for combination immunotherapy and pembrolizumab when compared to ipilimumab, seems to indicate a shorter PFS time for pembrolizumab and no difference in OS between the two treatments. This might be indicative of a similar cost-effectiveness profile, if the differences in costs are balanced by the potential difference in PFS time (determining a difference in terms of quality-adjusted life years), or else a favourable cost-effectiveness profile for pembrolizumab when compared to	Remove statement: This might be indicative of a similar cost-effectiveness profile, if the differences in costs are balanced by the potential difference in PFS time (determining a difference in terms of quality-adjusted life years), or else a favourable cost-effectiveness profile for pembrolizumab when compared to combination immunotherapy.	There is no clear basis for this statement as the ERG have not conducted their own comparison of the cost-effectiveness of the Regimen and pembrolizumab, whereas the analysis that we performed clearly shows that the Regimen is cost-effective compared with pembrolizumab. 	The ERG does not consider this statement factually inaccurate.

combination immunotherapy. However, the ERG considers the evidence provided by the company to be insufficient to support any conclusion for this comparison.”		[redacted]	

Issue 22 Incorrect statement regarding comparison of Regimen (combination immunotherapy) vs. pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state on page 3 “……On request, the company performed an adjusted indirect comparison	Amend statement to reflect that the company also performed a cost-effectiveness analysis versus pembrolizumab	The current statement is incorrect and suggests that only an adjusted ITC vs pembrolizumab was performed	The ERG does not consider this statement factually inaccurate.

Issue 23 Reference to treatment arm not relevant to decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state on page 2 “……median survival not reached in either treatment arms”	Remove statement	The is referencing a treatment arm not relevant to the decision problem and should be removed	The ERG does not consider this statement factually inaccurate.

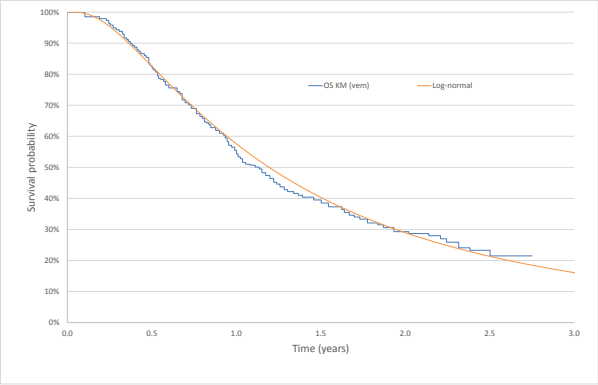
Issue 24 Other inaccuracies relating to the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 5 - ERG report suggested we used PrePS	Suggest clarify that as there are no PrePS	The lengths of time used for PrePS for ipilimumab and the regimen are 513 and 551 days which are	The ERG does not consider the statement to be factually incorrect.

KM data for different lengths of time for the 2 treatment arms.	events between day 513 (longest follow-up for ipilimumab arm) and 551 (longest follow-up for the regimen arm), the use of different lengths has limited impact on the results.	the longest follow-up for both arms. There are no PrePS events between day 513 and 551 for the Regimen arm, therefore there will be very limited impact on the results if both arms use 513 days as the length of time for PrePS KM data.	
Page 5 – "PrePS from end of maximum follow-up in the CheckMate 067 trial to end of time horizon: patients were assumed to die at the same rate of the general population."	Suggest change to "PrePS from end of maximum follow-up in the CheckMate 067 trial to model year 3: patients were assumed to die at the same rate of the general population." And add "PrePS from year 3 to end of time horizon: Gompertz parametric model estimated based on the pooled ipilimumab data reported by Schadendorf et al.; and gender- and age-matched general population is used to set the minimum mortality rate for the entire time horizon"	After year 3, Schadendorf long-term OS was used to model PrePS for the Regimen and ipilimumab arms for both BRAF mutation-negative and BRAF mutation-positive patients. Gender- and age-matched general population mortality was set as the minimum mortality for both PrePS and PPS from time zero to end of model (i.e. 40 years).	The ERG thanks the company for highlighting the error. The text has been changed as suggested.
Page 6 – "PPS from year 3 to end of time horizon: Gompertz parametric model estimated based on the pooled ipilimumab data	Suggest add "and gender- and age-matched general population is used to set the minimum mortality	Gender- and age-matched general population mortality was set as the minimum mortality for both PrePS and PPS from time zero to end of model (i.e. 40 years).	The ERG thanks the company for highlighting the error. The text has been changed as suggested.

