NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID845]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Nivolumab for treating advanced (unresectable or metastatic) 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

- Given that
  - the clinical trials of nivolumab are ongoing and results for many outcomes presented by the company are based on the interim analyses,
  - further results based on more matured data are expected later this year or next year
  - the ERG considered evidence for long-term survival benefit to be uncertain
  - the lack of mature data from head-to-head clinical trials made estimation of relative efficacy uncertain and
  - no UK centre was involved in the key trial (CheckMate 066) and a small proportion of the patients enrolled in CheckMate 067 and CheckMate 037 were from the UK

What is the Committee's view on completeness, quality and appropriateness of the evidence base in the company's submission and its generalisability to the clinical practice in England?

- What is the likely place of nivolumab in the treatment pathway for advanced melanoma?
- The summary of product characteristics recommends that 'treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient' while the company assumed that nivolumab will be given at the most for 2 years. Would nivolumab be used beyond 2 years in clinical practice?
- Nivolumab requires more frequent intravenous administration for a longer duration (every 2 weeks, potentially up to 2 years or more) than ipilimumab (every 3 weeks, to a maximum of 4 doses). What would be the implication for clinical use in terms of patient compliance and capacity pressure on the oncology units?
- For indirect comparison, the company made many assumptions such as
  - no difference in the clinical effectiveness in untreated and previously treated melanoma,
  - no difference in the effectiveness of nivolumab and ipilimumab in BRAF positive and BRAF negative melanoma.

  Are these assumptions clinically valid?
- In the clinical trials, nivolumab was continued even after the disease progression as assessed by RECIST criteria (which defines response in term of shrinkage of the tumour). The company noted the limitations of the RECIST criteria for assessing immune-oncology drugs because the size of the tumour may increase initially due to proliferation of immune cells surrounding the tumour. How do clinicians identify disease progression and decide when to stop treatment in people receiving immune therapy such as nivolumab?

Cost-effectiveness

- The company assumed the same clinical effectiveness for nivolumab in BRAF mutation-negative and positive melanoma based on the CheckMate 066 trial (which enrolled only people with BRAF negative disease). Given that a subgroup analysis of CheckMate 067 indicated that nivolumab was somewhat less effective

in BRAF mutation-positive disease compared with BRAF mutation-negative disease, is the Committee satisfied that this is a reasonable assumption?

- The data from CheckMate 067 trial which compared nivolumab with ipilimumab head to head were not used to inform the company's economic model. For modelling clinical effectiveness, it used indirect comparison by covariate-adjusted parametric survival curves fitted to the patient / 'pseudo patient' level data from different trials. Does the Committee consider that the model captures the relative treatment effects of nivolumab and the comparators appropriately?
- The cost-effectiveness results were highly sensitive to the choice of the fitted parametric curves. Did the company choose the best fitting parametric curves for various time-to-event data, appropriately?
- The company used long-term survival data from ipilimumab studies to model long-term survival for nivolumab (after initial 3 years). Does the Committee's consider this to be a reasonable assumption?
- The company assumed that all patients who were receiving nivolumab at 2 years would stop having nivolumab. The model using data for time on treatment from CheckMate 066 predicted; at least 20% of patients (figure 61 and 62 of the company's submission page 170 and 180) were having treatment at 2 years. The ERG suggested that clinicians and patients may be reluctant to stop treatment especially if they are still getting clinical benefit. The incremental cost-effectiveness ratio (ICER) was highly sensitive to the maximum duration of nivolumab treatment. Does the Committee think that some people could continue having nivolumab beyond 2 years?
- The model evaluated patients with previously untreated melanoma. It therefore allowed subsequent ipilimumab treatment for people receiving, nivolumab and 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. Is this treatment sequencing likely to happen in the clinical practice? Would it confound the cost-effectiveness of nivolumab by driving up the total cost and QALYs for nivolumab and the comparators other than ipilimumab? Are these results applicable to the people with advance melanoma previously treated with ipilimumab?

Other

- The company considered nivolumab to be innovative and a step-change in the management of advanced melanoma noting that it treats a life threatening and seriously debilitating condition, it meets a high unmet need and provides a significant advantage over other treatments used in the UK. Does the Committee consider nivolumab to be an innovative therapy?
- The company stated that nivolumab met all the criteria to be considered a life-extending treatment at the end of life. Is the Committee satisfied that all the criteria have been met, the estimates presented by the company are robust enough and the assumptions used in the model are plausible, objective and robust?

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 within its marketing authorisation for treating advanced (unresectable or metastatic) melanoma.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with advanced (unresectable or metastatic) melanoma	Adults with advanced (unresectable or metastatic) melanoma		
Intervention	Nivolumab	Nivolumab		The ERG noted that according to the SPC 'treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient' while the company assumed that nivolumab will be given to a maximum of 2 years.
Comparators	• BRAF inhibitors (dabrafenib and vemurafenib – for people with BRAF V600 mutation-positive melanoma who have not previously received a BRAF inhibitor) • Ipilimumab (for people who have not previously	• BRAF inhibitors (dabrafenib and vemurafenib – for people with BRAF V600 mutation-positive melanoma who have not previously received a BRAF inhibitor) • Ipilimumab (for people who have not previously	Economic comparison is presented versus: • BRAF inhibitors • Ipilimumab • Dacarbazine The company assumed dacarbazine to be representative of palliative chemotherapies that form part	The ERG commented that pembrolizumab, which is recently recommended by NICE for treating advanced (unresectable or metastatic) melanoma that has progressed after treatment with ipilimumab, was neither included in the scope nor in the company's decision problem.

	received ipilimumab) • Dacarbazine (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is unsuitable) • Best supportive care (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is unsuitable)	received ipilimumab) • Dacarbazine (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is unsuitable) • Best supportive care (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is/are unsuitable)	of best supportive care.	In the economic analysis, the company did not compare nivolumab with dacarbazine, in people with BRAF mutation-positive melanoma. The ERG noted that the company did not provide any justification for that.
Outcomes	The outcome measures to be considered include: • 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	A cost-effectiveness analysis expressed in terms		

	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 a National Health Service and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	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.		

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

Treatment pathway

2.2 The mainstay of treatment in advanced melanoma (unresectable or metastatic) is systemic immunotherapy (with ipilimumab) irrespective of BRAF 600 mutation status, or targeted therapy for BRAF 600 mutation positive melanoma (with vemurafenib and dabrafenib).

2.3 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. 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. 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). NICE is currently appraising pembrolizumab for advanced melanoma not previously treated with ipilimumab (topic ID 801).

2.4 NICE guideline 14 recommends dacarbazine as a systemic chemotherapy if immunotherapy or targeted therapy, are not suitable.

Figure 1: Treatment pathway for patients with advanced (unresectable or metastatic) melanoma in NHS England and potential position of nivolumab (Source; company's submission, figure 5, page 32)

Figure 1 Treatment pathway for advance melanoma and expected position of nivolumab

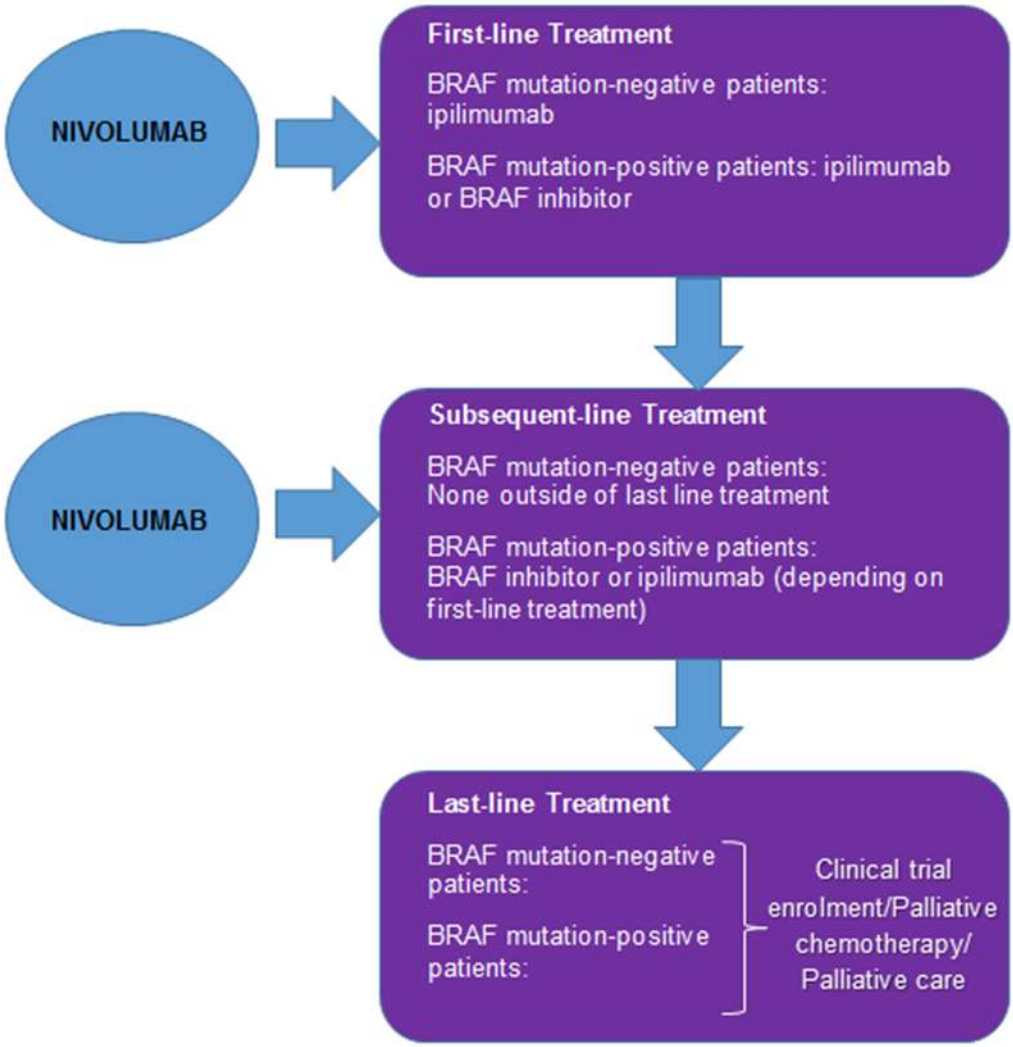


Table 2 Technology and comparators

	Nivolumab (Bristol-Myers Squibb)	**BRAF inhibitors**		**Ipilimumab** (Bristol-Myers Squibb)	**Dacarbazine** (Medac)
		Dabrafenib (Novartis)	**Vemurafenib** (Roche)		
Marketing authorisation	monotherapy 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.	for the treatment of patients with metastasized malignant melanoma.
Administration method	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.	Dacarbazine can be administered • as single agent in doses of 200 to 250 mg/m^2 body surface area/day as an intravenous injection for 5 days every 3 weeks or • as a short-term intravenous infusion (over 15 – 30 minutes) or • 850 mg/m^2 body surface area on day 1 and then once every 3 weeks as

					intravenous infusion.
Cost	£439 for 40mg (4ml) and £1,097 for 100mg (10 ml) Source; the company's submission, table 5 page 25	£933 for 28 tablets of 50 mg and £1400 for 28 tablets of 75 mg Source: MIMS April2015	£1,7500 for 56 tablets of 240 mg Source: MIMS April2015	£3750 for 50 mg (10ml) and £15,000 for 200 mg (40ml) Source MIMS April 2015	£34.75 for 10 vials of 100 mg, £48.21 for 10 vials of 200 mg and £20.05 for 1 vial of 500 mg. Source; eMit December 2014

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

3 Comments from consultees

3.1 Consultees commented that melanoma is a serious condition that is becoming increasingly more common in the UK and has a worrying effect on patients and their families, particularly for patients who are young or have young families. The disease affects different people in different ways and the severity of symptoms depends on the extent of the disease. Consultees noted that the patients value the access to the newer treatments for melanoma that allow them to live longer.

3.2 Consultees commented that there is no significant geographical variation in the clinical management of advanced melanoma but variation exists in the centres where clinical trials are ongoing. Consultees noted that first-line treatment depends on various factors such as presence of BRAF mutation, performance score, anatomical sites, the bulk of disease, and the speed of disease progression. Consultees noted that variation also exists in the sequencing of treatments For people who have melanoma with BRAF V600 mutations (BRAF mutation-positive disease), treatment options include a BRAF inhibitor (vemurafenib or dabrafenib) CTLA4 inhibitors (ipilimumab) and or cytotoxic chemotherapy (dacarbazine). For people with melanoma that does not have a BRAF V600 mutation (BRAF mutation-negative or 'wild type' disease) treatment options include ipilimumab and dacarbazine.

3.3 For BRAF mutation-positive disease, consultees highlighted that BRAF inhibitors have high response rate (approximately 70%), and moderate rate of adverse reactions, and provide a moderate (approximately 7 month) progression-free survival advantage. On the other hand, ipilimumab has low response rate (approximately 14%) and a higher rate of adverse reactions, but people whose disease responded have a durable response (lasting years) and improved overall survival.

Dacarbazine has a low response rate (approximately 10%), and short duration of response (nearly 3 months) but is associated with a relatively low rate and severity of toxicities.

3.4 Consultees commented that in the UK, melanoma is treated at tertiary referral centres where nivolumab will be prescribed by oncologists and will be administered in chemotherapy day units with similar administration costs to ipilimumab. Consultees anticipated that with the availability of nivolumab, chemotherapy units will come under significant capacity pressure because unlike ipilimumab that is given at 3 weeks interval for a total of 4 doses, nivolumab is given at 2 weeks interval until disease progression, which could be up to 2 years or even more. However consultees also acknowledged that because of significantly lower toxicity profile compared with ipilimumab, treatment with nivolumab will require less additional resources to manage severe adverse reaction however due to autoimmune toxicities, specialists' input (for example gastroenterologists, endocrinologists, etc.) may be needed.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review of clinical effectiveness identified 3 relevant phase III randomised controlled trials (RCTs) for nivolumab monotherapy. The company also included a phase 1 dose escalating study CheckMate 033 as supporting evidence. In the phase III trials, nivolumab (3mg/kg intravenous infusion [IV]) was administered every 2 weeks. All are currently ongoing for extended follow-up period. The trials differ in their populations and comparators as follows:

- CheckMate 066 was a multicenter, international (no centres in the UK), double-blind RCT that compared nivolumab (n=210) with dacarbazine (DTIC) 1000mg/m^2 IV every 3 weeks (n=208), in people with untreated advanced melanoma without a BRAF

mutation. After data-lock period, 17 months from the start of the study, the protocol was amended, all patients were unblinded and patients randomised to the DTIC group were allowed to cross over to receive nivolumab.

- CheckMate 067 trial was a multicenter, international (7 UK centres), double-blind RCT that compared nivolumab monotherapy (n=316 [27 from UK]) or nivolumab combined with ipilimumab (n=314) with ipilimumab monotherapy 3mg/kg IV every 3 weeks (n=315 [36 from UK]) in people with untreated advanced melanoma with and without the BRAF mutation. The company did not present results of nivolumab plus ipilimumab combination arm because it did not fall within the scope of the appraisal.

- CheckMate 037 trial was a multicentre, international (5 UK centres), open-label RCT that compared nivolumab (n=272 [32 from the UK]) with the investigator's choice of chemotherapy (ICC) (n=133 [11 from the UK]) , in people with

  - BRAF mutation negative advanced melanoma that has progressed on or after ipilimumab and

  - BRAF positive advanced melanoma that has progressed on or after ipilimumab and a BRAF inhibitor (vemurafenib or dabrafenib).

  ICC comprised DTIC or carboplatin plus paclitaxel.

For details of the trials' designs see company's submission Table 10 (page 45)

4.2 The company stated that in the trials, baseline demographics and disease characteristics were generally well balanced and noted the exception of a higher proportion of patients with a history of brain metastases (19.5% vs. 13.5%) and elevated LDH (51.1% vs. 34.6%) in the nivolumab arm of CheckMate 037. For details of baseline patients

characteristics in trials see table 13 of the company's submission (page 65 to 68).

ERG comments

4.3 The Evidence Review Group (ERG) commented that the company's systematic review was good quality and identified all relevant RCTs. The CheckMate RCTs were well-designed and well-conducted and provide appropriate evidence for clinical-effectiveness of nivolumab.

4.4 The ERG noted that because all 3 RCTs are ongoing many results (notably for overall survival) presented by the company to be interim and therefore uncertain. Further follow-up results are expected later this year or next year (see table 53 of the company's submission, page 150).

4.5 The ERG noted that in CheckMate 66 patients randomised to nivolumab arm were slightly younger (mean age years [SD]; 61.6 [13.0] vs. 63.7[12.6]) and had better Eastern Cooperative Oncology Group (ECOG) performance status (% with ECOG PS =0; 70.5% vs. 58.2%) than the patients in the comparator arm (DTIC). Similarly patients randomised to nivolumab arm in CheckMate 67 were slightly younger (mean age years [SD]; 58.7 [13.9] vs. 60.8 [13.2]) than the comparator ipilimumab arm. The ERG also noted that more patients randomised to nivolumab arm in CheckMate 37 had better ECOG performance status than the comparator arm (ICC) (% with ECOG PS =0: 59.6% vs. 63.2%).

4.6 The ERG was overall satisfied with the company's statistical approach for analysing trial results but noted that method of data censoring was not reported for the primary outcomes in CheckMate 037. The ERG further noted in this trial a number of patients randomised to comparator (ICC) arm withdrew consent that resulted in an imbalanced attrition.

Clinical trial results

4.7 Overall survival data were only available from CheckMate 066 trail. In CheckMate 067 and CheckMate 037 trials, the required minimum follow-up period was not reached or an insufficient number of events (deaths) had occurred at the time of analyses. The results of overall survival from CheckMate 066 based on intention-to-treat analyses are summarised in table 3.

Table 3 Overall survival in CheckMate 066

Outcomes	**Nivolumab (n=210)**	**DTIC (n=208)**	**Hazard ratio (95% CI) p value**
Events (death) n (%)	50 (23.8)	96 (46.2)	0.42 (0.30, 0.60) <0.001
Median (50%) survival (months)	Not reached	10.84	Not applicable
75% survival (months)	10.3	5.2	Not reported
6 months survival rate	84.1%	71.8%	Not significant
12 month survival rate	72.9%	42.1%	<0.05
Based on table 15 of the company' submission (page 72) and table 6 of the ERG report (page 49) CI = confidence interval; DTIC = dacarbazine			

4.8 Progression-free survival (PFS) is reported for all 3 trials and was defined as time interval between the randomisation and disease progression or death. The reported results are collated in table 4. 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 4 page 24). For this reason in all the trials, patients treated with nivolumab therapy 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.

4.9 The company considered relatively small PFS gain with nivolumab in CheckMate 037 trial, inconclusive because it could have been biased because of imbalances in the prognostic factors between trial groups (see section 4.2) and high withdrawal rates in the comparator arm (section 4.6).

4.10 Objective response rate (ORR) was the primary outcome in CheckMate 037 and a secondary outcome in CheckMate 066 and CheckMate 067. ORR was defined as the proportion of patients with complete or partial response. Tumour response was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) by trial investigators or an independent radiological review committee (IRRC). In CheckMate 066 and CheckMate 067, tumour response was assessed by the investigators and included all patients randomised (ITT population). For results see table 5.

4.11 In CheckMate 037, treatment response was assessed separately by IRRC and by investigators. IRRC analysed responses by both per protocol (PP) population and ITT population. The results are presented in table 6. The company's submission also included ORR by investigator's assessment (see company's submission table 19, page 84).

4.12 The company presented changes in tumour burden as 'waterfall plots' see company's submission figures 15 (page 79), 17 (page 82) and 20 (page 86). The waterfall plots demonstrated that more patients in the

nivolumab arm experienced a reduction in tumour size, and achieved at least a partial response, compared with the patients in the comparator groups.

Table 4 Progression free survival

Outcome	CheckMate 066			CheckMate 067			CheckMate 037		
	Nivolumab (n=210)	**DTIC (n=208)**	**Hazard ratio (95% CI) p value**	**Nivolumab**	**Ipilimumab**	**Hazard ratio (95% CI) p value**	**Nivolumab**	**ICC**	**Hazard ratio (95% CI) p value**
Progression-free survival									
Events, n (%)	108 (51.4)	163 (78.4)	0.43 (0.34 to 0.56) <0.001	174 (55.1)	234 (74.3)	0.57 (0.43, 0.76) <0.001	71 (58.2)	26 (43.3)	0.82, 99.99% CI 0.32 to 2.05
Median PFS (months)	5.06	2.17	<0.05	6.9	2.9	<0.05	4.67	4.24	Not significant
PFS rate at 6 months	48.0%	18.5	<0.05	Not reported	Not reported	Not reported	48	34	<0.05
PFS rate at 12 months	41.8%	Not produced *	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Based on the table 16, and narrative summary of the company' submission (page 74,76 and 77) and table 6 of the ERG report (page 49) CI = confidence interval; DTIC = dacarbazine * all PFS times were less than 12 months									

Table 5 Response rates

Outcome	CheckMate 066		CheckMate 067	
	Nivolumab (n=210)	**DTIC (n=208)**	**Nivolumab (n= 316)**	**Ipilimumab (n= 315)**
Objective response rate (ORR)				
Responders, n (%)	84 (40.0)	29 (13.9)	138 (43.7)	60 (19.0)
Complete response, n (%)	16 (7.6)	2 (1.0)	28 (8.9)	7 (2.2)
Partial response, n (%)	68 (32.4)	27 (13.0)	110 (34.8)	53 (16.8)
Unweighted ORR difference, % (95% CI)	26.1 (18.0, 34.1)		24.7 (not reported)	
Estimated odds ratio (95% CI) p-value	4.06 (2.52, 6.54) <0.0001		3.40 (2.02, 5.72) <0.0001	
Duration of response				
Median (range), months	Not reached (0.0, 12.5)	5.98 (1.1, 10.0)	Not reached	Not reached
Time to treatment response				
Median (range), months	2.10 (1.2, 7.6)	2.10 (1.8, 3.6)	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. Based on the table 8 of the ERG report (page 52), Response rates assessed by investigators and included all randomised patients (ITT)

Table 6 Response rate CheckMate 037 – intention to treat and pre protocol analyses

Outcome	CheckMate 037 (ITT analysis)		CheckMate 037 (PP analysis)	
	Nivolumab (n=122)	**ICC (n=60)**	**Nivolumab (n=120)**	**ICC (n=47)**
Objective response rate (ORR)				
Responders, n (%)	38 (31.1)	5 (8.3)	38 (31.7)	5 (10.6)
Complete response, n (%)	4 (3.3)	0	4 (3.3)	0
Partial response, n (%)	34 (27.9)	5 (8.3)	34 (28.3)	5 (10.6)
Unweighted ORR difference, % (95% CI)	22.8 (10.5, 32.7)		21.0 (6.8, 31.7)	
Duration of response				
Median (range), months	Not reached (0.0, 12.5)	5.98 (1.1, 10.0)	Not reached (1.4+, 10.0+)	3.5 (1.3+, 3.5)
Time to treatment response				
Median (range), months	2.10 (1.2, 7.6)	2.10 (1.8, 3.6)	2.1 (1.6, 7.4)	3.5 (2.1, 6.1)

CI = confidence interval; CR = complete response; DTIC = dacarbazine; ITT = intention-to-treat; ORR = Objective response rate; PP = per-protocol; PR; partial response rate. Based on the table 8 of the ERG report (page 52). Response was measured by IRRC.

4.13 Patients in nivolumab arms of all 3 trials continued to receive treatment after disease progression if they were having clinical benefit and were tolerating the treatment. In all the three trials progression was defined by RECIST criteria (version 1.1) and suitability for treatment continuation was determined by the trial investigators. 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).

Table 7 Post RECIST progression response

	CheckMate 066		**CheckMate 067**		**CheckMate 037**
	Nivolumab	**DTIC**	**Nivolumab**	**Ipilimumab**	**Nivolumab**
Patients treated post-progression, n	54	49	86	99	37
Responders, n (%)	12 (22.2)	2 (4.1)	Not reported	Not reported	10 (27.0)
Based on table 9 of the ERG report (page 54)					

ERG Comments

4.14 The ERG agreed with the company that the observed imbalances between patient groups in CheckMate 037are likely to introduce bias against the nivolumab. However the ERG was not convinced with the company's explanation, that the RECIST criteria may have resulted in false-positive progression assessments in the nivolumab arm of CheckMate 037, noting that the same criteria were also used in CheckMate 066 and CheckMate 067, where nivolumab was associated with statistically significantly better PFS than the comparators.

4.15 For post-progression treatment response in CheckMate 066, the ERG found that figures reported in the published paper (31% vs. 16%) was different from that reported in the company's submission (22.2% vs. 4.1%) and the reason for this discrepancy was not clear.

Health related quality of life

4.16 Health related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) in all 3 trials and the EuroQol-5 dimension questionnaire (EQ-5D) in CheckMate 066. Health related quality of life 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. The company included health related quality of life results only from CheckMate 066.

4.17 EORTC-QLQ-C30 global health status scores at baseline were similar in both treatment groups (nivolumab, 66.9; DTIC, 64.4). During the trial, EORTC QLQ-C30 subscale scores generally did not change over time for either treatment group. The exceptions with clinically meaningful improvements in quality of life in the nivolumab arm(defined as a minimally important difference of ≥10 points) were emotional (week 55, +13.0; week 61, +12.8) and social (week 55, +10.5) functioning scales at certain time points.

4.18 The company's submission reported a small deteriorating effect on daily activities, sleep, appetite loss, diarrhoea, pain, nausea and fatigue subscales in patients treated with DTIC, which was not seen in the nivolumab arm. However, overall symptom burden was limited and remained relatively stable over time across the two treatment groups.

4.19 EQ-5D utility scores at baseline were similar in both treatment groups at 0.778 for nivolumab and 0.711 for DTIC. Improvements from baseline in EQ-5D utilities were greater in the nivolumab versus DTIC (p=0.045) with improvements noted from week 7 (0.027; p=0.011 [n=132]) through week 49 (0.045; p=0.034 [n=38]) in the nivolumab group. Clinically meaningful changes (defined as a minimally important difference of ≥0.08 points) were also observed with nivolumab at some time points.EQ-5D visual analogue scale (VAS) scores at baseline were also similar in both treatment groups at 70.9 for nivolumab and

69.1 for DTIC. Significant improvements from baseline in EQ-5D VAS scores were observed at weeks 25, 31, 37, 49 and 61 ($p \leq 0.03$) in the nivolumab group. Clinically meaningful changes (defined as a minimally important difference of ≥7 points) were also observed with nivolumab at some time points.

4.20 The company used a Cox proportional hazard regression model to determine the time from randomisation to first deterioration and first improvement in quality of life (as defined by the minimally important difference for that scale applied at the individual patient level). The resulted are presented in the company's submission table 20 (page 88) showing that quality of life with nivolumab was significantly less likely to deteriorate before DTIC for the following items:

- EORTC QLQ-C30 global health (HR=066; p=0.021), physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, and constipation
- EQ-5D utility index score (HR=0.55; p=0.002)

4.21 In addition, nivolumab was significantly more likely to lead to improvement in quality of life before DTIC for the following items:

- EORTC QLQ-C30 global health (HR=1.52; p=0.043), physical functioning (HR=1.92; p=0.027), fatigue (HR=1.69; p=0.008), and dyspnoea (HR=2.20; p=0.013)
- EQ-5D utility index score (HR=1.86; p=0.002)

4.22 At clarification stage, the company provided additional health-related quality of life data for CheckMate 066 which demonstrated that EQ-5D utility index scores and EORTC QLQ-C30 global health status scores, were consistently higher for nivolumab than DTIC. However, there were no consistent differences between nivolumab and DTIC for change

from the baseline and there was also no improvement from baseline for the nivolumab arm.

ERG comments

4.23 The ERG agreed that treatment with nivolumab did not reduce the health-related quality of life, and concluded there was also no evidence that nivolumab led to a consistent and sustained improvement in health-related quality of life.

Subgroup analyses

4.24 The company included subgroup analysis for CheckMate 066 in the main submission (see section 4.8, page 89) and from CheckMate 067 and 037 in the Appendix 7 (page 78). The outcomes selected for the subgroup analysis were overall survival for CheckMate 066, progression-free survival for CheckMate 067 and objective response rate for CheckMate 037. In all reported subgroup analyses, outcomes were numerically better in patients treated with nivolumab than the comparators. These differences were statistically significant in most subgroups except,

- In CheckMate 066; people with ECOG PS 1 and people with stage III disease
- In CheckMate 067; women, people from US, rest of the world (other than US, EU and Australia), people with BRAF600 positive melanoma, people ageing 75 years or more, people with LDH level more than twice of upper limit.
- In CheckMate 037; people with BRAF600 positive melanoma, people with confirmed previous anti CTLA-4 treatment benefit, people with metastases stage M1C, men, people from rest of the world (except US), people with ECOG PS 1, people with LDH level more than twice of upper limit, people with PDL -1,status negative or intermediate.

4.25 The subgroup analyses by BRAF mutation status for CheckMate 067 and CheckMate 037 was available from the forest plots in the company's submission appendix 7 (Figure 3, page 78 and Figure 4 page 80). Please note that CheckMate 066 trial only included patients with BRAF mutation-negative disease. The results are summarised in table 8, which showed that the magnitude of benefit with nivolumab was more in people with BRAF negative melanoma. The differences between nivolumab and the comparator were statistically significantly better only in people with BRAF mutation-negative melanoma.

Table 8 Subgroups based on BRAF mutation status

Outcome	BRAF mutation-positive subgroup		BRAF mutation-negative subgroup	
	Nivolumab	**Comparator**	**Nivolumab**	**Comparator**
CheckMate 067				
Progression free survival (a priori analysis)				
Events (death or progression), %	58.2	66.0	53.7	78.1[a]
Median PFS months	5.62	4.04	7.98	2.83
HR 95% CI	0.77 (0.54 to1.09)		0.50 (0.39 to 0.63)	
CheckMate 037				
Objective response rate (a priori analysis)				
Responders, (%)	23.1	9.1	34.0	11.1
Unweighted ORR difference, % (95% CI)	14.0 (-17.1 to 34.4)		22.9 (6.2 to 35.0)	
Based on the ERG report table 12 (page 63) and table 13 and Appendix 7 of the company's submission (page 77 and 79). a: calculated by ERG				

4.26 Since nivolumab is an inhibitor of programmed cell death-1 receptor, the company presented subgroup analyses based on the expression of PDL-1 receptors (PD-L1-positive [≥ 5% expression] and PD-L1-negative/indeterminate [< 5% expression]). The results are summarised in table 9 below.

Table 9 Subgroups based on PD-L1 receptor expression

Outcome	PD-L1-positive subgroup		PD-L1-negative/indeterminate subgroup	
	Nivolumab	**Comparator**	**Nivolumab**	**Comparator**
CheckMate 066				
Overall survival (a priori analysis)				
Events (death), %	14.9	39.2	28.7	50.0
Median OS months	Not reached	12.39	Not reached	10.22
HR 95% CI	0.30 (0.15, 0.60)		0.48 (0.32, 0.71)	
Objective response rate (post-hoc analysis)				
Responders, (%)	52.7	10.8	33.1	15.7
CheckMate 067				
Progression-free survival				
Median PFS months	14.0	3.9	5.3	2.8
Objective response rate (post-hoc analysis)				
Response rate %	57.5	21.3	41.3	17.8
Odds ratio (95% CI)	5.03 **(**2.44 to 10.37**)**		3.25 (2.05 to 5.13)	
CheckMate 037				
Objective response rate (post-hoc analysis)				
Responders,	43.6	9.1	20.3	13.0

(%)				
Unweighted ORR difference, % (95% CI)	34.5 (12.2, 49.2)		7.3 (-13.4, 21.5)	
Based on the company's submission table 21, 22 (page 90) and Appendix 7 of the company's submission (page 77 and 79).				

ERG comment

4.27 The ERG commented that some of these subgroups are very small and therefore results should be interpreted with caution.

Meta-analyses

4.28 The company did not combine the trial results in a meta-analysis. The company justified its decision noting the differences across the trials in the populations (previous treatment experience; BRAF mutation status) and the comparison group (DTIC, ICC and ipilimumab).

ERG comments

4.29 The ERG agreed with the company that differences between the trials in would not allow a meaningful meta-analysis particularly because there was not a common comparison group.

Indirect and mixed treatment comparisons

4.30 The company conducted indirect treatment comparisons to estimate the relative efficacy between nivolumab and the comparators for economic analysis. The company identified 44 trials of DTIC, dabrafenib, vemurafenib, ipilimumab and nivolumab and presented a 'broad evidence' network diagram (see the company's submission Figure 23, page 95). The company included only those trials that reported data on overall survival in the network and therefore, excluded 2 nivolumab trials (CheckMate 067 and CheckMate 037) as well from its indirect comparison.

4.31 The company stated that a mixed treatment comparison, combining nivolumab with all comparators within 1 network meta-analysis was not possible for following reasons;

- BRAF inhibitors, palliative chemotherapy and immunotherapies have different mechanism of action; therefore an assumption of a constant difference between treatment-effects would not be reasonable (non-proportional hazards between treatments).
- There were high levels of crossover in the BRAF inhibitor trials and subsequent ipilimumab use. The company considered that because of the crossover, using a common comparator for BRAF inhibitors and nivolumab (that is DTIC), was 'problematic'.
- The company also noted that trial designs were not homogenous particularly in terms of line of therapy (first or subsequent) and difference in population (BRAF status).

4.32 The company therefore conducted 2 separate indirect comparison according to the type of comparators:

- comparison with ipilimumab and palliative chemotherapy
- comparison with BRAF inhibitors.

4.33 The company made following assumptions, stating that these have been accepted by the Appraisal Committee during previous NICE appraisals:

- DTIC and GP100 (glycoprotein 100) are equivalent, and both are equivalent to palliative chemotherapy. The company also included the results of published meta-analyses to justify this assumption, see the company's submission (page 99) for details.
- Line of treatment does not affect treatment effectiveness independently (not an independent prognostic factor)

- The treatment effects for nivolumab and ipilimumab are not different for BRAF mutation-negative and BRAF mutation-positive melanoma.

- ipilimumab +gp100 is equivalent to ipilimumab

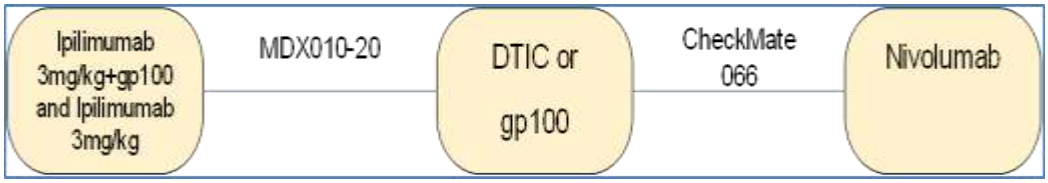
4.34 The network for comparing nivolumab with ipilimumab and palliative chemotherapy included following trials;

- CheckMate 066; compared nivolumab with DTIC (the company considered DTIC equivalent to palliative chemotherapy)

- MDX010-20; compared ipilimumab, ipilimumab + gp-100 and gp-100

- CA184-024 that compared ipilimumab plus DTIC vs DTIC: Note: this trial evaluated a higher dose of ipilimumab (10mg/kg) than the licensed dose (3mg/kg). The company used data from CA184-024 trial, in a scenario analyses.

Figure 2 Network for indirect comparison with ipilimumab



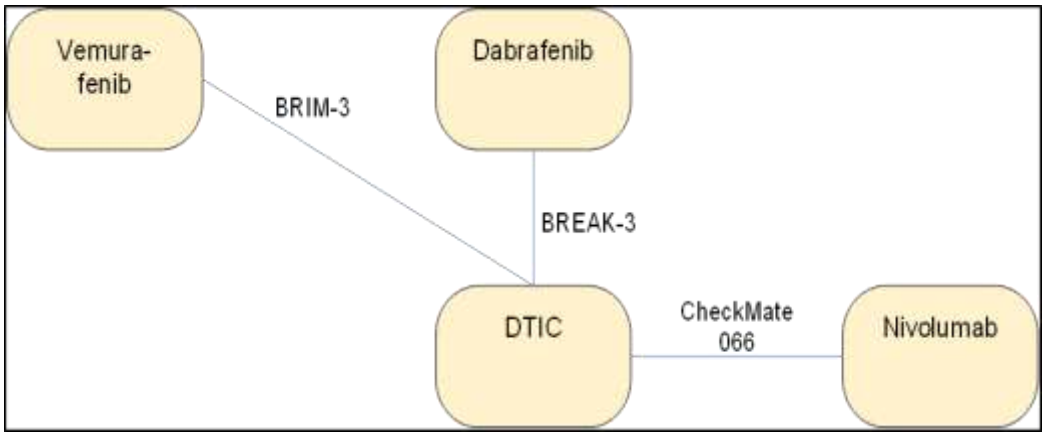
4.35 For comparing nivolumab with BRAF inhibitors, the company included following trials in the network;

- CheckMate 066: compared nivolumab with DCIT

- BRIM-3: compared vemurafenib with DTIC

- BREAK-3: compared dabrafenib with DTIC

Figure 3 Network for indirect comparison with BRAF inhibitors



4.36 The company used patient-level data from nivolumab ipilimumab and DTIC from trials. For BRAF inhibitors, the company estimated 'psuedo patient-level data' from the published Kaplan–Meier using 'digitalising software' and the Guyot (2012) method. The company used these data to inform covariate-adjusted parametric survival models.

4.37 The company stated that data on overall survival for nivolumab from CheckMate 066 were immature and therefore extrapolations were likely to be uncertain. The company therefore, used alternative outcomes for instance time to progression (TTP), pre-progression survival (PrePS) and post-progression survival (PPS) instead of overall survival and progression free survival for nivolumab and ipilimumab. For vemurafenib and dabrafenib, the company used overall survival and progression free survival data.

4.38 The company then fitted parametric survival curves for each outcome. The company stated that it adjusted each model for the covariates (prognostic factors) and also included trial indicator as a covariate in the survival models. The company stated that including trial indicator as a covariate meant that the treatment effect estimated from adjusted parametric curves can be considered relative treatment effects controlling for the study effect. The company considered its approach (of using the patient level data and covariate-adjusted parametric

survival curve), was similar to using summary-level relative treatment effects and a common comparator in the 'traditional' adjusted indirect comparator approach.

4.39 The company obtained the best fitting survival function for each treatment for the outcomes required for economic modelling. For details on parametric curves for each outcome used in the economic model see sections 5.8 to 5.12.

4.40 To check the validity of its approach, the company compared the relative effectiveness between nivolumab and ipilimumab obtained by its approach with a traditional approach of adjusted indirect comparisons. The company constructed adjusted indirect comparisons between nivolumab and ipilimumab for the endpoints TTP post 100 days, PPS, OS, and PFS. The company presented results of the adjusted indirect comparisons are shown in the company's submission table 36 (page 115). A comparison between the hazard ratios obtained from adjusted indirect comparison (traditional) and the company's approach is shown in table 10.

Table 10 Comparison of Hazard ratio obtained by traditional indirect comparison and the company's approach

Outcome	**Hazard ratio (95% CI) nivolumab vs ipilimumab**	
	Traditional approach (adjusted indirect comparison)	**Company's approach (covariate adjusted survival curves) Weibull for both nivolumab and ipilimumab**
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: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; TTP, time to progression. Based on the company's submission, table 36 (page 115-116)		

4.41 The company concluded that that nivolumab was better than ipilimumab with respect to overall survival and progression free survival. The company also stated that further exploration showed that relative treatment benefit of nivolumab compared to ipilimumab is mainly in delaying time to progression.

ERG comments

4.42 The ERG noted that the company's indirect comparisons were based upon a number of assumptions and covariate-adjusted survival data extrapolations. The ERG considered most of these assumptions reasonable and agreed with the company that they have been accepted in previous NICE appraisals.

4.43 The ERG was mainly concerned with 2 assumptions,

- that previous melanoma treatment experience does not have an independent impact on treatment effect in advanced melanoma, and
- that there is no difference between treatment effects by BRAF mutation status. The ERG noted that, pre-planned sub-group analyses in the CheckMate 067 and CheckMate 037 trials showed that BRAF mutation-negative patients had better outcomes (PFS and ORR, respectively) relative to comparators than BRAF mutation-positive patients.

4.44 The ERG did not agree with the company's choice of the best fit parametric curve for many outcomes for details please see sections 5.22 and 5.24.

Non-randomised evidence

4.45 The company included a non-randomised, dose-escalation study, CheckMate 003, in its submission. CheckMate 003 was a phase I study evaluating safety of nivolumab in patients with solid tumours, including

melanoma (n=107) (see the company's submission section 4.11, page 121-133). In the cohort of patients with advanced melanoma treated with licensed dose of nivolumab (3mg/kg) (n=17), median overall survival was 20.3 months and median duration of response to treatment was approximately 2 years. The company stated that results from CheckMate 003 support the long-term clinical benefit with nivolumab and the assumption that maximum duration of treatment with nivolumab will be 2 years.

ERG comments

4.46 The ERG commented that the results of CheckMate 003 should be interpreted with caution because the sample size for the relevant dose cohort was very small (n=17 only).

Adverse effects of treatment

4.47 The company presented detailed adverse event data from 3RCTs in section 4.12.2 (page 134–145) of its submission. These results are summarised in table 11. The company stated that adverse events observed in the trials were mild and transient in most patients and generally manageable according to established algorithms outlined in safety management guidelines and the summary of product characteristics.

4.48 The company highlighted that in CheckMate 067, nivolumab was associated with a favorable safety profile compared to ipilimumab, particularly for common immune system related adverse events.

ERG comments

4.49 The ERG noted that most of the patients (more than 93%) in the trials experienced adverse events, regardless of the drug. The ERG noted that in Checkmate 067, a higher proportion of patients discontinued treatment due to adverse events of any grade (nivolumab: 13.7%; ipilimumab: 22.5%) compared to CheckMate 066 (nivolumab: 6.8%; DTIC: 11.7%) and CheckMate 037 (nivolumab: 9.3%; ICC: 11.8%). The

ERG highlighted that the company did not explain these differences between the trials.

4.50 The ERG noted that most frequently reported treatment related adverse events in the nivolumab groups of the trials were fatigue, pruritus, rash, diarrhoea, and nausea.

Table 11 Percentage of patients with adverse events

	CheckMate 066				CheckMate 067				CheckMate 037			
	Nivolumab (n=206)[a]		DTIC (n=205)[a]		Nivolumab (n= 313)[a]		Ipilimumab (n= 311)[a]		Nivolumab (n=268)[a]		ICC (n=102)[a]	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
All AEs, n (%)	93.2	34.0	94.6	38.0	99.4	43.5	99.0	55.6	95.1	34.3)	93.1	43.1
TRAEs, n (%)	74.3	11.7	75.6	17.6	82.1	16.3	86.2	27.3	67.5	9.0	79.4	31.4
All SAEs, n (%)	31.1	20.9	38.0	26.3	36.1	28.1	52.1	38.3	44.0	29.1	21.6	15.7
TRSAEs, n (%)	9.2	5.8	8.8	5.9	8.0	5.8	22.2	16.4	6.3	4.5	9.8	8.8
DC due to AEs, n (%)	6.8	5.8	11.7	9.3	13.7	8.6	22.5	19.9	9.3	7.1	11.8	4.9
DC due to TRAEs, n (%)	2.4	1.9	3.4	2.4	7.7	5.1	14.8	13.2	2.2	2.2	7.8)	2.9
Deaths relating to study drug, **n**	0		0		1		1		0		0	

AEs = adverse events; DC = discontinuation; DTIC, dacarbazine; ICC = investigator's choice chemotherapy SAEs, serious adverse events; TRAEs, treatment-related adverse events; TRSAEs, treatment related serious adverse events.

[a] Patients who received at least one infusion of nivolumab or comparator drug (DTIC / ipilimumab / ICC).

Based on table 14 of the ERG report (page 65)

5 Cost-effectiveness evidence

Model structure

5.1 The company presented a new (de novo) semi-Markov survival model of nivolumab for 2 subpopulations: people with previously untreated BRAF-mutation-negative disease (compared with DTIC and ipilimumab) and people with previously untreated BRAF-mutation positive disease (compared with dabrafenib, ipilimumab 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 2). 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 death rates for patients in the progression state were derived from post-progression survival (PPS) data.

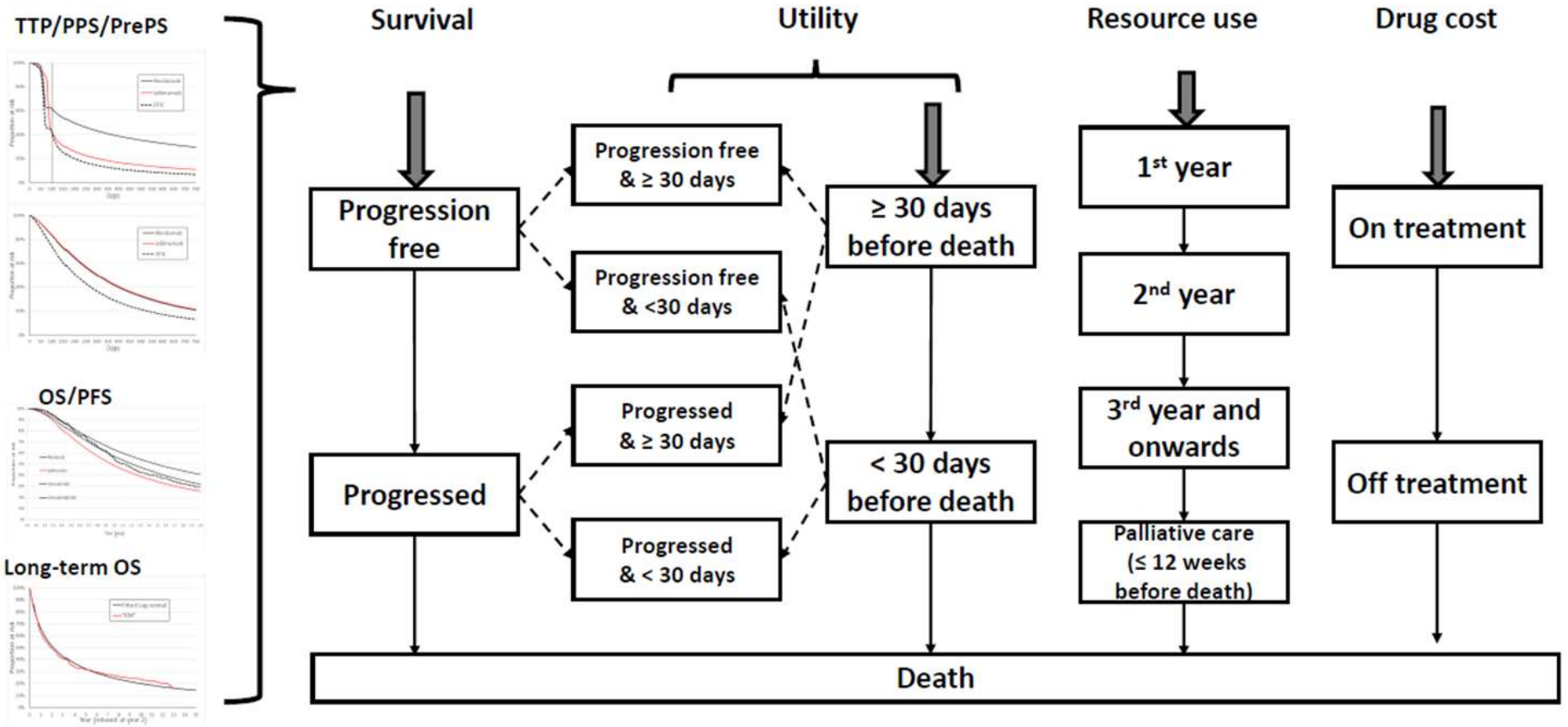
5.3 For modelling utility; the company further divided both progression-free and progressed states into 2 states as follows;

- ≥30 days before death, and
- <30 days before death

5.4 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 4: Economic model structure (simplified) (Figure 49 of the company's submission (page 155)



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

ERG comments

5.5 The ERG commented that the structure of the model was consistent with the disease pathway and the methods applied in the economic analyses were appropriate and reported transparently and followed the methodological guidance stipulated in the NICE reference case.

Model details

Modelling of clinical effectiveness

5.6 The clinical effectiveness estimates of nivolumab used in the model were based on the CheckMate 066 trial. The company conducted covariate-adjusted indirect comparisons between comparators using patient-level data from CheckMate 066 (for nivolumab and DTIC) and MDX010-20 (ipilimumab and GP100). The company considered GP 100 equivalent to palliative chemotherapy (DTIC). The company used alternative data for efficacy of ipilimumab and DTIC from CA184-024 trial as scenario analysis.

5.7 For BRAF 600 inhibitors (vemurafenib and dabrafenib), the company assumed that both are equally effective. The company used effectiveness data from vemurafenib trial (BRIM-3) in the base-case trial and used data from dabrafenib (BREAK 3) in a scenario analysis.

Survival Curve fitting

BRAF mutation negative disease

5.8 For TTP, the Kaplan Meier data from CheckMate 066 (nivolumab) and MDX010-20 (ipilimumab) were used for the first 100 days followed by fitted parametric curves. The company considered that Gompertz 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.

5.9 The company modelled PrePS using Kaplan-Meier data adjusted by covariates for the length of the trial follow-up. The company stated that

none of the fitted curves provided an acceptable visual fit to the observed data.

BRAF mutation-positive disease

5.10 For nivolumab and ipilimumab, the company used the same methods used for deriving transition probabilities as in BRAF mutation-negative disease (as described above) except that the baseline patient characteristics were taken from the BRIM-3 trial (vemurafenib, see table 12). For BRAF inhibitors, the company assumed that vemurafenib had an equal efficacy as dabrafenib based on the NICE TA321 where the Appraisal Committee accepted that vemurafenib and dabrafenib have approximately equal efficacy. The company used fitted survival curves to Kaplan-Meier data for progression free survival and overall survival from BRIM-3 trial. The company used data from dabrafenib trial BREAK 3 in a scenario analysis.

5.11 Individual patient data from the vemurafenib BRIM-3 were not available. The company generated 'pseudo patient-level data' from published Kaplan-Meier curves of the BRIM-3 trial using digitisation software. The company then fitted parametric curves the pseudo-patient data and considered the log-normal and generalised-gamma distributions best fit for overall survival and PFS respectively. The proportions of patients in the model in the progression-free, progressed and dead health states were calculated directly from the PFS and OS survival curves by the area under the curve method.

5.12 Please see company's submission sections 5.3.2 to 5.3.7 (page 165-180) for details of curve fitting exercise.

Long-term extrapolation

5.13 The survival methods outlined above are applied in the model for the first 2 years of for DTIC and BRAF inhibitors and for the first 3 years for

nivolumab and ipilimumab. Long-term overall survival was modelled using the following data:

- American Joint Committee on Cancer -registry on long term survival ; applied from year 2 onwards for BRAF inhibitors and DTIC,
- long-term survival pooled from 12 ipilimumab studies; applied from year 3 onwards for nivolumab and ipilimumab in the base case
- general England population mortality applied as background mortality.