reported by Schadendorf et al".	rate." to the end.		
Page 6 – ERG report mentioned BREAK-3 trial data was used for subsequent therapy after dabrafenib.	Suggest remove.	In line with the effectiveness data used subsequent therapy after dabrafenib is assumed to be the same as vemurafenib which was based on BRIM-3 trial. Therefore, the statement is not correct.	The ERG thanks the company for highlighting the error. The text has been changed as suggested.
Page 8 – "However, key parameters such as the baseline characteristics, which influenced all efficacy models as covariates were not varied stochastically."	Suggest clarify that although the baseline clinical characteristics (e.g., ECOG, LDH status) were not varied stochastically, the estimated coefficients for these clinical characteristics from the covariate adjusted regression models were varied stochastically in the PSA using variance-covariance matrix.	As far as we know, there is no standard practice for PSA for covariate adjusted models where uncertainties come from both the value of the covariate (e.g., ECOG, LDH status) and the estimated coefficients for the covariates. We have not seen precedence where both these two sources of uncertainties have been tested simultaneously. Instead, it is more intuitive to test the uncertainty associated with the estimated coefficients for the covariates which reflect the impact of these covariates on the dependent variable (e.g,, OS, PFS). The covariate adjusted regression model also produces variance-covariance matrix to facilitate the PSA. Therefore, we did not vary the baseline characteristics stochastically, but instead tested the uncertainty associated with the estimated coefficients for these baseline characteristics stochastically in the PSA.	The ERG does not consider the statement to be a factual inaccuracy.
Page 10 – "The ERG also considers unlikely that the survival rates of patients with advanced melanoma would be in line with the survival of the age- and gender-matched general English population."	Suggest clarify that age- and gender-matched general English population mortality is only applied directly from the end of the PrePS KM to year 3, after which	Statement in the ERG report was not true beyond year 3.	The ERG does not consider the statement to be a factual inaccuracy.

	Schadendorf long-term OS was applied.		
Page 108: "The ERG notes that it is not specified which patient characteristics were adjusted for and how; though it seems reasonable to assume that they were the same as the covariates used in the combination versus ipilimumab comparison (ECOG, LDH, M stage, brain metastases, age and gender)."	Suggest remove.	The patient characteristics that were used to adjust for the Regimen and ipilimumab PFS and OS for BRAF mutation-positive patients were reported in Table 52 in the CS (which are the same covariates used in the Regimen versus ipilimumab comparison for BRAF mutation-negative patients, but with different values). The text above the table also explains the method and assumptions.	The ERG thanks the company for highlighting the error. The text has been amended.
Page 134 – "While the company did not state clearly which figure was used as the source of OS data, the ERG it was likely to be Figure 1 in the Schadendorf et al. publication"	Suggest replace this statement with the following: "After confirming with the company, the source of the OS data was Figure 1 in the Schadendorf et al. publication.".	We can confirm we used Figure1 in the Schadendorf et al. publication. The suggested amendment would increase the accuracy and certainty of the document.	The ERG does not consider the statement to be a factual inaccuracy.
Page 139: Figure 34 shows the fit of the tested curves to the pseudo-PLD. The ERG notes that none of the curves seems to fit the data particularly well.	Suggest remove.	Standard parametric curves were fitted and log-normal was chosen as the base case based on AIC/BIC, visual inspection and clinically plausibility (see AIC/BIC and comparison of log-normal curve and KM data below). While we agree some of the fitted curves do not visually fit the data well, the log-normal curve we chose provides good statistical and visual fit (as can be seen in the figure below).	The company seem to have reported the AIC/BIC model fits and visual comparison between the data and the fitted curve relative to the analysis of the BRIM-3 trial OS data. The statement in page 138, "Figure 34 shows the fit of the tested curve […] the data particularly well" refers to the analysis of OS registry data, rebased at 3 years.