Treatment duration

5.14 The marketing authorisation of nivolumab recommends that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated based on the protocol of CheckMate 066 trial. It means that some patients could stop nivolumab treatment prior to progression due to toxicity or patient preference, while other patients (who are considered getting benefit clinically) could be treated even after disease has progressed (as defined by RECIST criteria). The model used parametric curves fitted to the time on treatment (TOT) data from CheckMate 066 trial to calculate the proportion of patients continuing to receive nivolumab in each cycle. In the base case, the company used log-logistic curve fit for TOT and other parametric curve fits were tested in the scenario analysis. The company assumed a maximum duration of treatment with nivolumab of be 2 years and explored the effect of varying the maximum duration of treatment in the sensitivity analyses. The base-case model estimated that at 2 years, 23% patients with BRAF mutation-negative melanoma (see the company's submission, figure 61, page 179) and 20% with BRAF mutation-melanoma see the company's submission, figure 62, page 180) would still be receiving nivolumab.

5.15 For dabrafenib, vemurafenib and DTIC the model assumes that treatment will continue until disease progression in accordance with the marketing authorisations. The company stated that although ipilimumab is usually given for a maximum of 4 doses, patients could receive ipilimumab for up to 16 doses as per marketing authorisation. The company calculated proportion of patients receiving each dose in induction 1(1 to 4) from the CA184-024 trial data, and proportion of patients who required subsequent inductions (induction 2 to 4) from the MDX010-20 trial data. The company stated that it used same estimated in the NICE appraisal for ipilimumab (TA319).

5.16 The company assumed that the treatment effect of nivolumab is maintained on discontinuation of therapy. The company stated that this assumption was based on observational data from CheckMate 003 trial and UK clinical expert opinion. The company conducted a range of scenario analyses assuming that, after 2 years, 0%, 25%, 50%, 75% and 100% of patients experience the same survival rate as estimated for the DTIC arm (that is melanoma registry OS) and varied the maximum treatment duration with nivolumab to up to 5 years.

Population

5.17 The company based the patient characteristics in the model on the CheckMate 066 trial for BRAF mutation-negative disease and from the vemurafenib arm of the BRIM-3 trial for BRAF mutation-positive disease (see table 12).

5.18 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 12 Baseline characteristics for the modelled population

Patient characteristics	BRAF mutation-negative	BRAF mutation-positive
Mean age	63	56
% male	58.9%	59.0%
% under 65	47.8%	100%
Mean weight (kg)	78.7	78.7[a]
Mean body surface (m^2)	1.9	1.9 [a]
% stage M1c	61.0%	66.0%
ECOG status = 0	64.5%	68.0%
% elevated LDH (>ULN)	36.6%	58.0%
% with brain metastases	3.6%	0%
% subsequent ipilimumab treatment	29.7%	22.0%

Key: ECOG, Eastern Cooperative Oncology Group; kg, kilogram; LDH, lactate dehydrogenase; m, metre; ULN, upper limit of the normal range.

Notes: [a], Assumed the same as BRAF mutation-negative patients in the absence of data.

Based on see table 59 and 60 of the company's submission, page 165 and 173

Adverse events

5.19 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 and DTIC, the company used data from CheckMate 066. For ipilimumab, dabrafenib and vemurafenib, the company used data from CheckMate 067, BREAK-3 and BRIM-3 trials respectively (see the company's submission for details, page 180). The values used in the model are summarised in table 13.

Table 13 Proportion of patients with adverse events and utility decrement applied for adverse events in the model

	Utility decrement	Modelled % of patients having AE				
		Nivolumab	Ipilimumab	DTIC	Dabrafenib	Vemurafenib
Endocrine disorder (any grade)	-0.11	8.7%	6.6%	1.0%	0.0%	0.0%
Diarrhoea (Grade 2+)	-0.06	4.4%	12.7%	3.4%	0.0%	8.9%
Other AEs (Grade 3+)	-0.12	9.7%	14.7%	17.6%	21.2%	12.8%
Overall utility decrements for each treatment		**-0.0239**	**-0.0325**	**-0.0236**	**-0.0279**	**-0.0218**
Based on the company's submission table 65 (page 188)						

ERG comment

5.20 The ERG considered that the company's approach to model the clinical effectiveness reasonable but complex and difficult for non-statisticians to understand and therefore lack accessibility and transparency. The ERG commented that that other, simpler, approaches may obtain similar results. The ERG considered that the CheckMate 067 trial data, if available, would have provided a direct comparison between nivolumab and ipilimumab. The ERG notes that there is considerable uncertainty around model results with respect to the assumptions adopted for long-term OS and time on treatment for nivolumab.

5.21 The ERG noted that the company presented economic analyses only for previously untreated melanoma although the marketing authorisation also includes people who have had previous treatment. The company had justified its approach noting that the line of treatment did not independently impact treatment effect in advanced melanoma and it had been accepted in previous NICE appraisals. The ERG commented that using data from CheckMate 037 trial, economic analyses for previously treated melanoma would have been possible.

5.22 The ERG did not agree with the company's choice of survival curve used in the model for TTP for nivolumab. The ERG suggested that other survival curves (instead of Gompertz) may be plausible for nivolumab and used a Weibull distribution (best visual fit) in its preferred scenario (see table 18).

5.23 The ERG questioned the company's assumption that patients receiving nivolumab would have similar long-term survival as ipilimumab (see section 5.13). The ERG commented that extrapolation of survival data from the CheckMate 67 trial would have been most appropriate method for estimating long-term survival. In exploratory analyses the ERG extrapolated long-term survival for nivolumab using a Gompertz distribution in its preferred scenario (see table 18).

5.24 For BRAF positive melanoma, the ERG noted that the total cost for the BRAF inhibitors in the model depended upon the type of survival curve chosen to model PFS for BRAF inhibitors. The company had used generalised-gamma curve, the ERG explored other survival curves for the BRAF inhibitors and considered a log-normal distribution the best fit for its preferred scenario (see table 18).

Utility

5.25 The company used EQ-5D values collected in the CheckMate 066 trial to estimate utility values for health states in the model using regression analysis (see the company submission's appendix 14, page 146 for details). The mean utility values from the trial and the utility values used within the model are presented in table 14 and 15, respectively. The company tested utility values used in the NICE appraisal TA329 in a scenario analysis.

Table 14 Mean utility values from the CheckMate 066 trial

Mean utility by treatment arm and progression status	Utility
Nivolumab arm pre-progression	0.7892
Nivolumab arm post-progression	0.7548
DTIC arm pre-progression	0.6963
DTIC arm post-progression	0.6565
Based on the ERG report table 21 (page 89)	

Table 15 utility values used in the model in all treatment arms

Health states (base case)	Mean EQ-5D utility
Pre-progression + days left >=30 days	0.8018
Pre-progression + days left <30 days	0.7795
Post-progression + days left >=30 days	0.7277
Post-progression + days left <30 days	0.7054
Based on the company's submission table 67 (page 189)	

5.26 The model included utility decrements for the adverse events. The value for utility decrements were taken from a study Beusterien et al., 2009 (see table 13). The company applied these values (in the first column of table 13) to the percentage of patients experiencing each category of the adverse event and estimated the overall utility decrement for each treatment arm (last row in table 13). The company applied this as a one-off average utility loss due to the adverse events. The model applied these treatment arm specific utility decrements at the start of the model, and then periodically to patients who are still on treatment at every 35 weeks.

ERG comments

5.27 The ERG noted that difference in the utility values for pre-progression and post-progression stages) in the trial (0.03, see table 14), was much smaller compared to that different in the corresponding health states of

the model (0.08, see table 15). The ERG noted that the company did not explain this discrepancy but the model results were not sensitive to changes in the utility values. The ERG also noted that although the company has data for both treatment arms, it did not incorporate the differences in quality of life for the treatments.

Resource use and costs

5.28 The resource use categories in the model were

- Treatment costs including
  - drug costs
  - administration cost depends upon type of administration (oral or IV)
  - one-off costs for treatment initiation and end-of-life
- health state resource use for
  - pre-palliative state and
  - palliative care state,
- cost for treating adverse events.

5.29 The model incorporated resource use by dividing the patient's lifetime into 4 health states as: first year after treatment initiation, second year, third and subsequent years following treatment initiation, and 12 weeks palliative care before death. The resource use and costs incorporated in the model are summarised in table 16.

5.30 The company's submission reported that the unit cost data and resource use for the one-off treatment initiation and end of life costs sources used were based on responses of an advisory board including four leading UK clinicians. The same sources were used for estimating these costs in the recent NICE appraisal of ipilimumab (TA319). The

costs were sourced from MIMS, NHS Reference costs 2013/4, and PSSRU 2014. Resource use for health states was estimated based on the MELODY observational study that collected data on resource use in patients with advanced melanoma. Please see the company's submission sections 5.5.2 to 5.5.5 (page 192 to 202) for details.

Table 16 Summary of resource use incorporated in the model

Resource use	Cost
Drug costs (depends on average dose)	
Nivolumab per IV	£2,809.47
Ipilimumab per IV	[redacted]
DTIC per IV	£48.21
Dabrafenib per day	£200.00
Vemurafenib per day	£250.00
Administration costs	
Administration cost of initial chemotherapy	£298.45
Administration cost of subsequent chemotherapy	£320.35
Administration cost of oral chemotherapy (one off)	£156.68
Resource use and costs	
Treatment initiation - one off	£663.18
Year 1 (per week)	£89.74
Year 2 (per week)	£44.87
Year 3 and beyond (per week)	£26.92
Palliative care period (per week)	£214.27
End of life care - one off	£1,450.91
Length of palliative care period (weeks)	12
Other costs	
Subsequent ipilimumab treatment (one-off)	[redacted]
Cost for treating adverse events	
AE costs for nivolumab	£205.22
AE costs for ipilimumab	£276.18
AE costs for DTIC	£116.51
AE costs for dabrafenib	£140.15
AE costs for vemurafenib	£87.47
Based on the company's submission table 79 (page 203-204)	

ERG comments

5.31 The ERG commented that costs incorporated in the model were taken from standard sources and reported transparently. The ERG also noted that administration cost assumptions for ipilimumab, DTIC, and vemurafenib are the same as those within the previous NICE technology appraisal of ipilimumab (TA316). The ERG was not able to check the reliability of some assumptions regarding resource use which were based upon expert opinion.

Company's base-case results and sensitivity analysis

Deterministic base-case

5.32 The company presented base-case results using the list prices for all drugs (see table 80 and 81 of the company's submission, page 206). Since ipilimumab, vemurafenib and dabrafenib are recommended by NICE with patient access schemes (PASs); the company also presented base-case analyses assuming different discount rates for these comparators (see table 82 and 83 of the company's submission, page 207). The company's analyses that incorporated hypothetical discounts for the comparators are not presented in this briefing paper. 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.

5.33 In the company's deterministic base case analyses, nivolumab provided a total of 4.31 and 4.27 quality-adjusted life years (QALYs), in the BRAF mutation-negative melanoma and BRAF mutation-positive melanoma respectively. The fully incremental comparisons with all comparators demonstrated that in the BRAF mutation-negative melanoma, nivolumab extendedly dominated ipilimumab, and was associated with the incremental cost effective ration (ICER) of £23,583 per QALY gained compared with dacarbazine (Table 17). Similarly, in BRAF mutation positive melanoma nivolumab dominated (that is, provided more QALYs at lower cost than) both dabrafenib and

vemurafenib. It was more costly and more effective than ipilimumab, with an incremental cost-effectiveness ratio (ICER) of £7,346 per QALY gained (Table 17). Full details of the base case results, including clinical outcomes and disaggregated costs, can be found in section 5.7 (page 204 to 217) of the company submission; details of the deterministic and probabilistic analyses can be found in sections 5.8.2 (page 226–230) and 5.8.1 (page 218–225).

Probabilistic base-case

5.34 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 17).

Table 17 Base case results

	Deterministic					Probabilistic				
Technology	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
BRAF mutation-negative melanoma										
Dacarbazine	[redacted]	1.23				[redacted]	1.23			
Ipilimumab	[redacted]	2.64	£48,429	1.41	Extendedly dominated	[redacted]	2.66	*£48,419*	*1.43*	Extendedly dominated
Nivolumab	[redacted]	4.31	£72,578	3.08	**£23,583**	[redacted]	4.30	*£72,751*	*3.07*	**£23,718**
BRAF mutation- positive melanoma										
Ipilimumab	[redacted]	2.44				[redacted]	2.46			
Nivolumab	[redacted]	4.27	£13,374	1.82	**£7,346**	[redacted]	4.24	*£13,234*	*1.78*	**£7,422**
Dabrafenib	[redacted]	1.69	£6,228	-2.57	Dominated	[redacted]	1.70	*£8,269*	*-2.54*	Dominated
Vemurafenib	[redacted]	1.70	£24,659	-2.56	Dominated	[redacted]	1.71	*£27,166*	*-2.53*	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. Incremental cost and QALYs are presented versus the next non-dominated comparator.
Dominated, treatment gives fewer QALYs at greater cost than the comparator. Extendedly dominated, a combination of 2 of its comparators provides equal health at a reduced cost.
Probabilistic results were mean value of the results obtained by running 1000 iterations of the model.
Based on the company's submission table 80-81 (page 206) and table 93-94 (page 225). Figures in italics calculated by NICE technical team.

Probabilistic sensitivity analyses

5.35 The company also presented scatter plots and cost-effectiveness acceptability curves demonstrating that there was 87% and 99% probability of nivolumab being cost-effective for BRAF-mutation-negative melanoma at a maximum acceptable ICER of £30,000 and £50,000 per QALY gained and a 100% probability of nivolumab being cost effective for BRAF-mutation-positive patients for both thresholds.

Deterministic sensitivity analyses

5.36 The model presented 53 one-way sensitivity analyses for BRAF mutation-negative melanoma and 58 analyses for BRAF mutation-positive melanoma. For sensitivity analyses, the company varied parameters between upper and lower 95% confidence intervals bounds or around a 20% variation in the value if confidence intervals were not available. In the submission, the company presented results as tornado diagrams (see Figure 75 and 76 of the company's submission page 228 to 232) that included 20 most influential parameters. In every tornado diagram, the company presented pair-wise comparison of nivolumab with a single relevant comparator. The tornado diagrams showed that the results were most sensitive to changes in the following parameters for nivolumab, ipilimumab as well as vemurafenib

- the fitted parameter curves for time to progression (post 100 days),
- post progression survival
- long-term overall survival
- progression free survival

The parameters to which the results were sensitive included

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

ERG comments

5.37 The ERG considered the company's conclusions relating to the most influential parameters impacting in the model to be reasonable.

Company scenarios

5.38 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

5.39 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.

ERG exploratory analyses

5.40 The ERG conducted exploratory analyses that included using:

- alternative survival functions for treatment efficacy as follows;
  - time to progression: Weibull, lognormal, log-logistic and generalised gamma distributions for nivolumab arm and Gompertz for DTIC and ipilimumab arms.
  - progression-free survival: exponential, Gompertz, log-logistic, lognormal and Weibull distributions for BRAF inhibitors (vemurafenib and dabrafenib).
- Modelling method: using the data extrapolation method to model long-term survival for nivolumab.
- including DTIC as a comparator for BRAF mutation-positive melanoma.

For details see the ERG report, section 4.3 (page 102 to 107).

5.41 The ERG's preferred scenario included a combination of some of the above mentioned scenarios as follows,

- a Weibull distribution for time to progression for nivolumab arm
- a lognormal distribution for progression free survival for BRAF inhibitors (vemurafenib and dabrafenib) .
- Long-term overall survival for nivolumab arm extrapolated from trial data using Gompertz distribution.

The ERG also explored effect of 2 alternative assumptions for maximum treatment duration with nivolumab on its preferred scenario; 3 years and with no maximum treatment duration.

Table 18 ERG exploratory analyses

S. No	Scenario	ICER	Reference to the ERG report
BRAF mutation-negative melanoma			
1	Company's Base-case	£23,583 (vs. DCIT)	Table 17 (page 73)
2	Weibull distribution for TTP in nivolumab arm	£26,483 (vs. DCIT)	Table 27 (page 103)
3	Long-term overall survival for nivolumab arm- extrapolated from trial data using Gompertz distribution	£36,072 (vs. ipilimumab)	Table 30 (page 104)
4	ERG's preferred scenario (combination of 2 and 3)	Dominated by ipilimumab	Table 33 (page 106)
5	4 plus maximum treatment duration for nivolumab 3 years	Dominated by ipilimumab	Table 35 (page 106)
6	4 plus without a maximum treatment duration for nivolumab	Dominated by ipilimumab	Table 37 (page 107)
BRAF mutation-positive melanoma			
A	Company's Base-case	£7,346 (vs. ipilimumab)	Table 18 (page 73)
B	Weibull distribution for TTP in nivolumab arm	£8,836 (vs. ipilimumab)	Table 28 (page 103)
C	a lognormal distribution for progression free survival for BRAF inhibitors	Nivolumab remained dominant compared to BRAF inhibitors	Table 29 (page 104)
D	Long-term overall survival for nivolumab arm extrapolated from trial data using Gompertz distribution	£27,171 (vs. ipilimumab)	Table 31 (page 105)
E	Including DCIT as a comparator	£21,201 (vs. DCIT)	Table 32 (page 105)
F	ERG's preferred scenario (combination of B, C and D)	Dominated by ipilimumab	Table 34 (page 106)
G	F plus maximum treatment duration for nivolumab 3 years	Dominated by ipilimumab	Table 36 (page 107)
H	F plus without a maximum treatment duration for nivolumab	Dominated by ipilimumab	Table 38 (page 107)

Key: DTIC, dacarbazine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. Dominated, treatment gives fewer QALYs at greater cost than the comparator.

Innovation

5.42 Justifications for considering nivolumab 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.
- Nivolumab is associated with significant clinical improvement, 45-50% of patients estimated to be in remission 2 years after treatment initiation.
- The Medicines and Healthcare products Regulatory Agency (MHRA) awarded nivolumab a Promising Innovative Medicine (PIM) designation and approved it through the Early Access to Medicines Scheme (EAMS).

6 End-of-life considerations

6.1 The company stated that advanced melanoma is associated with a short life expectancy, with median survival estimates of 6-10 months and the survival analyses of CheckMate 066 trial data indicate that nivolumab offers an extension to life of at least 3 months compared to palliative chemotherapy (DTIC). The company reported estimated the number of new cases and relapsed cases of advanced melanoma in England in 2016to 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 19 End-of-life considerations (company's submission table 52 [page 149])

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median life expectancy: 6-10 months Source: published systematic reviews and meta-analyses; pivotal clinical trials of novel; large patient database studies in the UK and US2 as stipulated in the company's submission sections 3.1 and 3.2
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	Restricted mean survival times (mean survival time calculated from within trial analysis): Nivolumab: 410 days DTIC: 301 days Between group difference: 109 days (3.6 months) 75% survival times: Nivolumab: 313 days DTIC: 157 days Between group difference: 156 days (5.1 months) Source: CheckMate 066 patient level data
The treatment is licensed or otherwise indicated for small patient populations	Advanced melanoma population for 2016: **1,304** Source: ONS population estimates for 2013 and melanoma incidence estimates for 2012 extrapolated using increased incidence rate of 3.5% previously used in melanoma submissions. Advanced or metastatic, relapsed squamous NSCLC population for 2015: **853** Source: Advanced or metastatic NSCLC estimates for 2013 and proportion of patients with squamous NSLC combined with estimates of proportion of patients receiving treatment and of those, patients who relapse

7 Equality issues

7.1 No equality issues were raised during the scoping process. The company stated that it had not identified or foreseen any equality issues related to the use of nivolumab.

8 Authors

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

Please see section 2.5 (page 53-80) of the European Public Assessment Report for the discussion clinical efficacy of nivolumab

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003840/WC500190651.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID845]

Company evidence submission

Bristol Myers Squibb Pharmaceuticals Ltd.

August 2015

File name	Version	Contains confidential information	Date
Company submission_BMS_Nivolumab for Advanced Melanoma Melanoma ID845	1	Yes	25.08.2015

Contents

Tables and Figures

Abbreviations

AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
AWMSG	All Wales Medicines Strategy Group
AUC	Area under the curve
BAD	British Association of Dermatologists
BCNU	Carmustine
BMS	Bristol-Myers Squibb
BOR	Best overall response
BRAF (V600)	A human gene that makes a protein, B-Raf
BSC	Best supportive care
CCNU	Lomustine
CD137	Cluster of differentiation 137 (a member of the tumour necrosis factor receptor family)
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CONSORT	Consolidated Standards of Reporting Trials
C/P	Carboplatin plus paclitaxel
CR	Complete response
CRF	Confirmed
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Programme
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DARE	Database of Abstracts of Reviews of Effects
DC	Discontinuation
DHA	Docosahexaenoic acid
DMC	Data monitoring committee
DOR	Duration of response
DSU	Decision Support Unit
DTIC	Dacarbazine
EAMS	Early Access to Medicines Scheme

ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EQ-5D	EuroQol-five dimension
EU	European Union
GCP	Good clinical practice
Gp-100	Glyocprotein-100
HDC	Histamine dihydrochloride
HR	Hazard ratio
HRT	Hormone replacement therapy
HRQL	Health-related quality of life
HTA	Health technology assessment
ICC	Investigator's choice chemotherapy
IFN-α	Interferon alpha
IFN-γ	Interferon gamma
IFN-γR	Interferon gamma receptor
IL-2	Interleukin-2
IRRC	Independent radiological review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
kg	Kilogram
KM	Kaplan–Meier
LDH	Lactate dehydrogenase
LY	Life year
LYG	Life years gained.
m	Metre
mAbs	Monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mm	Millimetre
mo	Month
MRI	Magnetic resonance imaging

MTD	Maximum tolerated dose
n	Number
NA	Not available
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCPE	National Centre for Pharmacoeconomics
NE	Not estimable
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
no.	Number
NSCLC	Non-small-cell lung cancer
ONS	Office for National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD-1	Programmed death receptor 1
PD-L1	Programmed death receptor ligand 1
PD-L2	Programmed death receptor ligand 2
PFS	Progression-free survival
PIM	Promising Innovative Medicine
PP	Per-protocol
PPS	Post-progression survival
PR	Partial response
PrePS	Pre-progression survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSS	Personal Social Services
QALY	Quality-adjusted life year
q2w	Every 2 weeks
q3w	Every 3 weeks
Q4	Quarter 4
RANK-L	Receptor activator of nuclear factor kappa-B ligand
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SD	Standard deviation

SITC	Society for Immunotherapy of Cancer
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMR	Society for Melanoma Research
TIC	Triazeno imidazole carboxamide
TOT	Time on treatment
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
TTP	Time to progression
TTR	Time to treatment response
UK	United Kingdom
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
VAS	Visual analogue scale
VAT	Value-added tax
VCR	Vincristine
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health
WTP	Willingness to pay
yr	Year

1 Executive summary

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 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.

Burden of disease

Melanoma is an aggressive disease and 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 expected 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).

Current management and unmet need

Survival rates are highest in melanoma patients diagnosed at an early stage. When detected early, and successfully treated with surgery, the prognosis of localised disease is excellent with greater than 95% survival. However, for patients with advanced disease, historically prognosis has been much poorer, with a median survival estimate of 6-10 months and a 5-year survival rate of ~10% commonly associated with historical standard of care (see Section 3.1).

The mainstay of treatment for advanced melanoma is systemic therapy, which traditionally consisted of chemotherapy. Over the last few years, a number of non-chemotherapy systemic treatment options (ipilimumab and BRAF inhibitor therapies) have become available, which have all demonstrated a significant clinical benefit over traditional chemotherapy. However, despite these advances in treatment, durable response and long-term survival remains elusive for many patients with advanced melanoma (see Section 3.3).

There is, therefore, a clear and substantial unmet medical need for a treatment that provides a durable response and improves long-term survival compared with currently available treatments for patients advanced melanoma. Nivolumab meets this need.

Nivolumab offers a durable clinical response and long-term survival benefit

Nivolumab is the first PD-1 immune checkpoint inhibitor to demonstrate long-term survival benefit in a clinical trial setting (see Section 4.11). The clinical evidence for nivolumab is derived from three Phase III trials involving more than 1400 patients with advanced melanoma and all at the licensed dose of 3mg/kg: Checkmate 066, Checkmate 067 and Checkmate 037 (see Section 4.7).

Checkmate 066 was terminated early in June 2014, after the results of an analysis of the primary endpoint of Overall Survival (OS) demonstrated clear evidence of a survival benefit in patients receiving nivolumab. The OS rate at 1 year was 73% in the nivolumab group

compared to 42% in the DTIC group. In the Intention-To-Treat (ITT) analysis, with a median follow-up of 8.9 months, the median OS (when half of the patients have died) had not yet been reached in the nivolumab group. In comparison, with a median follow-up of 6.8 months, the DTIC group had a confirmed median OS of 10.8 months. The corresponding Hazard Ratio (HR) for death confirmed a significantly superior survival time with nivolumab therapy compared to DTIC (0.42 [99.79% CI: 0.25, 0.73]; p<0.001).

Nivolumab treatment was also associated with significant progression-free survival (PFS) benefit compared with both DTIC (HR for death or disease progression: 0.43 [95% CI: 0.34, 0.56]; p<0.001, Checkmate 066) and ipilimumab (median PFS 6.9 months in the nivolumab group vs Median PFS 2.9 months in the ipilimumab group; HR for death or disease progression: 0.57 [95% CI: 0.43, 0.76); p<0.001], Checkmate 067).

Nivolumab offers a step-change in the management of advanced melanoma

Nivolumab builds upon the value of ipilimumab, demonstrating a magnitude of improved clinical benefit over current first-line treatment options similar to that which ipilimumab previously demonstrated over traditional chemotherapy (see Section 5.3) and irrespective of BRAF mutation status and treatment history (see Section 4.7). Extrapolated survival estimates from the Phase III data suggest 45-50% of advanced melanoma patients treated with nivolumab 3mg/kg monotherapy are still alive 2 years after treatment initiation. An indirect treatment comparison (ITC) using OS data from key comparator trials suggests this is approximately a 20% improvement over 2-year survival rates of ipilimumab and BRAF inhibitor therapies.