		<table><tr><th>Model</th><th>AIC</th><th>BIC</th></tr><tr><td>Exponential</td><td>3700.23</td><td>3704.05</td></tr><tr><td>Generalised Gamma</td><td>3647.94</td><td>3659.41</td></tr><tr><td>Gompertz</td><td>3698.01</td><td>3705.65</td></tr><tr><td>Log-logistic</td><td>3651.70</td><td>3659.34</td></tr><tr><td>Log-normal</td><td>3647.40</td><td>3655.04</td></tr><tr><td>Weibull</td><td>3677.80</td><td>3685.44</td></tr></table> 	The ERG does not consider the statement to be a factual inaccuracy.
Page 183 – “details regarding the parameters that were varied in the analysis were not provided”	Suggest remove.	Details regarding which parameters were included in the probabilistic sensitivity analyse, the distributions used and the parameters for the distributions can be found in Table 70 in the CS.	The ERG thanks the company for highlighting the error. The text has been changed as suggested.
Page 191 “In the ERG’s opinion this should have been set either earlier in time (e.g. at 11 weeks, or 77 days), thus completely	Suggest remove.	84 day was selected as the first scheduled tumour assessment was at week 12 in CheckMate 067. Selecting a cut-off either before or after 12 weeks may introduce unknown bias which is less robust and defendable than the 12 weeks used in the	The ERG does not consider the statement to be a factual inaccuracy.

avoiding the cluster of events, or after the cluster, e.g. at 13 weeks, or 91 days."		model. Furthermore, given unknown directions of bias for choosing 11 or 13 weeks, there is also a practical problem of which one to choose (11 or 13 weeks) for the base case. This is evidenced by the statement made where the suggestion appears to be that we should have chosen both 77 and 91 weeks for use in the model. Clearly this is not possible.	
Page 193: "The age- and gender-matched general population mortality should have been set as a lower bound for the mortality rates."	Suggest remove.	We did set age- and gender-matched general population mortality as the lower bound for the mortality rate for the entire time horizon for the PrePS (including the period where adjusted KM data was used).	The ERG thanks the company for highlighting the error. The text has been changed as suggested.
Page 200: "However, no comparison was made between the HRQoL values observed in the trial and data identified in the systematic literature review"	Suggest remove.	Scenario analyses were performed to test the impacts of alternative HRQoL values from previous literature and NICE submissions including utilities based on CheckMate 066 (used in TA384) and utilities reported by Porter et al. 2014 (as identified via the systematic review and also used for TA319).	In this context, the ERG refers specifically to the analysis of discrepancies among values of the utility scores in the data sources, and not to the impact of alternative values on the model results. The ERG does not consider the statement to be factually inaccurate.
Page 202: "The ERG notes that the subsequent therapy data from both the CheckMate 067 and BRIM-3 trials seem to be implemented incorrectly in the model. This is because the proportions of the total patients who received subsequent therapy are used as an estimate of the	Suggest remove.	ERG is correct that we used proportions of the total randomised patients who received subsequent therapy in CheckMate 067 and BRIM-3 as an estimate of the probability of receiving treatment after progression. However, we believe this is a standard assumption and method to model subsequent therapy, as rarely proportions of patients receiving subsequent treatments are reported conditional on progression. Although theoretically different, the two measures can be close given in most trials patients would	The ERG is aware that the difference would not bias the results towards a particular treatment and that the difference in results would is expected to be negligible. The ERG does not consider the statement to be factually inaccurate.

probability of receiving treatment after progression.”		progress before death, which means the denominators are very similar. We also believe this method/assumption currently used in the model doesn’t provide bias towards a particular treatment arm.	

Issue 25 Minor text inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following textual inaccuracies were identified within the ERG report	• Page 2; Page 44, “Objective response rate (ORR) was defined as the number of patients with a best objective response of complete or partial remission” – to strictly align with RECIST (and CSR definition), this should read “Objective response rate (ORR) was defined as the number of patients with a best overall response of complete or partial response • Page 23, “However, the proportion of BRAF- patients in the trials was substantially higher (68-78%)” – 78.7% BRAF-ve patients so should read 68-79% in brackets • Page 25, “The recommended dose of nivolumab is 1mg/kg of body weight plus 3mg/kg of body weight of ipilimumab given every three weeks for four doses followed by nivolumab 3mg/kg of body weight bi-weekly” – can we please rephrase to read “followed by nivolumab 3mg/kg of body weight every two weeks” to avoid any misinterpretation of bi-weekly as bi-weekly	Aid in both the accuracy and clarity of the document	The ERG thanks the company for highlighting the errors. The text has been changed as suggested.

	can also represent twice per week dosing • Page 62: “Patients in CheckMate 069 have a better performance status than patients in CheckMate 069 (approximately 80% of patients in CheckMate 69 have performance status 0 as opposed to 70% in CheckMate 67).” Last reference to CheckMate 069 and CheckMate 067 should state 069 and 067 and not 69 and 67 • Page 72, “Both the proportion of patients with partial and complete response to treatment were higher in the combination immunotherapy arm than the ipilimumab arm; 57.6% of patients versus 19.0% with partial response” – these figures refer to ORR • Page 91, “any grade TRAEs were similar in the combination immunotherapy arm (99.7% versus 91.5%, respectively) and ipilimumab arm (99.0% versus 93.5%, respectively)” – these figures refer to any grade AEs, for any grade TRAEs figures should read 95.5% (not 99.7%) and 86.2% (not 99.0%) • Page 91, “Also the proportion of grade 3-4 AEs were similar in CheckMate 067 and 069 and higher in the combination immunotherapy arm (55.0% versus 54.3%, respectively) compared to the ipilimumab arm (27.3% versus 23.9% respectively).” – these figures report grade 3-4 TRAEs		

	• Page 91, “proportion of discontinuation due to any grade AEs was higher in the combination immunotherapy arm in CheckMate 067 and 069 (36.4% and 46.8%, respectively) compared to the ipilimumab arm (14.8% versus 17.4%, respectively)” – again these figures refer to DCs due to TRAEs • Page 91, “versus the ipilimumab arm (13.0% versus 13.2%, respectively)” – these figures are the wrong way round – 13.2% in 067 and 13.0% in 069		