With a median life expectancy of less than 12 months in advanced melanoma, a mean extension to life of 3.6 months associated with nivolumab (compared with historical standard of care), and a small patient population potentially eligible for nivolumab in England (n=1,304 in year 1), nivolumab for the treatment of advanced melanoma meets NICE's end of life criteria (see Section 4.13).

Nivolumab was the first melanoma treatment to be announced as a Promising Innovative Medicine (PIM) by the Medicines and Healthcare products Regulatory Authority (see Section 2.5) and is also approved through the Early Access to Medicines Scheme (EAMS) both for previously untreated and pre-treated patients.

The clinical efficacy and survival data for nivolumab - demonstrated in three Phase III trials at the licensed dose of 3mg/kg - are compelling. Adoption of nivolumab monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in the National Health Service (NHS) in England would represent a further step-change in advancing the management of this life-threatening condition and improving long-term survival.

1.1 Statement of the decision problem

The decision problem addressed in this submission matches the final appraisal scope issued by NICE, as summarised in Table 1.

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	Nivolumab	-
Comparator(s)	• BRAF inhibitors (dabrafenib and vemurafenib – for people with BRAF V600 mutation-positive melanoma who have not previously received a BRAF inhibitor) • Ipilimumab (for people who have not previously received ipilimumab) • Dacarbazine (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is unsuitable) • Best supportive care (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is/are unsuitable)	• BRAF inhibitors (dabrafenib and vemurafenib – for people with BRAF V600 mutation-positive melanoma who have not previously received a BRAF inhibitor) • Ipilimumab (for people who have not previously received ipilimumab) • Dacarbazine (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is unsuitable) • Best supportive care (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is/are unsuitable)	Economic comparison is presented versus: • BRAF inhibitors • Ipilimumab • Dacarbazine In line with previous submissions outcomes with dacarbazine are assumed to be representative of the broader set of palliative chemotherapies which form part of best supportive care.
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	A cost-effectiveness analysis expressed in terms of incremental cost per quality-	

	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 a National Health Service and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	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.	
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

Programmed death-1 (PD-1) is an immune-system checkpoint expressed at high levels on activated T-cells, which has been shown to control the inhibition of T-cell response in the setting of human malignancy. Up-regulation of the checkpoint proteins that engage PD-1 with either programmed-death ligand 1 (PD-L1) or programmed-death ligand 2 (PD-L2) by cancer cells can exploit this control. Nivolumab is an immuno-oncology treatment that is a PD-1 inhibitor and the "first-in-class" in the UK. It is a fully human immunoglobulin G4 (IgG4) monoclonal antibody, and is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults (see Section 2.1).

Nivolumab stops the evasion of immune-mediated tumour destruction and stimulates 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 natural means. It is the first melanoma treatment to be announced with a PIM designation by the MHRA and is also approved through the EAMS.

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

Table 2: Technology being appraised

UK approved name	Nivolumab
Brand name	Opdivo®
Marketing authorisation status	CHMP positive opinion received 23 April 2015 Marketing authorisation received 19 June 2015
Indications and any restriction(s) as described in the summary of product characteristics	Nivolumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults
Method of administration and dosage	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. Maximum duration of treatment is anticipated to be 2 years.
Key: CHMP, Committee for Medicinal Products for Human Use; kg, kilogram; mg, milligram.	

1.3 Summary of the clinical effectiveness analysis

An extensive clinical trial programme supports the use of nivolumab monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, irrespective of BRAF status and treatment history.

This clinical trial programme includes three pivotal Phase III randomised controlled trials (RCTs) that provide direct evidence of the potential clinical effectiveness of nivolumab compared with both chemotherapy and ipilimumab (see Section 4.7). Taken together, the clinical data from these trials present a compelling case that nivolumab represents a 'step-change' in the treatment of advanced melanoma and improving long-term survival. A summary of these trials is provided below:

CheckMate 066

- Phase III, multicentre, double-blind RCT comparing the clinical efficacy and safety of nivolumab with dacarbazine (DTIC) in previously untreated patients who have advanced melanoma without a BRAF mutation.
- Significant benefit with respect to the primary endpoint of overall survival (OS) observed in the nivolumab group, compared with the DTIC group: hazard ratio (HR) for death, 0.42 (99.79% confidence interval [CI]: 0.25, 0.73); p<0.001.
- Significant benefit with respect to the secondary endpoints of progression-free survival (PFS) and objective response rate (ORR) also observed in the nivolumab group, compared with the DTIC group:
    - Median PFS of 5.1 months in the nivolumab group compared with 2.2 months in the DTIC group; HR for death or disease progression, 0.43 (95% CI: 0.34, 0.56); p<0.001;
    - ORR of 40.0% in the nivolumab group compared with 13.9% in the DTIC group; odds ratio (OR) for response, 4.06 (95% CI: 2.52, 6.54); p<0.0001.
- Durable responses in the nivolumab group represented by median duration of response not yet reached, compared with a median duration of response of 6.0 months in the DTIC group.
- Significant benefit with respect to health-related quality of life (HRQL) observed, with nivolumab significantly less likely to lead to deterioration and significantly more likely to lead to improvement in global health and utility, compared with DTIC (p<0.05).

CheckMate 067

- Phase III, multicentre, double-blind RCT comparing the clinical efficacy and safety of nivolumab 3mg/kg monotherapy 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 observed in the nivolumab group (median PFS, 6.9 months), compared with the ipilimumab group (median PFS, 2.9 months): HR for death or disease progression, 0.57 (95% CI: 0.43, 0.76); p<0.001.
- Significant benefit with respect to the secondary endpoint of ORR was observed in the nivolumab group (43.7%), compared with the ipilimumab group (19.0%): OR for response, 3.40 (95% CI: 2.02, 5.72); p<0.0001.

CheckMate 037

- Phase III, multicentre, open-label RCT comparing the clinical efficacy and safety of nivolumab 3mg/kg monotherapy with investigator's choice chemotherapy (ICC), either dacarbazine or carboplatin/paclitaxel, in previously treated patients who have advanced melanoma with or without a BRAF mutation.
- Significant benefit with respect to the co-primary endpoint of ORR observed in the nivolumab group (31.7%), compared with the ICC group (10.6%).

A manageable safety and tolerability profile was demonstrated for nivolumab in all three Phase III trials, which compared favourably with the profile of current treatment options in advanced melanoma (see Section 4.12).

Additionally, supportive Phase I dose-escalation study (CheckMate 003) provides evidence of nivolumab's long-term clinical benefit. In the advanced melanoma cohort of patients treated with nivolumab 3mg/kg monotherapy in this trial, median OS was 20.3 months. Furthermore, in patients responding to nivolumab therapy, median duration of response to treatment was approximately 2 years (see Section 4.11).

UK and international expert clinical opinion has confirmed that for those patients who have responded to nivolumab, treat to progression will not be reasonable in routine clinical practice, and that stopping therapy at an appropriate time point should be considered.

Based on available data from CheckMate 003 looking at various doses of nivolumab across a range of tumour types, including advanced melanoma, with a maximum duration of treatment of 96 weeks UK clinicians agreed that limiting the maximum duration of treatment could be supported. This assumption was validated extensively with UK and international melanoma clinicians in advisory board settings and 1:1 correspondence. The clinical trial evidence demonstrates that the majority of responses to nivolumab tend to occur relatively early, mostly within the first 24 weeks, after which responses tend to be maintained it is therefore expected that the majority of responding patients will continue to maintain response beyond discontinuation at two years.

Extrapolated survival estimates using OS data from the CheckMate 066 trial suggest that 45-50% of patients with advanced melanoma that are treated with nivolumab are still alive 2 years after treatment initiation. An indirect treatment comparison (ITC) using OS data from key comparator trials suggest this is approximately a 20% improvement over 2-year survival rates of ipilimumab and BRAF inhibitor therapies (see Section 5.3).

With a median life expectancy of less than 12 months in advanced melanoma, a mean extension to life of 3.6 months associated with nivolumab (compared with historical standard of care-DTIC), and a small patient population potentially eligible for nivolumab in England (n=1,304 in year 1), nivolumab for the treatment of advanced melanoma meets NICE's end of life criteria (see Section 4.13).

1.4 Summary of the cost-effectiveness analysis

A de novo economic model was developed based upon the previously-accepted economic models for TA268 and TA319. The model structure captures the unique characteristics of immunotherapy, including nivolumab, 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 nivolumab and the comparators using an ITC analysis, 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 is modelled to continue until the first of either loss of clinical benefit, unacceptable toxicity or 2 years of continuous treatment (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 clinician expectation and the cost-effectiveness results for comparators are in line with published cost-effectiveness literature.

The base case analyses show nivolumab is a cost effective option for all patients with advanced (unresectable or metastatic) melanoma versus all comparators at a cost-effectiveness threshold as low as £30,000, with ICERs of £7,346 and £23,583, in BRAF mutation-positive and BRAF mutation-negative patients, respectively (see Table 3 and Table 4 below).

Because nivolumab meets NICE's End of Life criteria, at the appropriate cost/QALY threshold of £50,000, the probabilities of nivolumab being most cost effective are 99% and 100% for BRAF mutation-negative and BRAF mutation-positive patients, respectively. At the threshold of £30,000, the probabilities of nivolumab being most cost effective are 87% 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.

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 per QALY – baseline (£)	Dominance	ICER per incremental QALY (£)
Dacarbazine	[redacted]	1.74	1.23						
Ipilimumab	[redacted]	3.66	2.64	£48,429	1.92	1.41	£34,261	Extended dominated	Excluded due to extended dominance
Nivolumab	[redacted]	5.75	4.31	£72,578	4.01	3.08	£23,583		£23,583

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)
Ipilimumab	[redacted]	3.40	2.44						
Nivolumab	[redacted]	5.70	4.27	£13,374	2.30	1.82	£7,346		£7,346
Dabrafenib	[redacted]	2.37	1.69	£6,228	-3.33	-2.57	-£26,054	Dominated	Excluded due to dominance
Vemurafenib	[redacted]	2.37	1.70	£24,659	-3.33	-2.56	-£51,397	Dominated	Excluded due to dominance

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.

Conclusions

The three Phase III clinical trials show remarkable results with nivolumab at the licensed dose of 3mg/kg demonstrating a magnitude of improved response over current first-line treatment options, including ipilimumab, similar to that which ipilimumab previously demonstrated over traditional chemotherapy (see Section 5.3). In Checkmate 066, an early data cut demonstrated overall survival at 1 year of 73% for nivolumab, compared to 42% in the DTIC group, which was deemed sufficient to terminate the study. Nivolumab offers proven survival benefit to patients and also a new option (where none currently exist) for patients who have failed to respond to previous treatments or for whom current therapies are inappropriate.

In summary, nivolumab is the PD-1 inhibitor which currently has the most comprehensive clinical dataset supporting its use in advanced melanoma at the licensed dose. Nivolumab is a new, innovative, cost-effective and step-changing treatment option, which meets an unmet medical need for patients with advanced (unresectable or metastatic) melanoma by offering durable response and improved long-term survival, regardless of BRAF status or treatment history.

2 The technology

2.1 Description of the technology

Brand name: Opdivo®

UK approved name: Nivolumab

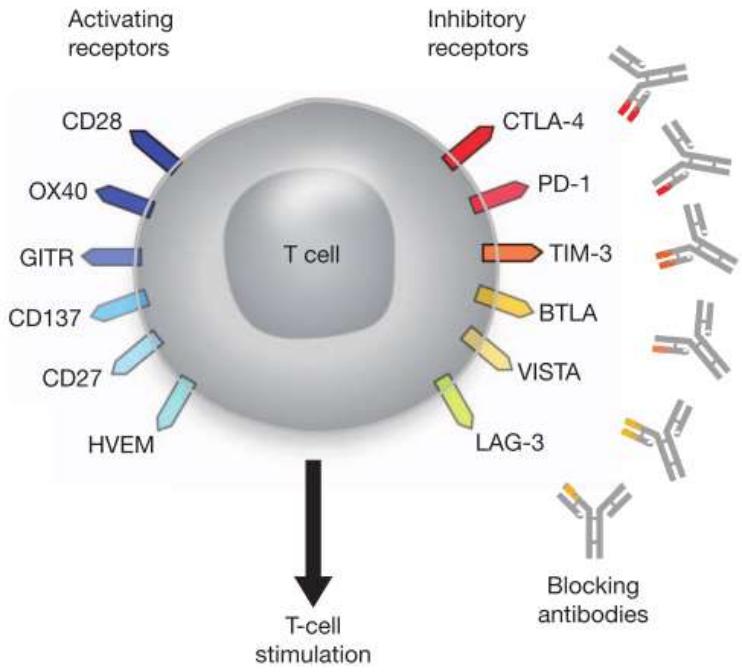
Therapeutic class: Programmed death-1 (PD-1) immune checkpoint inhibitor

Brief overview of the mechanism of action:

Conventional anti-cancer therapies generally act through cytotoxicity. They destroy cancer cells "preferentially" due to their fast growing and rapidly dividing nature but are in fact toxic to all cell types. Consequently, normal cells that are also fast growing and rapidly dividing in nature (such as hair follicles and gut mucosa) are often destroyed alongside cancer cells, resulting in undesirable side effects (such as hair loss and diarrhoea).[1] Resistance to conventional anti-cancer therapies is also a major problem facing current cancer research.[2] In recent years, alternative approaches for the treatment of cancer have therefore been investigated. Immunotherapy is one such alternative that has been at the forefront of therapeutic development in oncology, since the discovery that cancer cells evade destruction by exploiting the immune system.[3]

The typical immune response to foreign cells or antigens in the body is activation of T-cells that can destroy them. T-cells proliferate and differentiate in 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) can avoid T-cell destruction by stimulating inhibitory receptors known as checkpoints to suppress the T-cell response. Cancer cells exploit this pathway, mimicking 'self'-cells by stimulating inhibitory receptors themselves, to avoid destruction and facilitate tumour development.[3] Blocking antibodies designed to bind to these checkpoints, so-called 'checkpoint-inhibitors', target this tumour driven T-cell suppression, as depicted in Figure 1.

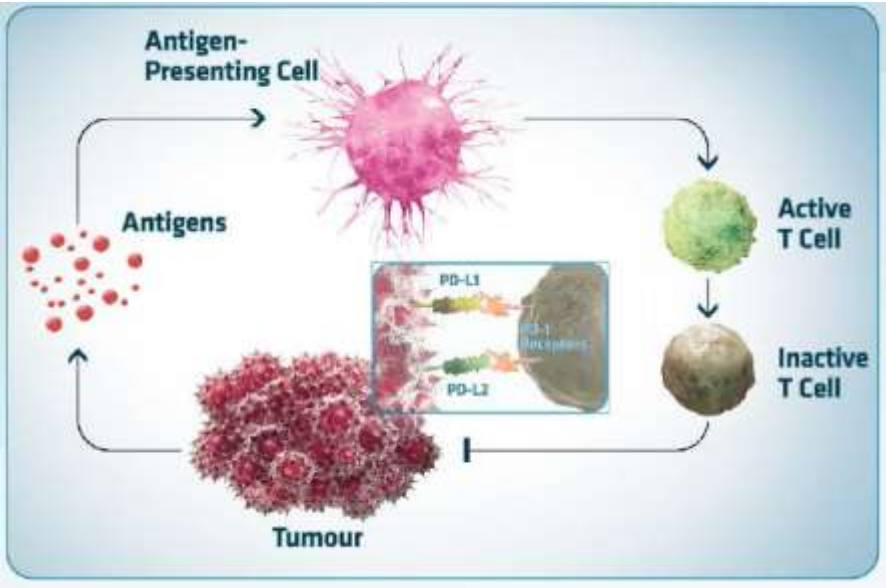
Figure 1: Regulation of the T-cell immune response



Source: Mellman et al., 2011[3]

Programmed death-1 (PD-1) is a checkpoint expressed at high levels on activated T-cells, which has been shown to control the inhibition of T-cell response in the setting of human malignancy.[4-6] Up-regulation of the checkpoint proteins that engage PD-1, found on the activated T-cell, with its ligands PD-L1 and PD-L2 (programmed-death ligand 1 [PD-L1] and programmed-death ligand 2 [PD-L2]) found on several types of cells including on the tumour itself, can exploit this control,, as depicted in Figure 2.[5, 7, 8]

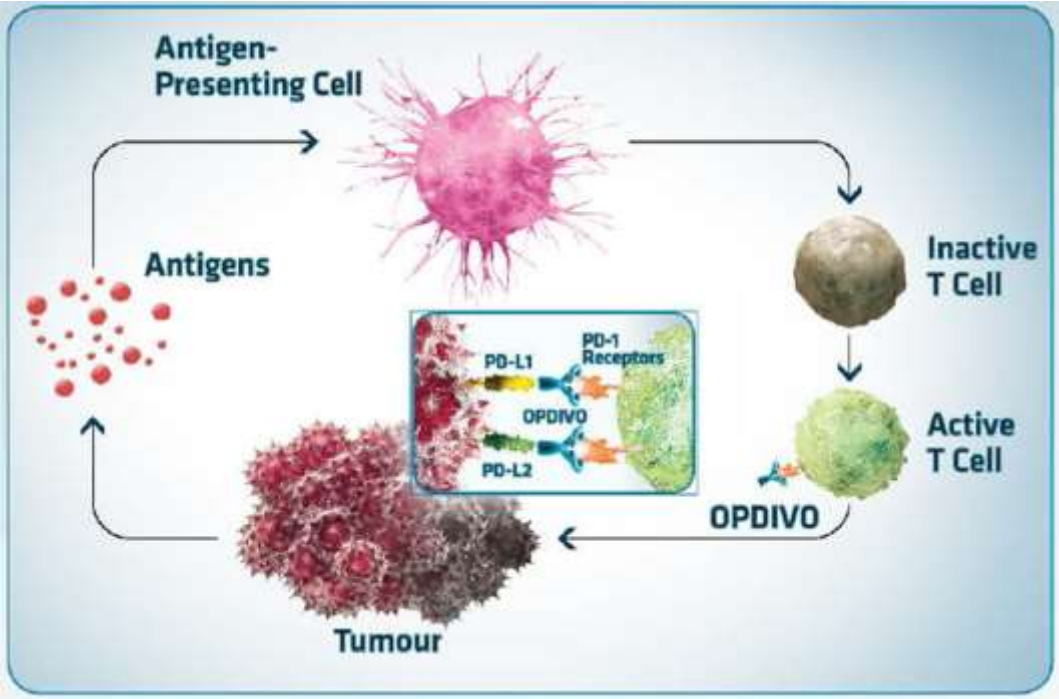
Figure 2: Evasion of immune-mediated tumour destruction



Key: PD-1, programmed death-1; PD-L1, programmed-death ligand 1, PD-L2, programmed-death ligand 2.

Nivolumab is a fully human, monoclonal immunoglobulin G4 antibody (IgG4 HuMAb) that acts as a PD-1 checkpoint-inhibitor; blocking the interaction of PD-1 with PD-L1 and PD-L2 (Figure 3).[7, 8] Nivolumab stops the evasion of immune-mediated tumour destruction and actually potentiates this process by restoring T-cell activity, i.e. nivolumab stimulates 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 3.

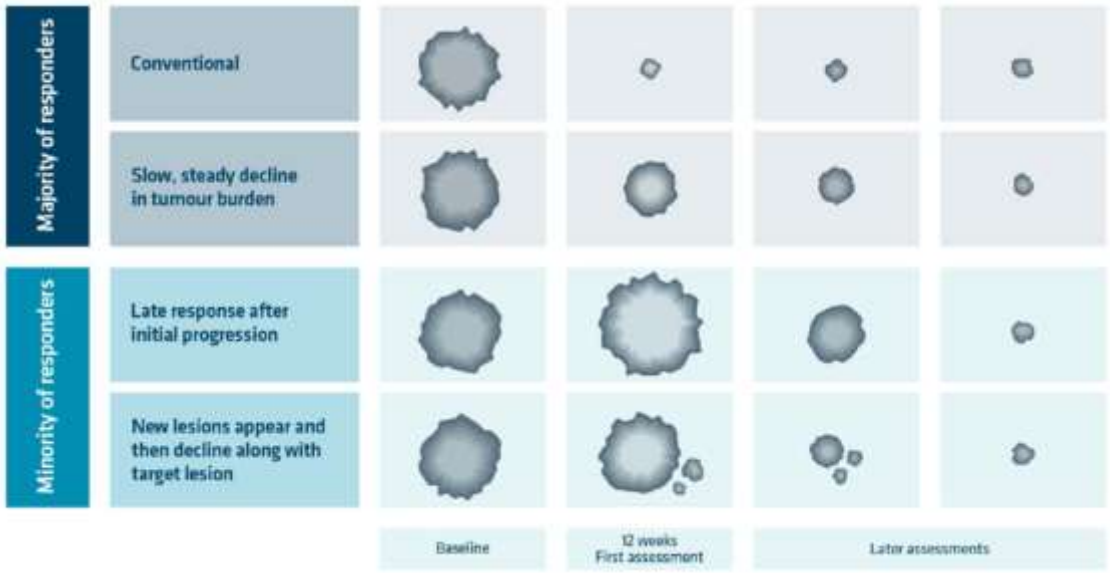
Figure 3: Nivolumab stimulation of immune-mediated destruction



Key: OPDIVO, nivolumab; PD-1, programmed death-1; PD-L1, programmed-death ligand 1, PD-L2, programmed-death ligand 2.

Contrary to conventional anti-cancer therapies where response to treatment is usually observed as an immediate shrinkage of the tumour, this immune-mediated destruction as described above has been shown in clinical trials to result in varying patterns of response. In some cases, immuno-oncology activity around the tumour cells can have the effect of making the tumour appear bigger, due to the proliferation of activated T-cells surrounding and infiltrating the tumour. These well recognised phenomena have been termed as 'unconventional immune related responses' and can result in 'pseudo-progression' where patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment. Typical patterns of response observed with immuno-oncology therapies are presented in Figure 4.

Figure 4: Typical patterns of response observed with immuno-oncology



2.2 Marketing authorisation and health technology assessment

Opdivo (nivolumab) as monotherapy received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 23 April 2015 for the treatment of advanced (unresectable or metastatic) melanoma in adults. This was approved by the European Medicines Agency (EMA) for a marketing authorisation on 19 June 2015 and has been available in the UK since this date.

In accordance with the summary of product characteristics (SmPC) (Appendix 1.1), nivolumab is only contraindicated in patients with hypersensitivity to the active substance or to any listed excipients. However, it should be noted that early identification of adverse reactions and intervention are an important part of the safe use of nivolumab.

During the assessment of the marketing authorisation application for Opdivo (nivolumab) as monotherapy, the following issues were discussed by the CHMP in the European Public Assessment Report (EPAR):

Clinical Aspects

From a clinical perspective, the efficacy and safety of nivolumab as monotherapy indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults were investigated in two pivotal studies:, a phase III, randomised, double-blind study of nivolumab versus dacarbazine in subjects with BRAF wild type, previously untreated, unresectable or metastatic melanoma (CheckMate 066) and a phase III, randomised, open-label trial of nivolumab versus ICC (dacarbazine or carboplatin and paclitaxel) in unresectable or metastatic melanoma patients progressing after prior therapy (CheckMate 037). Based on the results from these clinical trials, the CHMP considered the benefit-risk balance of nivolumab as monotherapy indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults favourable.

Conditions of Marketing Authorisation

As part of the conditions with regard to the safe and effective use of Opdivo (nivolumab), the CHMP requested the marketing authorisation holder to complete some post-authorisation measures including the submission of updated results from the pivotal trials as well as to further explore the value of PD-L1 and other biomarkers to predict the efficacy of nivolumab.

In addition, and as proposed in the nivolumab risk management plan, additional risk minimisation measures have to be undertaken. These measures entail that, at the time Opdivo (nivolumab) is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Opdivo (nivolumab) will have access to or will be provided with the following educational materials:

- The physician educational material, which contains the SmPC and Adverse Reaction Management Guide (it has information on immune-related adverse events [AEs] and on how to minimise the safety concern through appropriate monitoring and management)
- A Patient Alert Card, which contains information on other immune-related adverse reactions, signs and symptoms and when to seek help from a healthcare provider along with prescriber details

These materials are aimed at increasing awareness about the potential immune-related AEs associated with Opdivo (nivolumab) use, how to manage them and at enhancing the awareness of patients or their caregivers on the signs and symptoms relevant to the early detection of those AEs.

The summary of the EPAR for the public is provided in Appendix 1.2. The full CHMP assessment report is provided in the reference pack.[9]

In addition to European approval, nivolumab (Opdivo) already has marketing authorisation in US, Israel, Japan, Korea and Macau for the treatment of advanced melanoma. In the US, nivolumab has been granted a 'Breakthrough Therapy' designation for this indication.

Health technology appraisal submissions to the Scottish Medicines Consortium (SMC) and the National Centre for Pharmacoeconomics (NCPE) are planned in parallel to this submission for the advanced melanoma indication, with anticipated outcomes in Q1-2 2016. Form A was submitted to the All Wales Medicines Strategy Group (AWMSG) in July 2015 and an outcome is awaited.

Nivolumab (BMS Nivolumab) has also received a European Marketing Authorisation and is launched in the UK for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. Nivolumab (Opdivo) has Marketing Authorisation in US, Israel and Macau for the treatment of patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy.

2.3 Administration and costs of the technology

Administration and costs associated with nivolumab are summarised in Table 5.

Table 5: Costs of the technology being appraised

	Cost/description	**Source**
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate).	SmPC[10]
Acquisition cost (excluding VAT)*	£439 for 40mg £1,097 for 100mg	

	Cost/description	Source
Method of administration	Intravenous infusion.	SmPC[10]
Doses	3mg/kg	SmPC[10]
Dosing frequency	Every 2 weeks.	SmPC[10]
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.	SmPC[10] Clinical consensus[11, 12]
Average cost of a course of treatment	[redacted]	See Table 89 and Section 5.5
Anticipated average interval between courses of treatments	Nivolumab retreatment is not anticipated.	-
Anticipated number of repeat courses of treatments	Nivolumab retreatment is not anticipated	-
Dose adjustments	Dose escalation or reduction is not recommended.	SmPC[10]
Anticipated care setting	Hospital or clinic setting.	SmPC[10]

Key: kg, kilogram; mg, milligram; SmPC, Summary of Product Characteristics.
Notes: * Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

2.4 Changes in service provision and management

Nivolumab is not a targeted therapy, and as such, additional tests or investigations outside of those required for the diagnosis of advanced melanoma are not needed.

Nivolumab treatment 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 nivolumab would utilise this existing NHS infrastructure.

The main additional resource use to the NHS is associated with the administration regimen of nivolumab. The 2-weekly dosing requirement represents a more frequent administration regimen than current therapies (see Section 3.2). This is fully accounted for in the economic modelling presented in Section 5. As with other immune-therapies, patients should also be regularly monitored for signs or symptoms of Select AEs with a potential immunological cause during treatment, as early identification of AEs and intervention are an important part of the safe use of nivolumab. Clinicians will be familiar with monitoring patients for such AEs as this is also recommended for patients receiving ipilimumab therapy.

No concomitant therapies are specified in the marketing authorisation for nivolumab, other than those used to manage AEs. Common AEs are well characterised and, in the majority of cases, can be quickly resolved with a delay in study treatment, corticosteroid administration or both, as recommended in the safety management guidelines outlined in the SmPC.

2.5 Innovation

Durable response and long-term survival remain elusive for the majority of advanced melanoma patients despite recent therapeutic advancements (see Section 3). Building upon the value of ipilimumab, nivolumab demonstrates a magnitude of improved clinical benefit over current first-line treatment options similar to that ipilimumab previously demonstrated over traditional chemotherapy (see Section 5.3).

Advanced melanoma disproportionately affects younger patients and thus has a significant impact on the working age population (see Section 3.1). Negative implications of this include loss of economic productivity (see Section 3.1), which is not included in the quality-adjusted life year (QALY) calculation presented in Section 5, but should be considered when assessing health-related benefits to wider society.

Furthermore, whilst survival benefit will be captured in the QALY calculation for nivolumab, the significant clinical improvement associated with this therapy, demonstrated through 45-50% of patients estimated to still be in remission 2 years after treatment initiation (see Section 5.3), should be viewed as innovative and represents a step-change in the management of this condition.

The innovation of nivolumab is reflected in the Medicines and Healthcare products Regulatory Agency (MHRA) awarding nivolumab a Promising Innovative Medicine (PIM) designation for the treatment of advanced melanoma, and in the approval of nivolumab for use through the Early Access to Medicines Scheme (EAMS).

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.[13, 14] 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.[13, 15]

Often the first visible indication of melanoma is typically a mole that has changed in shape, colour, size or feel. 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.[16]

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.[16, 17] Melanoma can also originate from other sources, e.g. ocular and mucosal. In these cases the initial signs and symptoms may be less obvious.

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 4.[16] Nivolumab is 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.

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).[14, 17-20] 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.[17, 21-26] Stage IV (metastatic) disease and poor performance status at diagnosis have the worse prognosis, particularly when brain metastases are present.[17, 21-23, 25, 27]

Incidence and prevalence

Rates of melanoma have been steadily rising over the last 50 years.[28] Malignant melanoma increased by 78% among males and 48% among females from 2003 to 2012, making it the fifth most common cancer in England.[29]

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.[28, 30] Potentially as a reflection of lifestyle factors, melanoma is the most frequently diagnosed cancer in people aged 25 to 29.[31] 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.[15, 20, 32]

Survival

Survival rates are highest in melanoma patients diagnosed at an early stage. When detected early, and successfully treated with surgery, the prognosis of localised disease is excellent

with greater than 95% survival.[17, 24] However, for patients with unresectable or metastatic disease, historically prognosis has been much poorer, with a median survival estimate of 6-10 months[23, 25, 33-35] and a 5-year survival rate of ~10% commonly associated with historical standard of care.[25, 34, 36]

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.[37, 38]

Systemic therapy can decrease patients' 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.[39] 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.[40]

The impact of melanoma on patients' HRQL is thought to be comparable to that of other cancers[37], 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.[41] 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.[42]

The direct costs of melanoma are also substantial, increasing in the later stages of the disease.[43-47] Direct cost drivers include out-patient care, and hospitalisation/hospice stays, which increase during palliative care.[35, 45, 48]

The total cost of all skin cancer in England in 2002 was estimated at around £240 million with NHS costs accounting for 42% of the total value.[49] The mean total cost of each case of malignant melanoma was estimated to be £19,981 with a mean cost to NHS England of £2,945.[49] 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.

Unmet medical need

Despite the significant advancements in therapeutics in recent years (see Section 3.2), the long-term survival of a broad range of advanced melanoma patients remains elusive.[50] This has a significant, negative impact on patients, carers and the wider society.

Whilst ipilimumab does offer the potential of long-term survival, not all patients with advanced melanoma will respond to ipilimumab therapy.[51] There is a strong correlation between induction therapy completion and long-term survival with ipilimumab. However, the indirect mechanism-of-action of ipilimumab means response times can be delayed[52-58], and as a result, patients with an estimated survival of less than 3 months at presentation are less likely to achieve long-term survival with ipilimumab therapy. Alternative therapies that specifically target BRAF mutations are available, but their clinical benefit is generally short-lived. Reports suggest that resistance to BRAF inhibition often develops[59-61] with patients demonstrating progressive disease within 5-8 months of therapy initiation.[62-64] Importantly, these therapies target the BRAF mutation, which is only observed in approximately 50% of melanoma tumours.[60, 65-69]

For advanced melanoma patients who are ineligible for, or unresponsive to, ipilimumab or BRAF inhibitor therapy, there are still no alternative treatment options outside of palliative chemotherapy (which has limited clinical benefit[23, 25, 33, 34]), or clinical trial enrolment (see Section 3.2).

There are clearly still a number of advanced melanoma patients with an unmet medical need.

3.2 Clinical pathway of care

In advanced melanoma (unresectable or metastatic) the mainstay of treatment is systemic therapy, traditionally chemotherapy. Over the last few years, a number of non-chemotherapy systemic treatment options have become available (summarised in Table 6). These therapies have all demonstrated a significant clinical benefit over traditional chemotherapy[54, 55, 62, 63], such that chemotherapy (which has no proven effect on survival times)[23, 25, 33, 34] is now only used in the palliative setting outside of clinical trials.

Table 6: Non-chemotherapy systemic treatment options in advanced melanoma

Product (brand)	Treatment class	Dosing regimen	Marketing authorisation	NICE recommendation
Ipilimumab (Yervoy®)	Anti-neoplastic agents, monoclonal antibodies	3mg/kg IV every 3 weeks for a total of 4 doses	Indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults	TA319: recommended as a possible treatment for adults with advanced (unresectable or metastatic) melanoma that has not been treated before. TA268: recommended as a possible treatment for people with previously treated advanced (unresectable or metastatic) melanoma.
Vemurafenib (Zelboraf®)	BRAF inhibitor	960mg (4 × 240mg tablets) twice daily until disease progression or toxicity	Indicated as a monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	TA269: recommended as a possible treatment for unresectable or metastatic melanoma with the BRAF V600 mutation
Dabrafenib (Tafinlar®)	BRAF inhibitor	150mg (2 x 75mg capsules) twice daily until disease progression or toxicity	Indicated as a monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	TA321: recommended as a possible treatment for people with melanoma that has spread, can't be removed by surgery and is BRAF V600 mutation-positive
Key: IV, intravenous; kg, kilogram; mg, milligram; NICE, National Institute for Health and Care Excellence **Source:** Dabrafenib SmPC[70]; Ipilimumab SmPC[71]; Vemurafenib SmPC[72]; NICE TA321[73]; NICE TA319[4]; NICE TA269[74]; NICE TA268[75]				

Clinical management guidelines have been updated to reflect this progression in melanoma therapeutics (see Section 3.4). These guidelines do not make specific recommendations on treatment sequencing as there is no conclusive, generalisable evidence for the optimal treatment sequence in advanced melanoma. Decisions on the first- and subsequent-line treatment choices are therefore left to the clinician, with a number of factors needing to be considered when deciding on the best therapeutic approach for individual patients. These include the BRAF mutation status of the melanoma tumour (as the BRAF inhibitor therapies available are only indicated for the treatment of patients with BRAF mutation-positive

melanoma), tumour burden, symptom burden, anticipated speed of disease progression and LDH levels.[76-79]

As both the BRAF inhibitors (dabrafenib, vemurafenib) and ipilimumab are licensed and recommended for use in both the first- and second-line setting in England, patients with BRAF mutation-positive melanoma who fail to respond to ipilimumab can be switched to BRAF inhibitor therapy, and vice versa.[4, 70, 72-75, 80] The remaining 50% of the advanced melanoma population who are BRAF mutation-negative (wild-type) can only be treated with ipilimumab of the non-chemotherapy systemic treatment options presented in Table 5.

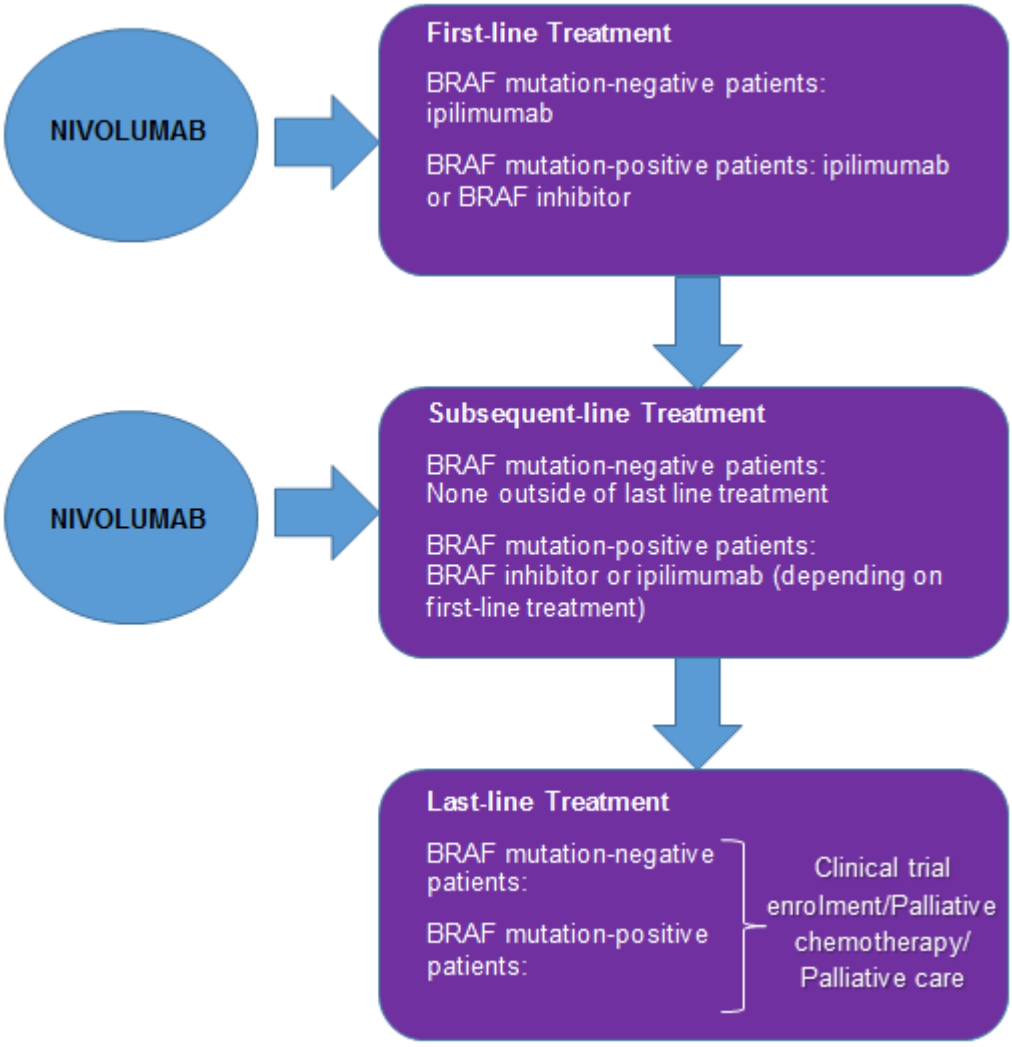
Patients who fail to respond to ipilimumab or BRAF inhibitor therapy, and patients in whom the use of these therapies is considered inappropriate, have limited treatment options. Outside of palliative care, DTIC chemotherapy (which has not demonstrated an effect on OS) is the most commonly adopted treatment in England[33-35]; the only alternative option is entry into a clinical trial. However, not all patients are eligible for clinical trials (or view it as a valid treatment option).

Nivolumab is a new treatment option for patients with advanced melanoma that is associated with long-term clinical benefits of durable response and extended survival, regardless of BRAF status (see Section 4).[81-84] Indeed, nivolumab demonstrates a magnitude of improved survival benefit over current first-line treatment options, including ipilimumab, which is similar to that which ipilimumab previously demonstrated over traditional chemotherapy (see Section 5.3).

Thus nivolumab offers an improved long-term survival to patients with advanced melanoma in the first-line setting. Nivolumab also offers a treatment option with proven survival benefit to patients in whom the use of current therapies is inappropriate, and to patients who fail to respond to current treatments.[81, 83]

The current treatment pathway for patients with advanced melanoma in England is depicted in Figure 5, and shows where nivolumab would fit into this pathway.

Figure 5: Treatment algorithm for patients with advanced (unresectable or metastatic) melanoma in NHS England and potential nivolumab positioning



Continuation of treatment with nivolumab

The patients enrolled in Phase III trials described in this submission demonstrating the clinical efficacy and safety of nivolumab monotherapy in advanced melanoma continued to receive study drug until their disease progressed, or they experienced unacceptable toxicity, as per protocol. UK and international expert clinical opinion has confirmed that for those patients who have responded to nivolumab, treat to progression will not be reasonable in routine clinical practice, and that stopping therapy at an appropriate time point should be considered.[11, 12] Based on available data from BMS' Phase I study Checkmate 003 (CA209-003) looking at various doses of nivolumab across a range of tumour types, including advanced melanoma, UK clinicians agreed that limiting the maximum duration of treatment could be supported. Checkmate 003 had a protocol specified stopping rule for discontinuation of therapy at 96 weeks (1.8 years). The majority of patients who achieved complete or partial response before 96 weeks, maintained their response. This treatment pattern is confirmed across all tumour types and all doses of nivolumab in Checkmate 003.

These data support a 2 year duration of therapy for nivolumab monotherapy particularly for patients who have a complete or partial response at this time.

The cost-effective analysis in this submission therefore assumes a 2 year maximum duration of therapy for nivolumab monotherapy. This is a conservative stopping point based on the clinical trial evidence that the majority of responses to nivolumab tend to occur relatively early, mostly within the first 24 weeks, after which their responses tend to be maintained. This assumption has also been validated extensively with UK and international melanoma clinicians in advisory board settings and 1:1 correspondence. Beyond two years it is expected that the majority of responding patients will continue to maintain response beyond discontinuation (see section 4.11).

3.3 Life expectancy, prevalence and incidence of the disease

Population estimates

Based on an incidence rate of 0.0211% in 2012[29] increasing at 3.5% per year[74] and a population size of 53,865,800[85] the expected 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.[86-88] Assuming the incidence of melanoma is still increasing at 3.5% per year[74], the expected number of new cases of advanced (unresectable or metastatic) 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[75], thus the expected number of relapsed cases of advanced (unresectable or metastatic) melanoma in England for 2016 is 273.

It is difficult to quantify the likely number of patients who would be treated with nivolumab rather than current treatment options if it is approved for use, considering the patient-specific treatment pathway (see Section 3.2). Market share estimates are provided in Section 6.

In order to satisfy the End of Life criteria (see Section 4.13), population estimates are required for all indications for which nivolumab is licensed. As mentioned previously in addition to its indication in advanced melanoma, nivolumab received concurrent marketing authorisation for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults (see Section 2.2).

Based on a population size of 53.9 million people in England and Wales, it is estimated that 27,300 patients will be diagnosed with NSCLC.[89] Of these patients approximately 19,138 are expected to be diagnosed with advanced or metastatic NSCLC[89], of whom approximately 36% will present with advanced or metastatic squamous NSCLC (6,822 patients).[90] It is estimated that 25% of these patients will receive first-line therapy (1,706 patients)[91], 50% of whom will fail and be eligible for second-line treatment.[92] Therefore, the likely number of patients in England and Wales with squamous NSCLC who will be eligible for second-line treatment with nivolumab will be around 853 in 2015.

Life expectancy

Life expectancy of advanced melanoma patients is historically poor and commonly estimated at less than 1 year from diagnosis (see Section 3.1). Whilst these survival statistics are expected to have improved with the recent introduction of new therapies, it is too early to assess their full impact (ipilimumab was only approved for use in the first-line setting in England in July 2014). A significant impact on median survival estimates is yet to be confirmed (and is indeed unlikely given the ipilimumab mechanism of action which results in notable long-term survival in approximately 20% of patients[51]).

In patients who have failed to respond to non-chemotherapy systemic treatment options, current life expectancy is not expected to have improved from historical estimates. If anything, by this stage of disease, patients ‘remaining’ life-expectancy may be even shorter.

In UK practice, median OS from the start of second-line therapy is reported to be markedly lower than median OS from the start of first-line therapy.[35]

3.4 Clinical guidance and guidelines

NICE guidance

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

- NICE Guidelines
    - July 2015. 'Melanoma: assessment and management'[93]
- NICE Guidance on Cancer Services
    - May 2010. 'Improving outcomes for people with skin tumours including melanoma'[94]
    - Feb 2006. 'Improving outcomes for people with skin tumours including melanoma: the manual'[95]
    - Mar 2004. 'Improving supportive and palliative care for adults with cancer. The manual'[96]
- NICE Public Health Guidance
    - Jan 2011.'Skin cancer prevention: information, resources and environmental changes'[97]
- NICE Clinical Guidance
    - Apr 2011. 'Referral guidelines for suspected cancer'[98]
    - Jul 2010, 'Metastatic malignant disease of unknown primary origin: diagnosis and management of metastatic malignant disease of unknown primary origin'[99]
- NICE Technology Appraisal Guidance
    - Oct 2014. 'Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma'. TA321[73]
    - Jul 2014. 'Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma'. TA319[4]
    - Dec 2012. 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'. TA268[75]
    - Dec 2012. 'Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma'. TA269[74]

Clinical guidelines

There are also a number of clinical guidelines relating to malignant melanoma:

- The National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology, melanoma 2015 (v3). National Comprehensive Cancer Network, Inc.[79]
- Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow up (2012)[78]
- Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline – Update 2012[13]
- Revised UK guidelines for the management of cutaneous melanoma 2010, British Association of Dermatologists (BAD)[100]
- Royal College of Physicians and BAD. The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. No 7. 2007[101]

- Cutaneous Melanoma. A national clinical guideline – No.72. Scottish Intercollegiate Guidelines Network (2003)[102]

3.5 Issues relating to current clinical practice

There are a number of issues with the advanced melanoma treatment options available in current practice. These have been touched upon previously and are summarised in Table 7. As a result, there are still a significant number of advanced melanoma patients for whom there are no effective treatment options available that provide the potential for long-term survival. This identifies a clear unmet medical 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[60, 65-69]
	• Long-term survival benefit not demonstrated[103]
	• Resistance to BRAF inhibitors has been observed[59, 60, 65]
	  ○ Progression thought to be due to the emergence of resistance often observed between 5-8 months post initiation[62-64]

Ipilimumab	• Long-term survival observed in 20% of patients[51] ○ Strongly correlated with induction completion[58, 104] • Typically slower response times[54, 55] than BRAF inhibitors[62, 63]
Chemotherapy (e.g. DTIC)	• Limited clinical benefit[23, 25, 33, 34] • No survival benefit[23, 25, 33, 34]
Key: DTIC, dacarbazine.	

3.6 Assessment of equality issues

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

4 Clinical effectiveness

Summary

- Despite significant advancements in therapeutics in recent years, durable response and long-term survival remains elusive for a broad range of patients with advanced melanoma
- An extensive clinical evidence base supports the use of nivolumab monotherapy at the licensed dose of 3mg/kg for the treatment of advanced melanoma:
    - CheckMate 066: pivotal Phase III RCT in previously untreated patients who have advanced melanoma without a BRAF mutation that investigates the clinical efficacy of nivolumab 3mg/kg monotherapy compared with DTIC monotherapy
    - 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 3mg/kg monotherapy compared with ipilimumab 3mg/kg monotherapy
    - CheckMate 037: pivotal Phase III RCT in previously treated patients who have advanced melanoma with or without a BRAF mutation that investigates the clinical efficacy of nivolumab 3mg/kg monotherapy compared with ICC
    - CheckMate 003: supportive Phase I dose-escalation study in previously treated patients with selected advanced solid tumours (including melanoma) with or without a BRAF mutation that provides long-term survival data for nivolumab monotherapy
- Nivolumab monotherapy provides an additional immuno-oncology treatment option, stimulating the body's own immune system to fight cancer cells
- Nivolumab is the first PD-1 checkpoint inhibitor to demonstrate long-term survival in a clinical trial setting (Phase I data)
- Extrapolated survival estimates from Phase III data suggest 45-50% of advanced melanoma patients treated with nivolumab 3mg/kg monotherapy are still alive 2 years after treatment initiation
- Nivolumab monotherapy was associated with high rates of rapid and durable clinical response, irrespective of BRAF status and treatment history
- Nivolumab has a predictable and medically manageable safety profile, with observed AEs mild and transient in the majority, irrespective of BRAF status and treatment history
- Contrary to conventional cytotoxic agents, nivolumab treatment did not result in reduced HRQL and was actually shown to potentially enhance HRQL whilst conferring survival benefit
- Nivolumab meets the current unmet medical needs in the advanced melanoma arena and, if recommended for routine use in the NHS in England, would represent a step-change in the management of this condition

4.1 Identification and selection of relevant studies

Search strategy

A systematic literature review designed to identify RCTs of nivolumab and comparator therapies used in the first-line treatment of advanced melanoma in adults was initiated in October 2014. A systematic literature review designed to identify RCTs of the same nature in the subsequent-line setting had previously been initiated in July 2014. These reviews were both updated and aligned to the decision problem of interest to NICE in May 2015.

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

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 (CENTRAL)
    - The Database of Abstracts of Reviews of Effects (DARE)
    - The Health Technology Assessment (HTA) database
- PubMed (searched for e-publications ahead of print)

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)
- The European Society for Medical Oncology (ESMO) (2012-2014)
- The Society for Immunotherapy of Cancer (SITC) (2012-2014)
- The Society for Melanoma Research (SMR) (2012-2014)

The search strategies used are provided in Appendix 2.

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

Study selection

The full eligibility criteria applied to the identified evidence base is presented in Table 8. Eligibility criteria applied in the original reviews were wider in scope than the eligibility criteria presented in Table 8 in regard to comparator agents of interest as these reviews were designed with a global perspective. In addition, these reviews were designed with a specific focus on line of therapy and studies with mixed patient populations (treatment naïve and treatment exposed) were excluded on this basis. Results of these reviews in regard to included studies and excluded studies on the basis of mixed patient populations were therefore reassessed against the eligibility criteria presented in Table 8 when the review was updated and aligned with the decision problem.

RCTs were included in the final evidence base of relevant studies if they investigated the clinical efficacy and/or safety of interventions currently used in the NHS (and thus named in the decision problem) for the treatment of advanced melanoma in adults. Studies investigating combination regimens, newer agents or palliative chemotherapy/palliative care

outside of palliative DTIC therapy were only included when compared with the interventions of relevance to the decision problem, as such regimens are not established care in the NHS.

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). Non-randomised and non-controlled evidence was identified independently as discussed in Section 4.11.

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
Interventions	Nivolumab 3mg/kg Ipilimumab 3mg/kg Dabrafenib 150mg Vemurafenib 960mg Dacarbazine	Combination regimens[a] Newer agents not approved for use in the NHS[a] Palliative care outside of dacarbazine chemotherapy[a]
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[b]	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], only included when comparing to the interventions of interest; [b], included for reference review only.