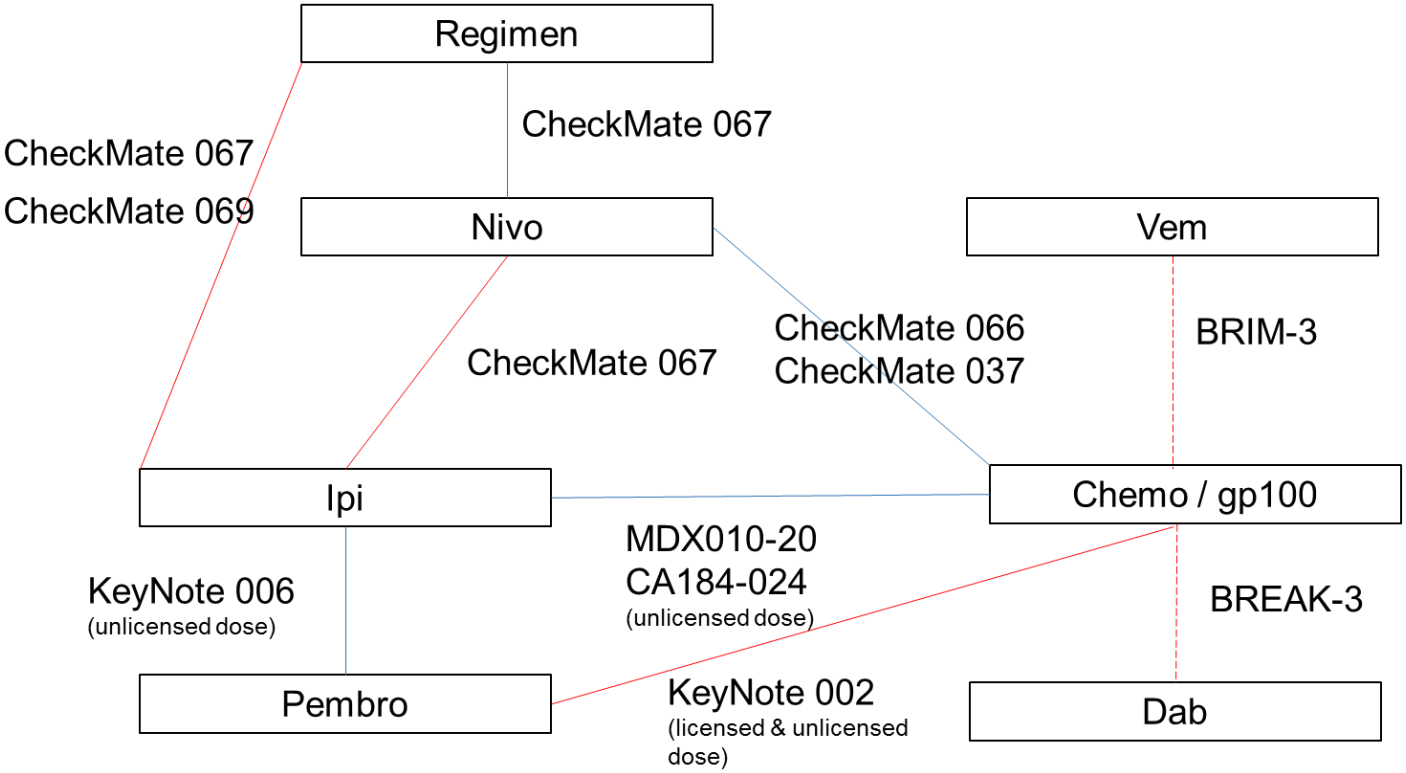
Appendix

Table 1 Full list of RCTs including scoped interventions plus nivolumab monotherapy

Trial	Interventions (n)	Max length follow-up	Line of therapy	BRAF status of patients	Formal crossover allowed (Y/N)?	Number of progression events per arm (%)	Number receiving subsequent therapy (%)			Validity of PH assumption within trial	Patient level data available?
							PD-1s	Ipilimumab	BRAF inhibitors		
CheckMate 067	Regimen (n=314) Nivolumab (n=316) Ipilimumab (n=315)	[redacted]	First	69% BRAF mutation negative	No	[redacted]	[redacted]	[redacted]	[redacted]		√
CheckMate 069	Regimen (n=95) Ipilimumab (n=47)	[redacted]	First	77% BRAF mutation negative	No[a]	[redacted]	[redacted]	[redacted]	[redacted]		√
CheckMate 066	Nivolumab (n=210) DTIC (n=208)	28 months	First	100% BRAF mutation negative	Yes (from July 2014)	58% (18 months) 90% (18 months)	NR 25%	27% NR	NR NR		√
Keynote 002	Pembro 2mg (n=180) Pembro 10mg (n=181) ICC (n=179)	12 months	Second or later	77% BRAF mutation negative	No	72% 70% 87%	NR NR 48%	NR NR NR	NR NR NR		X
Keynote 006	Pembro 10 q2w (n=279) Pembro 10 3qw (n=277) Ipilimumab (n=278)	12 months	First / second	64% BRAF mutation negative	No	56% 57% 68%	NR NR NR	NR NR NR	NR NR NR		X
MDX010-20	Ipilimumab + gp100 (n=403) Ipilimumab (n=137) Gp100 (n=136)	55 months	Second or later	Unknown	No	92% 90% 93%	None	None	None	Reasonable with long term dataset	√
CA184-024	Ipilimumab 10 + DTIC (n=250) DTIC (n=252)	60 months	First	Unknown	No	81% 89%	None	None	None	Reasonable with long term dataset	√
CheckMate 037	Nivolumab (n=272) ICC (n=133)	6 months	Second or later	78% BRAF	No	43% 58%	0% 5%	2% 2%	4% 5%		√

				mutation negative							
BRIM-3	Vemurafenib (n=337) DTIC (n=338)	33 months	First	100% BRAF mutation positive	Yes	Not available for final OS datacut	NR NR	22% 24%	1% 25%	Curves converge for OS in latest datacut	X
BREAK-3	Dabrafenib (n=187) DTIC (n=63)	24 months	First	100% BRAF mutation positive	Yes	NR	NR NR	14% 5%	27% 70%	Per TA321 submission FAD	X
Combi-d	Dabrafenib (n=212) Dabrafenib plus trametinib (n=211)	24 months	First	100% BRAF mutation positive	Yes	76% 66%	7% 3%	28% 18%	11% 8%		X
Combi-v	Vemurafenib (n=352) Dabrafenib plus trametinib (n=352)	12 months	First	100% BRAF mutation positive	Yes	NR	3% 1%	22% 12%	15% 8%		X
coBRIM	Vemurafenib (n=248) Vemurafenib plus cobimetinib (n=247)	9 months	First	100% BRAF mutation positive	No	73% 58%	NR NR	NR NR	NR NR		X
Notes: [a], though patients in ipi arm could receive nivo upon progression and unblinding											

Figure 1 Network diagram for all treatments in scope



Red: subsequent therapy pollution >30% in the comparator arm; dashed line known non PH between the two treatment arms