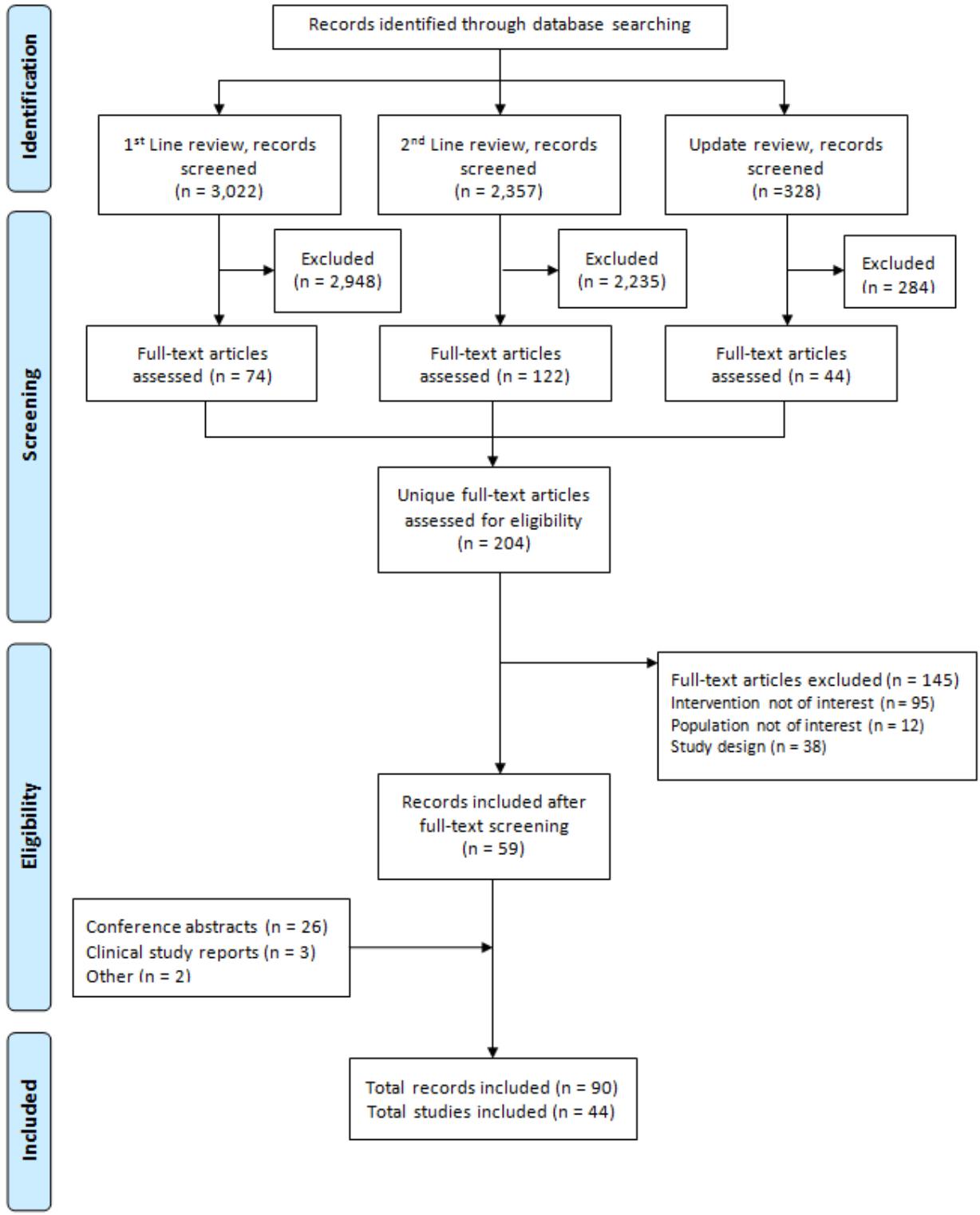
Two reviewers independently inspected each reference (title and abstract) identified by the literature searches and applied basic study selection criteria based on the eligibility criteria presented in Table 8 (primary screening). Citations meeting basic study selection criteria (or

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 PRISMA 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, which focused on the first- and subsequent-line setting, identified a total of 3,022 and 2,357 citations of potential relevance to the research question, respectively. Update searches of electronic databases identified an additional 328

citations of potential relevance to the research question. There was significant overlap between the results of these searches.

During independent primary screening of all searches, a total of 5,467 citations were excluded as they were clearly not of relevance to the research question. Common reasons for exclusion at this stage included non-advanced melanoma patient populations, investigations of regimens not of interest to the research question and non-RCT trial designs.

Across the three searches, a total of 204 unique citations were accessed in full (where applicable and necessary) for further evaluation. Of these citations, 40 were original publications of trials meeting the eligibility criteria of the review and a further 19 were secondary publications, providing additional data sources. In addition, conference proceedings searches identified 4 studies that were not reported in a full publication at the time of electronic database searches, and 22 abstracts that were associated with studies identified in the electronic database searches. A further 5 secondary sources of unpublished data were also included in the final evidence base: 3 clinical study reports held on file by BMS that provided data for nivolumab 3mg/kg monotherapy[105, 106]; and full publications of CheckMate 067[84] and CheckMate 069[107], identified within the systematic searches in abstract form, that became available post completion of electronic database searches.

A reference list of citations excluded at the secondary screening stage is provided in Appendix 5.

All sources of data for each study meeting the eligibility criteria presented in Table 8 are listed in Table 9.

Table 9: Data sources for included studies

Trial	Comparator(s)	Primary study reference	Secondary study reference(s)
Studies investigating nivolumab 3mg/kg monotherapy			
CheckMate 066 (CA209-066)	DTIC	Robert et al., 2015[82]	Long et al., 2015[108] Long et al., 2014[109] CheckMate 066 CSR[106]
CheckMate 067 (CA209-067)	Ipilimumab 3mg/kg Nivolumab 1mg/kg + ipilimumab 3mg/kg	Larkin et al., 2015[84]	Wolchok et al., 2015[110] CheckMate 067 CSR[111]
CheckMate 037 (CA209-037)	ICC (DTIC or carboplatin plus paclitaxel)	Weber et al., 2015[112]	Wang et al., 2015[113] D'Angelo et al., 2014[114] Weber et al., 2014[81] CheckMate 037 CSR[105]
Studies investigating ipilimumab 3mg/kg monotherapy			
CheckMate 069 (CA209-069)	Nivolumab 1mg/kg + ipilimumab 3mg/kg	Postow et al. 2015[107]	Abernethy et al., 2015[115] Hodi et al., 2015[116]
CA184-004	Ipilimumab 10mg/kg	Hamid et al., 2011[117]	-
CA184-022	Ipilimumab 0.3mg/kg Ipilimumab 10mg/kg	Wolchok et al. 2010[118]	-
MDX010-08	Ipilimumab 3mg/kg + DTIC	Hersh et al., 2011[119]	-
MDX010-20	Ipilimumab 3mg/kg + gp-100 gp-100	Hodi et al., 2010[55]	McDermott et al., 2013[120] Revicki et al. 2012[38]

Trial	Comparator(s)	Primary study reference	Secondary study reference(s)
Studies investigating dabrafenib 150mg monotherapy			
BREAK-3	DTIC	Hauschild et al., 2012[63]	Grob et al., 2014[121] Hauschild et al., 2014[122] Hauschild et al., 2013[123] Latimer et al., 2013[124] Grob et al., 2012[125]
COMBI-d	Dabrafenib + trametinib	Long et al., 2014[126]	Long et al., 2015[127] Schadendorf et al., 2015[128] Latimer et al., 2014[129] Long et al., 2014[130] Schadendorf et al., 2014[131]
NCT01072175	Dabrafenib + trametinib	Flaherty et al. 2012[132]	Daud et al., 2015[133] Menzies et al., 2015[134] Flaherty et al., 2014[135] Johnson et al., 2014[136] Long et al., 2012[137]
Studies investigating vemurafenib 960mg monotherapy			
BRIM-3	DTIC	Chapman et al., 2011[62]	Zabor et al., 2015[138] McArthur et al., 2014[139] Hauschild et al., 2013[103] McArthur et al., 2012[140]
COMBI-v	Dabrafenib + trametinib	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., 2014[147]
Grippo et al., 2014	Vemurafenib 240mg Vemurafenib 480mg Vemurafenib 720mg	Grippo et al., 2014[148]	-
Studies investigating DTIC monotherapy			
AGENDA	DTIC + oblimersen	Bedikian et al., 2014[149]	-
CA033	*Nab*-paclitaxel	Hersh et al., 2012[150]	Hersh et al., 2014[151] Hersh et al., 2013[152]
CA184-024	Ipilimumab 10mg/kg + DTIC	Robert et al., 2011[54]	Maio et al., 2015[153] Maio et al., 2013[154] Sherrill et al. 2013[155] Maio et al., 2012[156]
NCT00005052	Temozolomide	Patel et al., 2011[157]	-
NCT00779714	Paclitaxel + cisplatin or treosulfan + gemcitabine	Ugurel et al., 2015[158]	-

Trial	Comparator(s)	Primary study reference	Secondary study reference(s)
NCT01359956	DTIC + fotemustine DTIC + IFNα DTIC + fotemustine + IFNα	Daponte et al., 2013[159]	-
Avril et al., 2004	Fotemustine	Avril et al., 2004[160]	Hauschild et al. 2002[161]
Bajetta et al., 1994	DTIC + IFNα	Bajetta et al., 1994[162]	-
Bedikian et al., 2011	DHA-paclitaxel	Bedikian et al., 2011[163]	-
Carter et al. 1975	DTIC + CCNU + VCR DTIC + BCNU + VCR DTIC + BCNU + hydroxyurea	Carter et al. 1975[164]	-
Chapman et al. 1999	DTIC + cisplatin + carmustine + tamoxifen	Chapman et al. 1999[165]	-
Chauvergne et al. 1982	DTIC + detorubicin	Chauvergne et al. 1982[166]	-
Chiarion-Sileni et al., 2001	DTIC + carmustine + cisplatin + tamoxifen	Chiarion-Sileni et al., 2001[167]	-
Cocconi et al. 1992	DTIC + tamoxifen	Cocconi et al. 1992[168]	-
Costanza et al., 1976	TIC mustard	Costanza et al., 1976[169]	-
Costanza et al., 1977	Methyl-CCNU	Costanza et al., 1977[170]	-
Cui et al. 2013	DTIC + endostar	Cui et al. 2013[171]	-
Falkson et al., 1991	DTIC + IFNα	Falkson et al., 1991[172]	-
Falkson et al., 1995	DTIC + IFNα	Falkson et al., 1995[173]	-
Falkson et al., 1998	DTIC + IFNα	Falkson et al., 1998[174]	-
Fiedler et al. 1990	DTIC + VCR + ftorafur + hydroxycarbamide	Fiedler et al. 1990[175]	-
Hill et al. 1979	DTIC + CCNU + VCR DTIC + BCNU + VCR	Hill et al. 1979[176]	-
Luikart et al., 1984	Vinblastine + bleomycin + cis-dichlorodiammine-platinum	Luikart et al., 1984[177]	-
Middleton et al., 2000	Temozolomide	Middleton et al., 2000[178]	Kiebert et al., 2003[179]
Middleton et al. 2007	IL-2 + IFNα + HDC	Middleton et al. 2007[180]	-
O'Day et al.,	Intetumumab	O'Day et al., 2011[181]	-

Trial	Comparator(s)	Primary study reference	Secondary study reference(s)
2011	DTIC + intetumumab		
Ringborg et al. 1989	DTIC + vindesine	Ringborg et al. 1989[182]	-
Thomson et al., 1993	DTIC + IFNα	Thomson et al., 1993a[183]	Thomson et al. 1993b[184]
Young et al., 2001	DTIC + IFNα	Young et al., 2001[185]	-
Key: BCNU, carmustine; CCNU, lomustine; DHA, docosahexaenoic acid; DTIC, dacarbazine; HDC, histamine dihydrochloride; ICC, investigator's choice chemotherapy; gp-100, glycoprotein-100; IFNα, interferon-alpha; IL-2, interleukin-2; kg, kilogram; mg, milligram; TIC, triazeno imidazole carboxamide; VCR, vincristine.			

4.2 List of relevant randomised controlled trials

There are three pivotal Phase III RCTs that provide evidence on the clinical benefit of nivolumab 3mg/kg monotherapy within the indication being appraised, as shown in Table 10.

In CheckMate 066, DTIC was chosen as the relevant comparator as, until the recent approval of ipilimumab, DTIC was the most common first-line therapy used to treat patients with advanced melanoma without a BRAF mutation.[82]

The more recently initiated CheckMate 067 includes a direct comparison of nivolumab to ipilimumab, which is a more appropriate comparator in this population in UK current practice (see Section 3.2). CheckMate 067 enrolled patients with advanced melanoma regardless of BRAF mutation status, thus a proportion of patients had BRAF mutation-positive melanoma that may also be treated with BRAF inhibitor therapies in clinical practice (see Section 3.2). No head-to-head data are available comparing nivolumab with BRAF inhibitor therapy; their comparative efficacy has therefore been estimated using indirect comparison methods (see Section 4.10 and Section 5.3).

In CheckMate 037, DTIC or carboplatin plus paclitaxel could be administered as part of an ICC treatment group. This allowed patients who had previously received DTIC (or paclitaxel/carboplatin), and whose melanoma had progressed, to receive a different chemotherapeutic agent. This gave the trial clinicians a degree of flexibility in treating patients who had previously received chemotherapy, but who had progressed on that chemotherapy.

Table 10: List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
CheckMate 066	Advanced (unresectable or metastatic) melanoma patients who are treatment naïve and BRAF mutation-negative (wild-type).	Nivolumab 3mg/kg q2w	DTIC 1000mg/m^2 q3w	Robert et al. 2015[82]
CheckMate 067	Advanced (unresectable or metastatic) melanoma patients who are treatment naïve.	Nivolumab 3mg/kg q2w	Ipilimumab 3mg/kg q3w Nivolumab 1mg/kg + ipilimumab 3mg/kg q3w	Larkin et al. 2015[84]
CheckMate 037	Advanced (unresectable or metastatic) melanoma patients who have progressed on or after prior anti-CTLA-4 therapy and, if BRAF mutation-positive, BRAF inhibitor therapy.	Nivolumab 3mg/kg q2w	ICC: DTIC 1000mg/m^2 q3w **or** Carboplatin AUC6 + paclitaxel 175mg/m^2 q3w	Weber et al. 2015[112]
Key: AUC, area under the curve; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DTIC, dacarbazine; ICC, investigator's choice chemotherapy; kg, kilogram; m, metre; mg, milligram; RCT, randomised controlled trial; q2w, every 2 weeks; q3w, every 3 weeks.				

In addition to the published primary study references, data are taken from the clinical study reports for each of the trials. Data from CheckMate 066, CheckMate 067 and CheckMate 037 have also been presented at the following conferences:

CheckMate 066:

- Long 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). Presented at ASCO 2015.[108]
- Long et al. Nivolumab improved survival vs dacarbazine in patients with untreated advanced melanoma. Presented at SMR 2014.[109]

CheckMate 067:

- 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.[110]

CheckMate 037:

- Wang et al. Characterization of exposure-response (E-R) relationship for nivolumab in subjects with advanced melanoma progressing post anti-CTLA4. Presented at ASCPT 2015.[113]
- D'Angelo et al. Efficacy and safety of nivolumab vs investigator's choice chemotherapy (ICC) in subgroups of patients with advanced melanoma after prior anti-CTLA-4 therapy. Presented at SMR 2014.[114]
- Weber et al. A phase 3 randomized, open-label study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus investigator's choice chemotherapy (ICC) in patients with advanced melanoma with prior anti-CTLA-4 therapy. Presented at ESMO 2014.[81]

4.3 Summary of methodology of the relevant randomised controlled trials

A comparative summary of the methodology of the RCTs is presented below and summarised in Table 11.

CheckMate 066

CheckMate 066 was a Phase III, multicentre, double-blind RCT conducted to determine whether nivolumab, compared with DTIC, improves OS among previously untreated patients who have advanced melanoma without a BRAF mutation.[82, 106]

CheckMate 066 was initiated on 18 January 2013. In response to a recommendation from the data monitoring committee (DMC), the CheckMate 066 study protocol was amended on 10 June 2014 to allow patients randomised to the DTIC group who were not benefitting from treatment to be offered the option of crossing over to receive treatment with nivolumab. This recommendation came after the results of an analysis of a DMC-requested database lock (23 May 2014) that showed clear evidence of a survival benefit in patients receiving nivolumab (see Section 4.7). As a result of the DMC recommendations, all study patients were unblinded, allowing those who were not benefiting from DTIC treatment to receive nivolumab therapy in an extension phase.

The data presented in this submission are based on the most recent database lock, dated 5 August 2014. At this time, no data on patients randomised to DTIC and treated with nivolumab post study drug discontinuation were available; therefore, the results of the DTIC arm reported in Section 4.7 are not confounded by subsequent nivolumab use.

CheckMate 067

CheckMate 067 is a Phase III, multicentre, double-blind RCT conducted to evaluate the safety and efficacy of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy.[84, 111]

CheckMate 067 was initiated on 11 June 2013, and the study is currently ongoing. Data presented in this submission are based on a clinical database lock of 17 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 (at least 22 months follow-up are required). Results for progression-free survival (PFS) and objective response rate (ORR) are available and presented in Section 4.7; analyses of HRQL are not available at this time.

As the focus of this submission is on nivolumab monotherapy (in accordance with its current licence terms), results are presented for nivolumab monotherapy and its direct comparator, ipilimumab monotherapy, in Section 4.7. The results of the nivolumab and ipilimumab combination arm are not presented, as they are not the subject of this submission. Nivolumab in combination with ipilimumab is not currently licensed, and will be the subject of a future NICE single technology appraisal (STA), anticipated early in 2016.

CheckMate 037

CheckMate 037 is a Phase III, multicentre, open-label RCT designed to evaluate nivolumab monotherapy versus ICC in advanced melanoma patients who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor in addition to anti-CTLA-4-therapy.[105, 112] ICC consisted of either DTIC or carboplatin plus paclitaxel.

CheckMate 037 was initiated on 21 December 2012, and this study is currently ongoing. Data presented in this submission are based on the most recent clinical database lock date of 30 April 2014 and an independent radiology review committee (IRRC) database lock date of 20 May 2014. The imaging cut-off date for this database lock was 10 March 2014.

The results for ORR, one of the two co-primary endpoints of the study, and descriptive PFS are available and are presented in this submission (see Section 4.7). Analyses of HRQL are not yet available. In December 2014, an interim ad-hoc analysis of OS, the second co-primary endpoint for Checkmate 037, was performed in response to a specific request from the CHMP. The results of this analysis are published in the full EPAR.[9]

At the time of this interim ad hoc analysis, the survival data remained immature, due to insufficient follow up. Only 70% [182/260] of the pre-specified number of events (deaths) required for final OS analysis had occurred at the time of data extraction (database lock 12th November 2014).

In addition to data immaturity and insufficient number of events, several other factors may have confounded the OS results observed in this interim ad hoc analysis, including: the large number of patients who were randomised to the ICC arm, but dropped out of the study early to pursue alternative treatment options; and the high proportion of patients in the ICC arm (31.6% [42/133]) who received subsequent systemic therapy compared to only 5.5% in the nivolumab arm. Preliminary OS data showed a median OS of 15.5 months for the nivolumab group vs 13.7 months in the ICC group (Hazard Ratio of 0.93, [CI95 0.68-1.26]).

In accordance with the study protocol for Checkmate 037, the final analysis of the OS co-primary endpoint will be performed in the treated population when the number of events (deaths) reaches 260. This analysis is expected to occur towards the end of 2015.

Across all three 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 which were immune-related and potentially associated with the use of nivolumab (these were termed

‘Select AEs’). All trials were conducted in accordance with good clinical practice (GCP) by qualified investigators using a single protocol to promote consistency across sites.

Of note, in all the trials, patients treated with nivolumab therapy 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 that shows some patients treated with immune system stimulating agents develop disease progression, as defined by conventional response criteria, before demonstrating subsequent clinical objective responses and/or stable disease (see Section 2.1). In clinical practice, response is not assessed against as strict criteria based on radiological data as it is in clinical trials; rather it is based on a more general assessment of clinical benefit. The design of the CheckMate trials therefore reflects how clinicians would act in practice.

It is also important to note that progression assessments of immuno-oncology therapies against RECIST criteria for tumour progression in clinical trials are therefore a conservative estimate of progression compared to clinical practice assessment of immune-oncology treatment effect.

Table 11: Comparative summary of RCT methodology

	CheckMate 066	CheckMate 067	CheckMate 037
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 treated across 137 sites in Australia, Europe, Israel, New Zealand and North America	Patients were treated across 78 sites in Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, the Netherlands, Spain, Switzerland, US and UK
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 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 III, randomised, open-label, active-controlled, multi-centre clinical trial Patients were randomised in a 2:1 ratio through an IVRS. Randomisation was stratified by PD-L1 status, BRAF mutation status and prior anti-CTLA-4 best response Patients and investigators were not blinded to treatment assignment; outcome assessors were blinded to treatment assignment
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 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	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	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 • PD-L1-positive, PD-L1-negative or PD-L1-intermediate classification according to recent biopsy from an unresectable or metastatic site • objective evidence of progressive disease during or after anti-CTLA-4 therapy and any other treatment regimen received for advanced melanoma if BRAF mutation-negative • objective evidence of progressive

	CheckMate 066	CheckMate 067	CheckMate 037
	• 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 pathways	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 pathways	disease during or after anti-CTLA-4 therapy and BRAF inhibitor therapy for advanced melanoma (in any sequence or in any combination) if BRAF mutation-positive • prior chemotherapy or immunotherapy completed ≥4 weeks before study drug administration and all AEs returned to baseline or stabilised • prior anti-CTLA-4 therapy completed at least 6 weeks before study drug administration • prior radiotherapy completed at least 2 weeks prior to first dose of 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 the study eligibility criteria: • active brain metastases or leptomeningeal metastases • ocular melanoma • patients whose melanoma BRAF status was unknown • 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-

	CheckMate 066	CheckMate 067	CheckMate 037
			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 except for anti-CTLA-4 therapy • prior systemic melanoma therapy with both DTIC and carboplatin and paclitaxel • patients with previous malignancies[a] were excluded • patients with a known history of pre-specified anti-CTLA-4 therapy related AEs
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.	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 group (n=210): nivolumab 3mg/kg q2w by IV infusion plus a DTIC-matched placebo q3w by IV infusion DTIC group (n=208): DTIC 1000mg/m^2 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	Nivolumab group (n=316): nivolumab 3mg/kg q2w by IV infusion plus an ipilimumab placebo Ipilimumab group (n=315): ipilimumab 3mg/kg q3w by IV infusion plus a nivolumab placebo Combination group (n=314): nivolumab 1mg/kg plus ipilimumab 3mg/kg q3w by IV infusion	Nivolumab group (n=272): nivolumab 3mg/kg q2w by IV infusion ICC group (n=133): DTIC 1000mg/m^2 q3w by IV infusion or carboplatin AUC6 plus paclitaxel 175mg/m2 q3w by IV infusion Patients in the ICC group were treated with a regimen that they had not previously received as therapy for metastatic melanoma Treatment continued until there was disease

	CheckMate 066	CheckMate 067	CheckMate 037
	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 DTIC were permitted to cross-over to nivolumab therapy post progression in accordance with a DMC-recommended protocol amendment Dose escalations were not permitted. Dose reductions were permitted for DTIC 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)	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)	progression or discontinuation due to toxicity or any other reason. Treatment after disease progression was permitted for patients in the nivolumab group who had a clinical benefit and were tolerating treatment, as determined by the investigator Patients who received ICC were not permitted to cross-over to nivolumab therapy or to be treated beyond progression Dose escalations were not permitted. Dose reductions were permitted for ICC 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)
Permitted and disallowed concomitant medication	Antiemetic premedications were administered prior to dosing of DTIC or DTIC-matched placebo. 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.	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	Antiemetic premedications were not routinely administered Immunosuppressive agents, immunosuppressive doses of systemic corticosteroids, non-palliative radiation therapy or antineoplastic therapy and surgical resection of lesions were prohibited during the study. Palliative radiation therapy was permitted if the patient was considered to have progressive disease at the time of palliative therapy, met the criteria to continue treatment beyond progression and the case was discussed with the medical monitors.

	CheckMate 066	CheckMate 067	CheckMate 037
		allergen) was allowed.	
Primary outcomes	OS: defined as the 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.	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: defined as the number of patients with a BOR of CR or PR divided by the number of randomised patients. IRRC-and investigator-assessed. Performed when the first 120 patients treated with nivolumab have a minimum follow-up of 6 months. OS: defined as the time between the date of randomisation and the date of death. Tumour response was assessed according to the RECIST, version 1.1. Tumour assessments began 9 weeks (±1 week) from randomisation 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. Assessments for survival were performed continuously during treatment and every 3 months during follow-up.
Secondary outcomes	PFS: defined as the time from randomisation to the date of the first documented progression or death due to any cause. Investigator-assessed ORR: defined as the number of patients with a BOR of CR or PR divided by the number of randomised patients. Investigator-assessed 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	ORR: defined as the number of patients with a BOR of CR or 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: 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 Tumour response was assessed according to the RECIST, version 1.1. Tumour	TTR: defined as the time from randomisation to the date of the first documents response (CR or PR). IRRC- and investigator-assessed DOR: defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression (including death). IRRC- and investigator-assessed. PFS: defined as the time from randomisation to the date of the first documented progression or death due to any cause. IRRC- and investigator-assessed

	CheckMate 066	CheckMate 067	CheckMate 037
	Tumour response was assessed according to the RECIST, version 1.1. Tumour assessments began 9 weeks (±1 week) from randomisation 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 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	assessments began 12 weeks (±1 week) from randomisation 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 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	Efficacy based on PD-L1 expression level: defined as ORR, OS, PFS and/or AE 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
Key exploratory outcomes	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 DOR: defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression (including death). Investigator-assessed TTR: defined as the time from randomisation to the date of the first documented response (CR or PR). Investigator-assessed 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	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 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	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. HRQL: measured by mean changes from baseline in health status, assessed using the EQ-5D tool.

	CheckMate 066	CheckMate 067	CheckMate 037
Pre-planned subgroups	Subgroup analyses assessing the impact of age, gender, race, region, baseline ECOG PS, PD-L1 expression status, M stage at study entry, history of brain metastases, smoking status, baseline LDH, AJCC stage, or prior neo-adjuvant or adjuvant therapy on clinical efficacy outcomes were pre-planned. Subgroup analyses assessing the impact of age, gender, race and region on frequency of AEs regardless of causality were also pre-planned.	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 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, AJCC stage and prior anti-CTLA-4 benefit on clinical efficacy outcomes were pre-planned. Subgroup analyses assessing the impact of age, gender, race and region on frequency of AEs regardless of causality were also pre-planned.

Key: AE, adverse event; AJCC, American Joint Committee on Cancer; AUC, area under the curve; 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; DTIC, dacarbazine; 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; HRT, hormone replacement therapy; ICC, investigator's choice chemotherapy; IRRC, independent radiological review committee; IV, intravenous; IVRS, interactive voice response system; kg, kilogram; LDH, lactate dehydrogenase; m, metre; mg, milligram; n, number; 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; RANK-L, Receptor activator of nuclear factor kappa-B ligand; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; TTR, time to treatment response; UK, United Kingdom; US, United States; WPAI:GH, Work Productivity and Activity Impairment Questionnaire: General Health.
Notes: [a], except non-melanoma skin cancers, in situ bladder cancer, gastric or colon cancers, cervical cancers/dysplasia, or breast carcinoma in situ or unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy was anticipated to be required during the study period.
Source: CheckMate 066 CSR[106]; CheckMate 067 CSR[111]; CheckMate 037 CSR[105]; Larkin et al., 2015[84]; Robert et al., 2015.[82]; Weber et al., 2015[112]

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 066, CheckMate 067 and CheckMate 037 are presented in Table 12.

CheckMate 066

The primary datasets used in CheckMate 066 were the all randomised population (intention-to-treat [ITT] population) for primary efficacy analysis and the all treated population for the safety analyses.[82, 106] Response outcomes were assessed on the response-evaluable population, defined as all randomised patients with at least one on-treatment tumour assessment. Censoring methods were used to take account of missing data in primary OS analysis. HRQL analysis was performed in all patients who had a baseline assessment and at least one follow-up assessment.

At the time of the CheckMate 066 database lock for analysis presented in this submission, 146 deaths were observed. The boundary for statistical significance was calculated based on the Lan-DeMets alpha spending function with O'Brien-Fleming type boundaries and required the unadjusted log rank p-value to be less than 0.0021 to conclude OS benefit for nivolumab relative to DTIC. The corresponding CI is 99.79% [(1-.0021)*100%]. As this study was stopped early (due to the overwhelming clinical benefit shown by nivolumab vs DTIC), the requirement for reporting survival and progression-free survival (PFS) rates was not met; that is, the study analysis took place before the earliest planned time point (6 months). Nevertheless, OS and PFS rates at 6 and 12 months have been produced (see Section 4.7).

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.[84, 111] Response outcomes were assessed on the response-evaluable population, defined as all randomised patients with at least one on-treatment tumour assessment. Censoring methods will be used to take account of missing data in primary OS analysis and were used to take account of missing data in secondary PFS analysis available at this time.

CheckMate 037

The primary datasets used in CheckMate 037 were the per-protocol (PP) objective response population for primary efficacy analysis, defined as all patients who received at least one dose of treatment and had at least 6 months of follow-up at the time of the ORR analysis, and the all treated population for safety analyses.[105, 112] The primary analysis of ORR was performed when the first 120 patients treated with nivolumab (i.e. approximately 180 treated patients in total: 120 in the nivolumab group and 60 in the investigator's choice group) had a minimum follow-up of 6 months, and formal analysis was restricted to the patients treated with nivolumab with at least 6 months of follow-up.

The proportion of patients with an objective response in the ITT population was also analysed at this interim time point (ITT objective response population) and a descriptive interim PFS analysis was conducted on an ITT basis (ITT objective response population).

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 066	Treatment with nivolumab will improve OS when compared to DTIC in patients with previously untreated, unresectable or metastatic melanoma	Time to event distributions (OS, PFS, DOR, TTR) were estimated using KM techniques. When appropriate, the median along with 95% CI were estimated based on Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Rates at fixed time points (e.g. OS at 12 months) were derived from the KM estimate along with their corresponding log-log transformed 95% CIs. CIs for binomial proportions were derived using the Clopper–Pearson method OS and PFS were compared between the two treatment groups using a two-sided, log-rank test stratified by PD-L1 status and M stage. The HR of nivolumab to dacarbazine and the corresponding CIs were estimated using a stratified Cox proportional hazards model ORR was compared between the two treatment groups using a two-sided, CMH test stratified by PD-L1 status and M stage. An associated OR and 95% CI were calculated. An estimate of the difference in ORRs and corresponding 95% CI were to be calculated using CMH methodology and adjusted by the same stratification factors P-values other than those provided for the OS primary analysis and the hierarchical analysis of key secondary endpoints are for descriptive purpose only and not adjusted for multiplicity.	A sample of approximately 410 patients, randomly assigned in a 1:1 ratio to the two treatment groups was planned The study design required at least 312 deaths to ensure approximately 90% power to detect a HR of 0.69 with an overall type I error of 0.05 (two-sided). The HR of 0.69 corresponds to a 45% increase in the median OS, assuming a median OS of 10 months for dacarbazine and 14.49 months for nivolumab The stopping boundaries at the interim and final analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. It was projected that an observed HR of 0.7966 or less, corresponding to 2.6 months or greater improvement in median OS (10 months versus 12.6 months), would result in a statistically significant improvement in OS for nivolumab at the final analysis	For patients without documentation of death, OS was censored on the last date the patient was known to be alive. 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 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	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 each OS comparison, at least 460 events in the two respective treatment arms were 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 Assuming the distribution of events follows the alternative hypothesis, approximately 247 events in the control group and 213 in each of the experimental groups are expected It was projected that an observed HR of 0.8114 or less, corresponding to 3.3 months or greater improvement in median OS (14 vs 17.3 months) for each comparison, would result in a statistically significant improvement in the final analysis of OS	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
CheckMate 037	The administration of nivolumab provides meaningful clinical activity as measured by ORR and/or increased OS compared with the administration of ICC in	Discrete variables were tabulated by the frequency and proportion of patients falling into each category. Percentages reported in tables were rounded and, therefore, may not always sum to 100% Continuous variables were summarised using the mean, SD, median, minimum and maximum	A sample of approximately 390 subjects, randomly assigned in a 2:1 ratio to the two treatment groups was planned This sample size accounts for the co-primary efficacy endpoints: ORR (per IRRC) and OS with an alpha allocation	For non-responders, TTR was censored at the maximum time of response + 1 day of all subjects in their respective treatment group

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	patients with advanced melanoma who have progressed on anti-CTLA-4 therapy, and, if BRAF V600 mutation-positive, to also have progressed on a BRAF inhibitor	values Time to event distributions (e.g. PFS, DOR, TTR) were estimated using KM techniques. When appropriate, the median, along with 95% CIs, were estimated based on Brookmeyer and Crowley methodology (using log-log transformation for constructing the CIs) CIs for binomial proportions were derived using the Clopper–Pearson method The difference in the rates between the two treatment arms along with their two-sided 95% CI was estimated using the Newcombe approach To investigate ORR in different subsets, a "forest" plot of the IRRC-determined unweighted differences in ORR and the corresponding 95% CIs using the method of Newcombe were produced	of 0.1% and 4.9%, respectively The maximum width of the exact two-sided 95% CI was 17.1% when the ORR was expected to be in the 5% to 30% range The study design requires at least 260 deaths to ensure approximately 90% power to detect a HR of 0.65, corresponding to a median OS of 8 vs 12.3 months (4.3 month difference) for the ICC and nivolumab groups, respectively, with an overall two-sided type I error of 4.9% The stopping boundaries at the interim and final OS analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis of OS is performed at exactly 169 events, the study could be stopped for efficacy if the p-value is less than 0.0105. The nominal significance level for the final OS after 260 events would then be 0.0457	

Key: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; DOR, duration of response; DTIC, dacarbazine; HR, hazard ratio; ICC, investigator's choice chemotherapy; IRRC, independent radiological review committee; KM, Kaplan–Meier; M, metastasis; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SD, standard deviation; TTR, time to treatment response.
Source: CheckMate 066 CSR[106]; CheckMate 067 CSR[111]; CheckMate 037 CSR[105]; Larkin et al., 2015[84]; Robert et al., 2015[82]; Weber et al., 2015[112]

4.5 Participant flow in the relevant randomised controlled trials

Participant flow

CheckMate 066

Of 583 patients who enrolled in CheckMate 066, 418 patients were randomised (210 to nivolumab and 208 to DTIC), and 411 patients were treated (206 with nivolumab and 205 with DTIC).[82, 106] The seven patients not treated did not receive the study drug because they failed to meet study eligibility criteria, withdrew consent, were not compliant or had an AE preventing them from starting treatment.

At the time of the database lock, 108 (26.3%) patients were continuing treatment, with a higher proportion of patients in the nivolumab group continuing treatment compared with the DTIC group (46.1% vs 6.3%). The main reason, in both groups, for not continuing treatment was disease progression (nivolumab 46.6% and the DTIC 85.4%).

Participant flow for CheckMate 066 is presented as a Consolidated Standards of Reporting Trials (CONSORT) diagram in Figure 7.

CheckMate 067

Of the 1,296 patients who enrolled in CheckMate 067, 316 patients were randomised to nivolumab and 315 patients were randomised to ipilimumab.[84, 111] A further 314 patients were randomised to combination treatment, but as these are not relevant to this submission, they are not discussed further. Three nivolumab randomised patients and four ipilimumab randomised patients withdrew from the study before starting treatment.

At the time of the current database lock, 117 of 313 (37.0%) patients randomised to nivolumab were continuing treatment. The most frequent reason for discontinuation was disease progression (49.2%). In the ipilimumab group, 50 of 311 (15.9%) patients randomised to ipilimumab were continuing in the treatment period of the study. Again, the most frequent reason for discontinuation was disease progression (65.0%).

Participant flow for CheckMate 067 is presented as a CONSORT diagram in Figure 8.

CheckMate 037

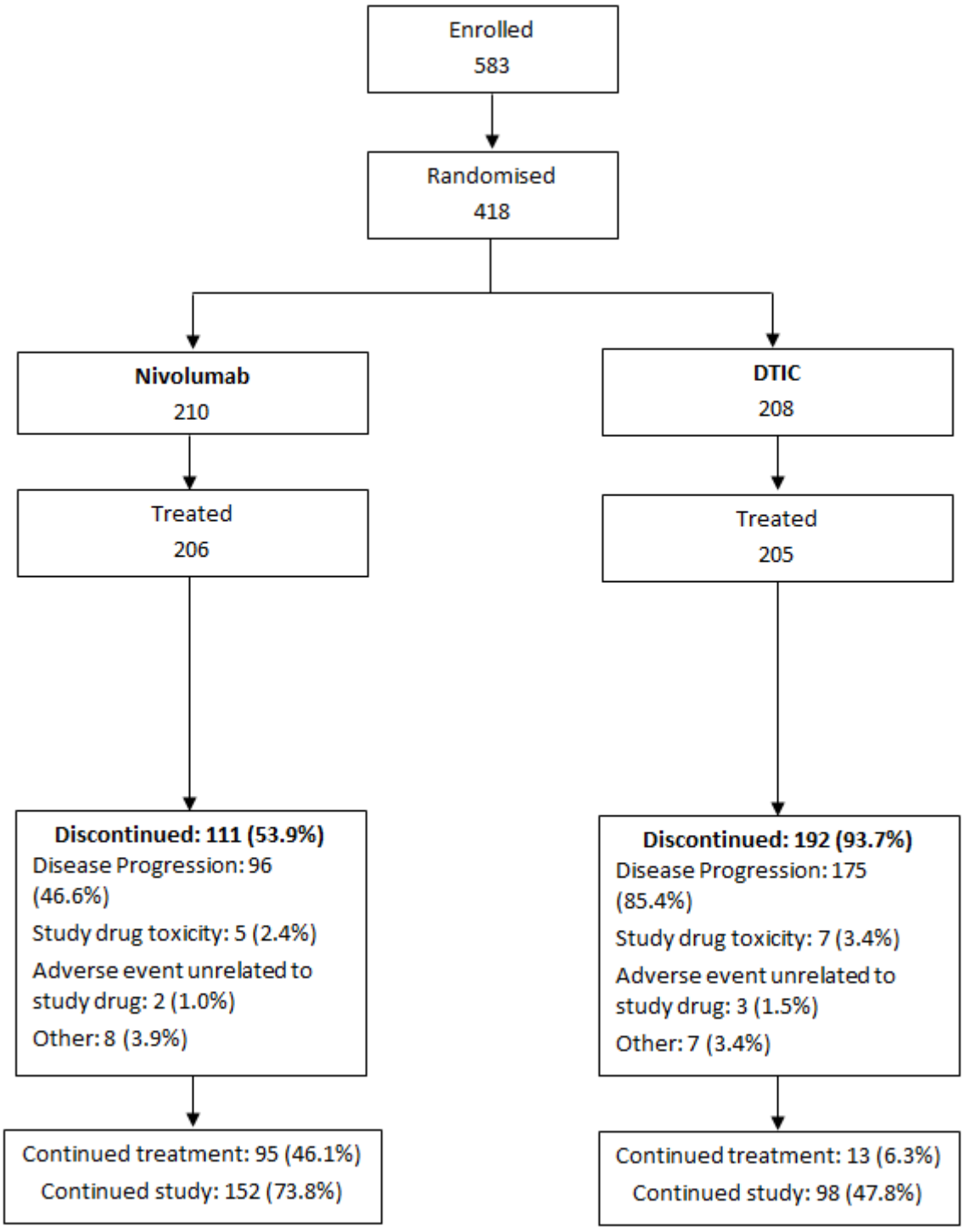
Of the 631 patients who enrolled in CheckMate 037, 405 patients were randomised (272 to nivolumab and 133 to ICC), and 370 patients were treated (268 with nivolumab and 102 with ICC).[105, 112] The most common reason for not being treated was no longer meeting study criteria (2 patients) in the nivolumab group and consent withdrawal (22 patients) in the ICC group.

At the time of the current database lock, 147 (39.7%) patients were continuing treatment in the study, with a higher proportion of patients in the nivolumab group (48.1%) continuing treatment compared with the ICC group (17.6%). The main reason for not continuing treatment in both groups was disease progression (nivolumab 43.3% and ICC 60.8%).

Of all randomised patients, 182 were included in the objective response population for which results are available at this time. Of the 182 patients randomised in the objective response population, 120 were treated with nivolumab and 47 were treated with ICC.

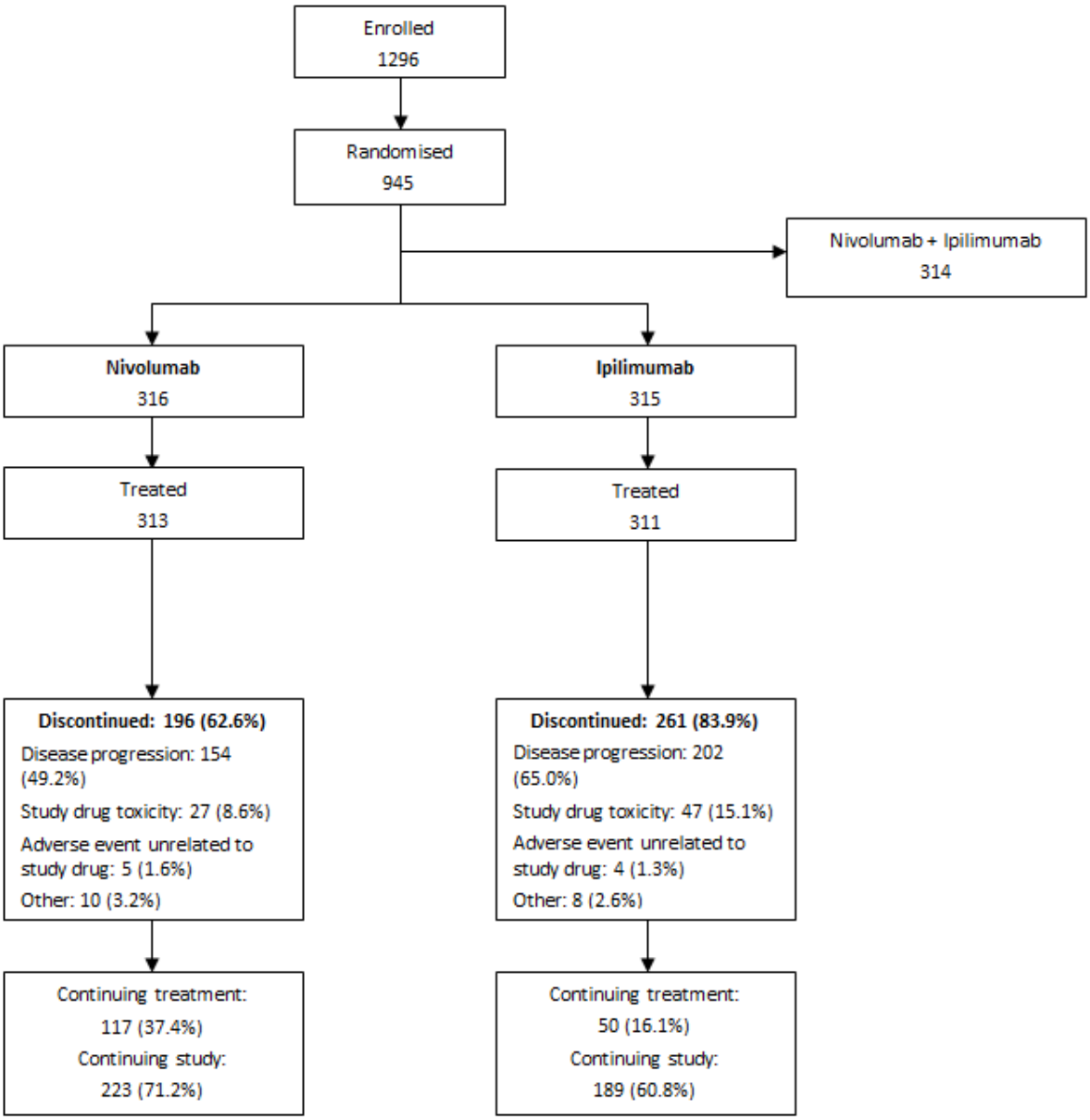
Participant flow for CheckMate 037 is presented as a CONSORT diagram in Figure 9.

Figure 7: CONSORT diagram of participant flow at the time of the current database lock in CheckMate 066



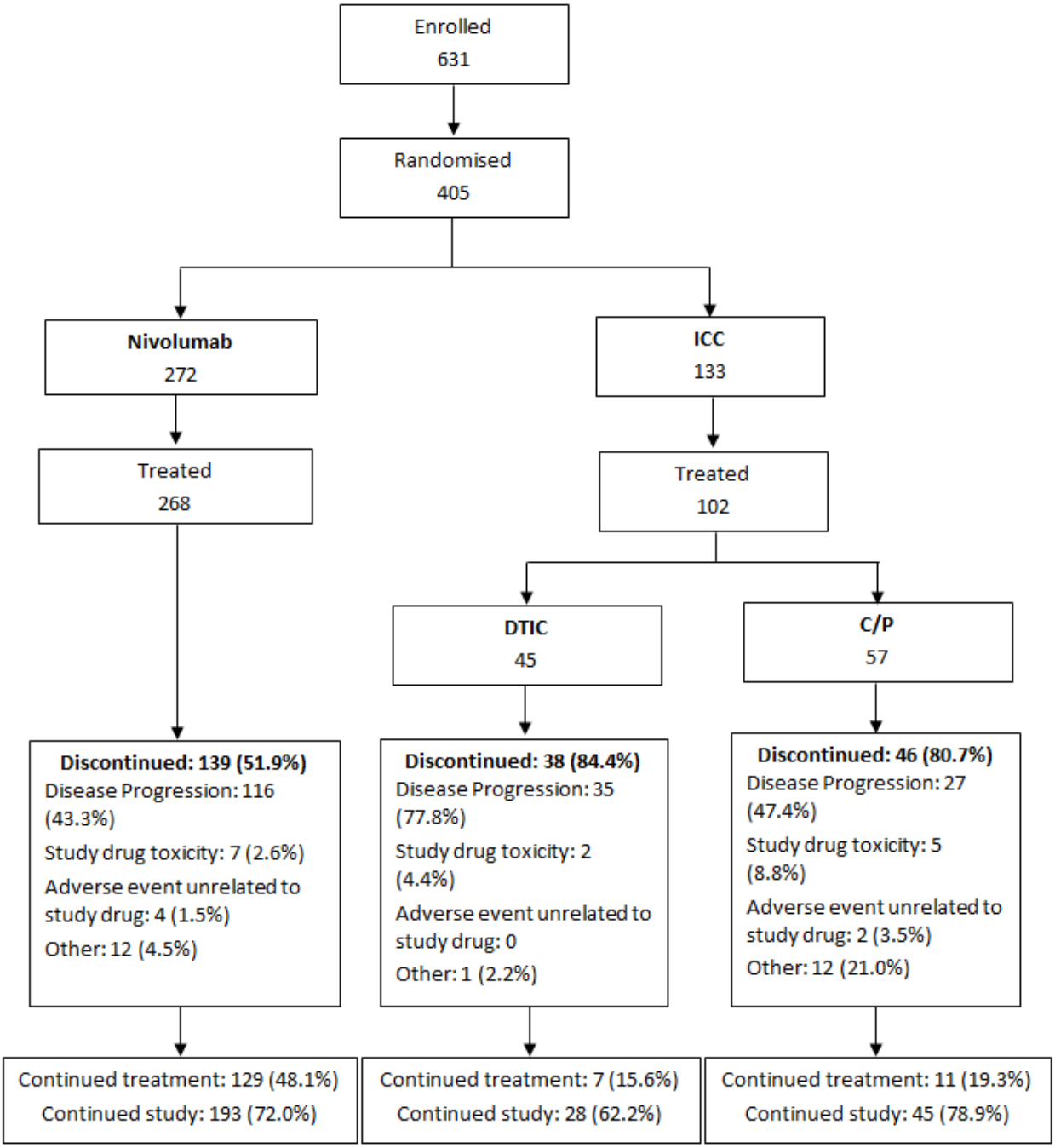
Key: CONSORT, Consolidated Standards of Reporting Trials; DTIC, dacarbazine.
Notes: Continuing treatment means patients are continuing to receive study drug; continuing study means patients have discontinued study drug but are still being followed for survival analysis.
Source: CheckMate 066 CSR[106]

Figure 8: 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[111]

Figure 9: CONSORT diagram of participant flow at the time of the current database lock in CheckMate 037



Key: CONSORT, Consolidated Standards of Reporting Trials; C/P, carboplatin plus paclitaxel; DTIC, dacarbazine; ICC, investigator's choice chemotherapy.
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: Weber et al., 2015[112]

Patient characteristics

CheckMate 066

In CheckMate 066, the baseline demographics and disease characteristics of randomised patients across treatment groups were well balanced with no key differences between the treatment groups.[82, 106] As specified in the study protocol, all patients had advanced, BRAF mutation-negative (wild-type) melanoma and had not received prior systemic therapy for advanced melanoma.

A high percentage of patients in CheckMate 066 had poor prognostic factors, including M1c stage disease (visceral disease) and elevated LDH at enrolment. Four patients presented with an ECOG performance status of 2 at randomisation and were thus identified as protocol deviations.

CheckMate 067

In CheckMate 067, the baseline demographics and disease characteristics of patients were well balanced with no key differences between the monotherapy treatment groups.[84, 111] As specified in the study protocol, all patients had advanced melanoma and had not received prior systemic therapy.

As was observed in CheckMate 066, a high percentage of patients had poor prognostic factors at enrolment. One patient randomised to nivolumab monotherapy presented with an ECOG performance status of 2 at randomisation and was thus identified as a protocol deviation.

CheckMate 037

In CheckMate 037, the baseline demographics and disease characteristics of the ITT objective response population were generally well balanced across treatment groups, although there was a higher proportion of patients with a history of brain metastases and elevated LDH in the nivolumab arm.[105, 112] This suggests that the patients randomised to nivolumab treatment had a poorer prognosis than those randomised to ICC; this was also the case for patients who went onto receive treatment. As specified in the study protocol, all patients had advanced disease and had previously progressed on or after anti-CTLA-4 therapy and where patients were BRAF mutation-positive, also on a BRAF inhibitor. One patient who presented with an ECOG performance status of 2 at randomisation was identified as a protocol deviation.

Of the patients randomised to ICC in CheckMate 037, 42.1% (n=56) were assigned to DTIC by the investigator, with the remaining 57.9% (n=77) of patients assigned to carboplatin plus paclitaxel. Of the patients randomised to ICC and included in the objective response population (see Section 4.4), this distribution was similar, with 41.7% (n=25) of patients receiving DTIC therapy.

Key baseline demographics and disease characteristics of patients enrolled in CheckMate 066, CheckMate 067 and CheckMate 037 are presented in Table 13.

Any differences of note in the baseline characteristics of randomised patients across the trials are reflective of the individual trial eligibility criteria. In CheckMate 037, where patients were all previously treated, patients had a longer median time from diagnosis and a higher number of patients with a history of brain metastases. Patients enrolled in CheckMate 037 were (on average) younger than patients enrolled in CheckMate 066 and CheckMate 067 (first-line studies); this may be reflective of the fact that younger patients tend to be able to withstand multiple lines of therapy.

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

CheckMate 066		
	Nivolumab (n=210)	**DTIC (n=208)**
Age, median years (range) **Age, mean years (SD)**	64 (18, 86) 61.6 (13.0)	66 (25, 87) 63.7 (12.6)
Gender, male n (%)	121 (57.6)	125 (60.1)
Race, Caucasian n (%)	209 (99.5)	207 (99.5)
Region, n (%)	Western Europe & Canada: 145 (69.0) Rest of World: 65 (31.0)	Western Europe & Canada: 145 (69.7) Rest of World: 63 (30.3)
ECOG PS, n (%)	0: 148 (70.5) 1: 60 (28.6) 2: 1 (0.5) Missing: 1(0.5)	0: 121 (58.2) 1: 84 (40.4) 2: 3 (1.4)
Metastasis stage, n (%)	M0: 17 (8.1) M1A: 21 (10.0) M1B: 44 (21.0) M1C: 128 (61.0)	M0: 13 (6.3) M1A: 20 (9.6) M1B: 48 (23.1) M1C: 127 (61.1)
Common metastasis site, n (%)	Lymph node: 120 (57.1) Lung: 128 (61.0) Liver: 68 (32.4)	Lymph node: 121 (58.2) Lung: 125 (60.1) Liver: 60 (28.8)
Elevated LDH, n (%)	79 (37.6)	74 (35.6)
History of brain metastases, yes n (%)	7 (3.3)	8 (3.8)
Disease duration, median years (range)	1.93 (0.1, 32.6)	1.65 (0.1, 22.2)
PD-L1-positive, n (%)	74 (35.2)	74 (35.6)

BRAF mutation-negative (wild-type), n (%)	210 (100)	208 (100)
Prior treatment, n (%)	None	None
CheckMate 067		
	Nivolumab (n=316)	**Ipilimumab (n=315)**
Age, median years (range) **Age, mean years (SD)**	60 (25-90) 58.7 (13.9)	62 (18-89) 60.8 (13.2)
Gender, male n (%)	202 (63.9)	202 (64.1)
Race, Caucasian n (%)	308 (97.5)	303 (96.2)
Region, n (%)	US: 68 (21.5) EU: 170 (53.8) Australia: 38 (12.0) Rest of World: 40 (12.7)	US: 75 (23.8) EU: 170 (54.0) Australia: 37 (11.7) Rest of World: 33 (10.5)
ECOG PS, n (%)	0: 238 (75.3) 1: 77 (24.4) 2: 1 (0.3)	0: 224 (71.1) 1: 91 (28.9) 2: 0
Metastasis stage, n (%)	M0-M1B: 132 (41.8) M1C: 184 (58.2)	M0-M1B: 132 (41.9) M1C: 183 (58.1)
Common metastasis site, n (%)	Lymph node: 180 (57.0) Lung: 183 (57.9) Liver: 89 (28.2)	Lymph node: 196 (62.2) Lung: 184 (58.4) Liver: 92 (29.2)
Elevated LDH, n (%)	112 (35.4)	115 (36.5)
History of brain metastases, yes n (%)	8 (2.5)	15 (4.8)
Disease duration, median years (range)	2.18 (0.1, 35.4)	1.95 (0.1, 24.7)
PD-L1-positive, n (%)	80 (25.3)	75 (23.8)

BRAF mutation-negative (wild-type), n (%)	216 (68.4)		218 (69.2)	
Prior treatment, n (%)	None		None	
CheckMate 037				
	Nivolumab		**ICC**	
	Randomised patients (n=272)	ITT objective response population (n=122)	Randomised patients (n=133)	ITT objective response population (n=60)
Age, median years (range) **Age, mean years (SD)**	59 (23, 88) 58.7 (14.1)	58 (25, 88) 57.9 (13.8)	62 (29, 85) 60.3 (12.4)	63.5 (29, 84) 61.1 (13.1)
Gender, male n (%)	176 (64.7)	79 (64.8)	85 (63.9)	36 (60.0)
Race, Caucasian n (%)	269 (98.9)	120 (98.4)	129 (97.0)	57 (95.0)
Region, n (%)	US: 166 (61.0) Rest of World[a]: 106 (39.0)	US: 52 (42.6) Rest of World[a]: 70 (57.4)	US: 58 (43.6) Rest of World[a]: 75 (56.4)	US: 29 (48.3) Rest of World[a]: 31 (51.7)
ECOG PS, n (%)	0: 162 (59.6) 1: 110 (40.4) 2: 0	0: 72 (59.0) 1: 50 (41.0) 2: 0	0: 84 (63.2) 1: 48 (36.1) 2: 1 (0.8)	0: 37 (61.7) 1: 22 (36.7) 2: 1 (1.7)
Metastasis stage, n (%)	M0: 5 (4.1) M1A: 8 (6.6) M1B: 17 (13.9) M1C: 92 (75.4)	M0: 10 (3.7) M1A: 15 (5.5) M1B: 28 (15.4) M1C: 138 (75.8)	M0: 0 M1A: 3 (5.0) M1B: 11 (18.3) M1C: 46 (76.7)	M0: 2 (1.5) M1A: 11 (8.3) M1B: 18 (13.5) M1C: 102 (76.7)
Common metastasis site, n (%)	Lymph node: 159 (58.5) Lung: 151 (55.5) Liver: 102 (37.5)	Lymph node: 79 (64.8) Lung: 68 (55.7) Liver: 53 (43.4)	Lymph node: 74 (55.6) Lung: 73 (54.9) Liver: 38 (28.6)	Lymph node: 33 (55.0) Lung: 35 (58.3) Liver: 20 (33.3)
Elevated LDH, n (%)	139 (51.1)	69 (56.6)	46 (34.6)	23 (38.3)
History of brain metastases, yes n (%)	53 (19.5)	22 (18.0)	18 (13.5)	8 (13.3)
Disease duration, median	3.57 (0.4, 25.3)	3.37 (0.4, 21.4)	3.73 (0.3, 31.1)	4.03 (0.5, 31.1)

years (range)				
PD-L1-positive, n (%)	134 (49.3)	57 (46.7)	67 (50.4)	28 (46.7)
BRAF mutation-negative (wild-type), n (%)	212 (77.9)	95 (77.9)	104 (78.2)	46 (76.7)
Prior treatment, n (%)	Dabrafenib: 10 (3.7) Vemurafenib: 49 (18.0) Anti-CTLA-4: 99 (36.4)	Dabrafenib: 4 (3.3) Vemurafenib: 23 (18.9) Anti-CTLA-4: 44 (36.1)	Dabrafenib: 3 (2.3) Vemurafenib: 23 (17.3) Anti-CTLA-4: 47 (35.3)	Dabrafenib: 2 (3.3) Vemurafenib: 11 (18.3) Anti-CTLA-4: 23 (38.3)

Key: CTLA-4, cytotoxic T-lymphocyte associated antigen 4; DTIC, dacarbazine; ECOG, Eastern Cooperative Oncology Group; EU, European Union; ICC, investigator's choice chemotherapy; LDH, lactose dehydrogenase; n, number; ORR, objective response rate; PD-L1, programmed death-ligand 1; PS, performance status; US, United States.
Notes: [a], including Western Europe & Canada.
Source: CheckMate 066 CSR[106]; CheckMate 067 CSR[111]; CheckMate 037 CSR[105]; Larkin et al., 2015[84]; Robert et al., 2015[82]; Weber et al., 2015[112]

4.6 Quality assessment of the relevant randomised controlled trials

CheckMate 066, CheckMate 067 and CheckMate 037 were all conducted in line with GCP (see Section 4.3), with measures taken to reduce the risk of bias.[82, 84, 105, 106, 112] All trials are thought to reflect routine clinical practice in England in respect of population, comparator choice, treatment administration and outcomes assessed. Outcome assessments of response, including progressive disease, were conducted in accordance with trial validated methodology. The CheckMate trials allowed nivolumab treatment beyond progression as assessed by RECIST; this better reflects clinical practice and acknowledges the limitations of the RECIST criteria for assessing immune-oncology drugs (see Section 4.3).

A central randomisation system with stratification for key prognostic factors was adopted in all trials. Both CheckMate 066 and CheckMate 067 blinded treatment assignment from participants and investigators with a double-blind RCT design. CheckMate 037 was an open-label study with blinding of treatment assignment not conducted at site level (patients and care providers); however, primary efficacy assessment of ORR was conducted by an IRRC who were blinded from treatment, and thus, the risk of bias from the open-label design was minimised.

The most common reason for study withdrawal was disease progression, accounted for within efficacy assessments. Patient withdrawals for reasons other than disease progression were accounted for with standard censoring methods.

In CheckMate 037, a number of patients randomised to ICC withdrew consent, resulting in an imbalance in numbers of patients withdrawing between groups prior to treatment initiation. This included a proportion of patients who went on to receive other PD-1 therapies outside of the trial, which would have had an impact on the outcome of OS of the ITT population. Good concordance between ITT and per-protocol analyses suggests this did not markedly impact comparative efficacy estimates (see Section 4.7). Moreover, the analysis of ORR was planned as a non-comparative estimate. An estimate of difference in ORR between the two treatment groups is provided for completeness in the context of a randomised study with a descriptive 95% CI and no statistical test on the proportion; therefore, there is no power implication in interpreting the ORR analysis of this imbalance in withdrawal rates. A further imbalance between treatment groups was observed in CheckMate 037 when considering poorer prognostic factors, with a higher proportion of patients in the nivolumab arm presenting with brain metastases and elevated LDH (see Section 4.5). These factors could have biased the results in favour of the ICC group.

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 3.

Table 14: Quality assessment results for parallel group RCTs

	CheckMate 066	CheckMate 067	CheckMate 037
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	No
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Outcome assessors only
Were there any unexpected imbalances in drop-outs between groups?	No	No	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	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.	Population, treatment arms, administration and outcomes all relevant to clinical practice in NHS England.

Key: NHS, National Health Service; RCT, randomised controlled trial.
Source: CheckMate 066 CSR[106]; CheckMate 067 CSR[111]; CheckMate 037 CSR[105]; Larkin et al., 2015[84]; Robert et al., 2015[82]; Weber et al., 2015[112]

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Summary

- Nivolumab 3mg/kg monotherapy was associated with a significant survival benefit in advanced melanoma
    - CheckMate 066: significant OS benefit compared with DTIC, HR for death: 0.42 (99.79% CI: 0.25, 0.73); p<0.001
    - CheckMate 066: additional 3.6 to 5.1 months survival observed with nivolumab in restricted mean OS and 75% OS analysis, respectively
    - CheckMate 066: significant PFS benefit compared with DTIC, HR for death or disease progression: 0.43 (95% CI: 0.34, 0.56); p<0.001
    - CheckMate 067: significant PFS benefit compared with ipilimumab, HR for death or disease progression: 0.57 (95% CI: 0.43, 0.76); p<0.001
- Nivolumab 3mg/kg monotherapy was associated with a significant clinical response benefit in advanced melanoma
    - CheckMate 066: unweighted ORR difference of 26.1% compared with DTIC; OR for response: 4.06 (95% CI: 2.52, 6.54); p<0.0001
    - CheckMate 067: unweighted ORR difference of 24.7% compared with ipilimumab; OR for response: 3.40 (95% CI: 2.02, 5.72); p<0.0001
    - CheckMate 037: unweighted ORR difference of 21.0% compared with ICC
    - CheckMate 066, 067 and 037: durable responses in the nivolumab group represented by median duration of response not yet reached
    - CheckMate 066, 067 and 037: median time to response of 2-3 months but many patients showed signs of response at first assessment
    - CheckMate 066 and 037: the majority of responding patients in the nivolumab group experienced a best reduction in target lesion burden of at least 50%
    - CheckMate 067: median change in tumour burden of -34.5% in the nivolumab group compared with +5.9% in the ipilimumab group
- Clinical response post progression (RECIST defined) observed in patients continuing nivolumab treatment (as per study protocol); demonstrating the non-conventional response associated with the immune-oncology mechanism of action
    - CheckMate 066: 22.2% ORR in patients treated beyond progression
    - CheckMate 037: 27.0% ORR in patients treated beyond progression
- Nivolumab 3mg/kg monotherapy was not associated with a negative impact on patient HRQL and may enhance it (whilst conferring survival benefit)
    - CheckMate 066: improvements from baseline in EQ-5D utilities significantly (p<0.05) greater with nivolumab compared with DTIC
    - CheckMate 066: significant improvements (p≤0.03) from baseline in EQ-5D VAS scores at multiple time points
    - CheckMate 066: nivolumab significantly (p<0.05) less likely to lead to deterioration and significantly more likely to lead to improvement in EORTC QLQ-C30 global health and the EQ-5D utility index compared with DTIC

The data from CheckMate 066, CheckMate 067 and CheckMate 037 demonstrates clear evidence of the clinical benefit of nivolumab at the licensed dose of 3mg/kg, supporting its use in the treatment of adult patients with advanced melanoma.

Survival analysis: CheckMate 066

OS analysis based on a database lock date of 5 August 2014 in the CheckMate 066 trial demonstrated the clear survival benefit of nivolumab observed by the DMC that led to the early termination and unblinding of this study (see Section 4.3).[82, 106]

In ITT analysis, with a median follow-up of 8.9 months in the nivolumab group, the median OS (i.e. when half of the patients have died) had not been reached. This should be considered a positive indicator of nivolumab's potential clinical benefit. In comparison, with a median follow-up of 6.8 months, the DTIC group had a confirmed median OS of 10.8 months. The corresponding HR for death confirms a significantly superior survival time with nivolumab therapy compared to DTIC (0.42 [99.79% CI: 0.25, 0.73]; p<0.001).

The 75% OS (i.e. when a quarter of the patients have died) has been reached in both arms and shows an additional 5.1 months survival in the nivolumab group compared with the DTIC group (10.3 months for nivolumab versus 5.2 months for DTIC). In addition, survival rates at 1 year are 72.9% in the nivolumab group; this is 30.8% higher than the DTIC group despite the unusually high 1-year survival rate observed in the DTIC group, potentially as a result of 38% of the DTIC arm patients receiving subsequent treatment with ipilimumab (post-progression), within the first year.

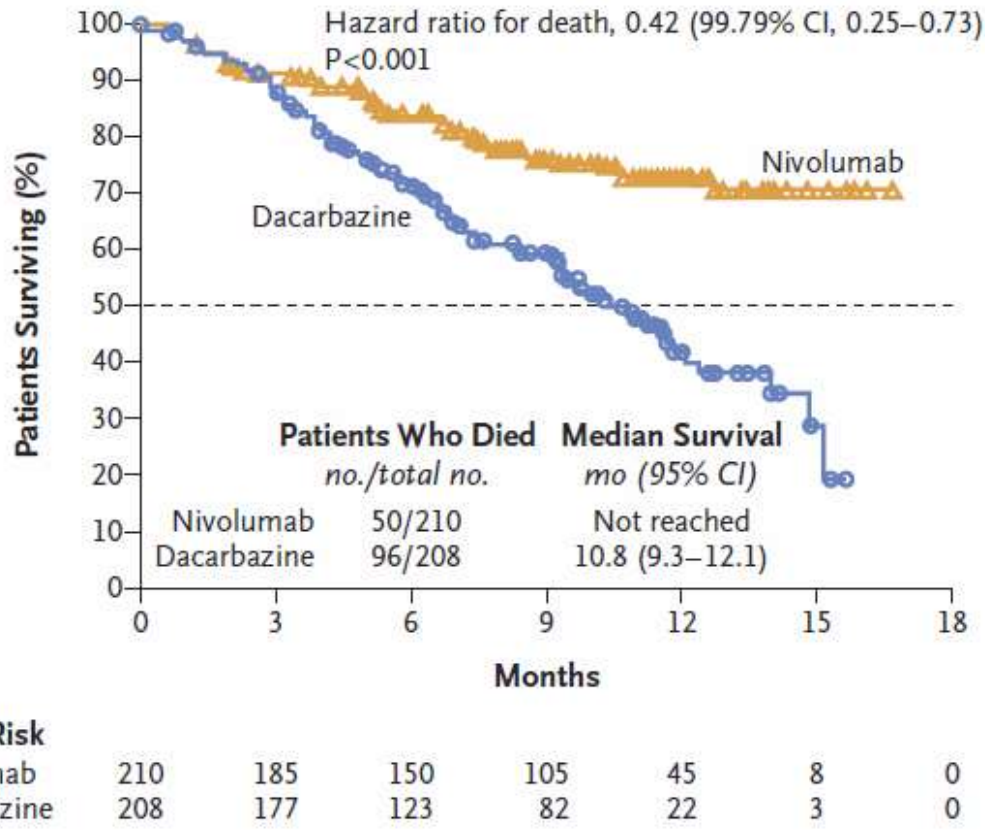
Summary OS data are presented in Table 15 and the Kaplan–Meier (KM) curve for survival is presented in Figure 10.

Table 15: Summary of overall survival in CheckMate 066, ITT analysis set

	Nivolumab (n=210)	**DTIC (n=208)**
Events, n (%)	50 (23.8)	96 (46.2)
Hazard ratio (99.79% CI)* (95% CI) p-value	0.42 (0.25, 0.73) (0.30, 0.60) <0.001	
Median OS (95% CI), months	Not reached	10.84 (9.33, 12.09)
OS rate at 6 months, % (95% CI)	84.1 (78.3, 88.5)	71.8 (64.9, 77.6)
OS rate at 12 months, % (95% CI)	72.9 (65.5, 78.9)	42.1 (33.0, 50.9)

Key: CI, confidence interval; DTIC, dacarbazine; ITT, intention-to-treat; n, number; OS overall survival
Notes: The boundary for statistical significance required for early stopping of the trial required the log rank p value to be less than 0.0021, corresponding to a 99.79% CI. This value is therefore shown above together with data relating to the conventional 99.5% CI interval.
Source: CheckMate 066 CSR[106]; Robert et al., 2015[82]

Figure 10: Kaplan–Meier curves for OS in CheckMate 066, ITT analysis set



Key: CI, confidence interval; ITT, intention-to-treat; OS, overall survival; mo, month; no., number.
Notes: Circles on the dacarbazine curve and triangles on the nivolumab curve represent censoring.
Source: Robert et al., 2015[82]

In the absence of median survival for the nivolumab arm, mean survival times have been calculated from within trial analysis. This restricted means analysis demonstrated an extension to survival of 3.6 months in the nivolumab group compared with the DTIC group (410 days vs 301 days).

At the time of this survival analysis, 95 of 210 (45.2%) patients randomised to nivolumab, and 13/208 (6.3%) patients randomised to DTIC, continued to receive study therapy. Ipilimumab was the most common subsequent anti-cancer therapy (administered in 45 [21.4%] patients randomised to nivolumab; 79 [38.0%] patients randomised to DTIC).

PFS analysis further demonstrates the significant benefit observed with nivolumab. In ITT analysis, the median PFS was 5.1 months in the nivolumab group compared with 2.2 months in the DTIC group. The corresponding HR for death or disease progression confirms this is a significantly superior PFS with nivolumab therapy: 0.43 (95% CI: 0.34, 0.56); p<0.001.

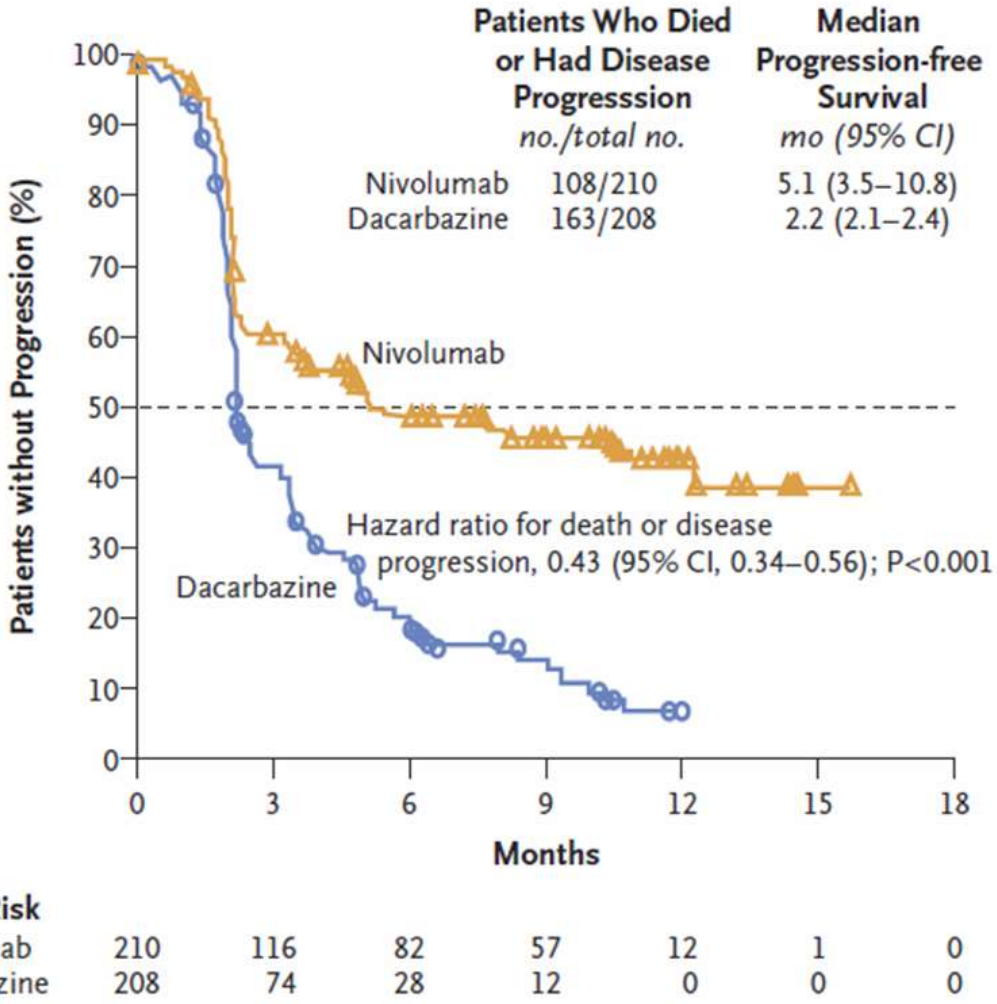
Summary PFS data are presented in Table 16, and the KM curve for PFS is presented in Figure 11.

Table 16: Summary of PFS in CheckMate 066, ITT analysis set

	Nivolumab (n=210)	DTIC (n=208)
Events, n (%)	108 (51.4)	163 (78.4)
Hazard ratio (95% CI) p-value	0.43 (0.34, 0.56) <0.001	
Median PFS (95% CI), months	5.06 (3.48, 10.81)	2.17 (2.10, 2.40)
PFS rate at 6 months (95% CI)	48.0 (40.8, 54.9)	18.5 (13.1, 24.6)
PFS rate at 12 months (95% CI)	41.8 (34.0, 49.3)	Not produced[a]

Key: CI, confidence interval; DTIC, dacarbazine; ITT, intention-to-treat; n, number; PFS, progression-free survival.
Notes: [a], all PFS times were less than 12 months for the DTIC group.
Source: CheckMate 066 CSR[106]; Robert et al., 2015[82]

Figure 11: Kaplan–Meier curves for PFS in CheckMate 066, ITT analysis set



Key: CI, confidence interval; ITT, intention-to-treat; mo, month; no., number; PFS, progression-free survival.
Notes: Circles on the dacarbazine curve and triangles on the nivolumab curve represent censoring.
Source: Robert et al., 2015[82]

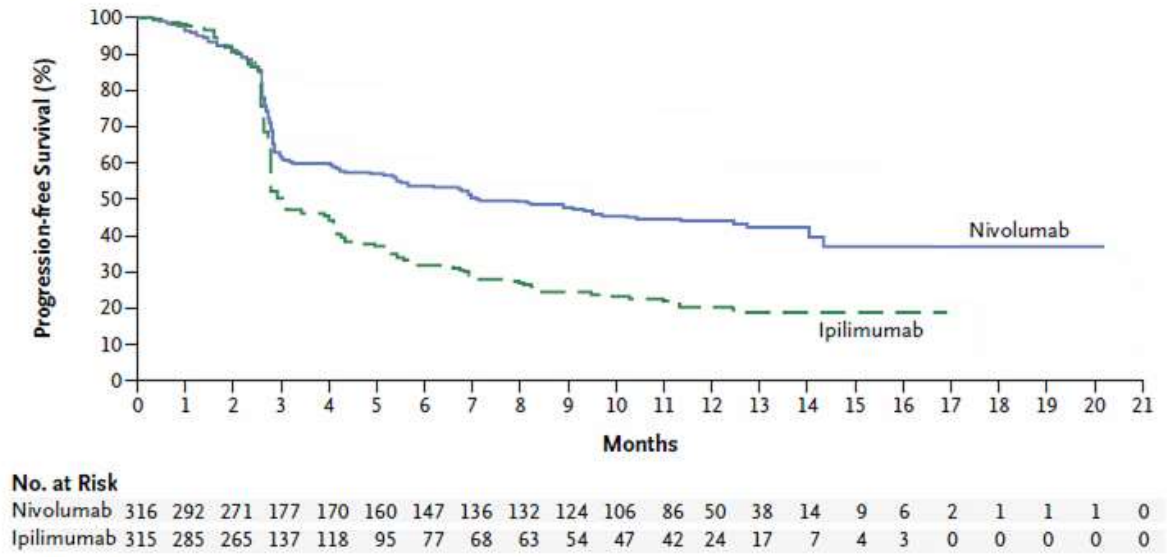
The steep initial decline observed in the KM curves for PFS in both arms is a result of the measurement schedule adopted in CheckMate 066 in which the first scheduled tumour assessment was conducted 8-10 weeks from randomisation.

Of note, 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 (see Section 2.1). This also applies to the PFS analyses of CheckMate 067 and CheckMate 037 (presented below).

Survival analysis: CheckMate 067

In ITT analysis, with a median follow-up ranging between 12.2 and 12.5 months across treatment groups, the median PFS was 6.9 months in the nivolumab group compared with 2.9 months in the ipilimumab group.[84] The corresponding HR for death or disease progression confirms a significantly superior PFS with nivolumab therapy: 0.57 (99.5% CI: 0.43, 0.76); p<0.001. The KM curve for PFS is presented in Figure 12.

Figure 12: Kaplan–Meier curves for PFS in CheckMate 067, ITT analysis set

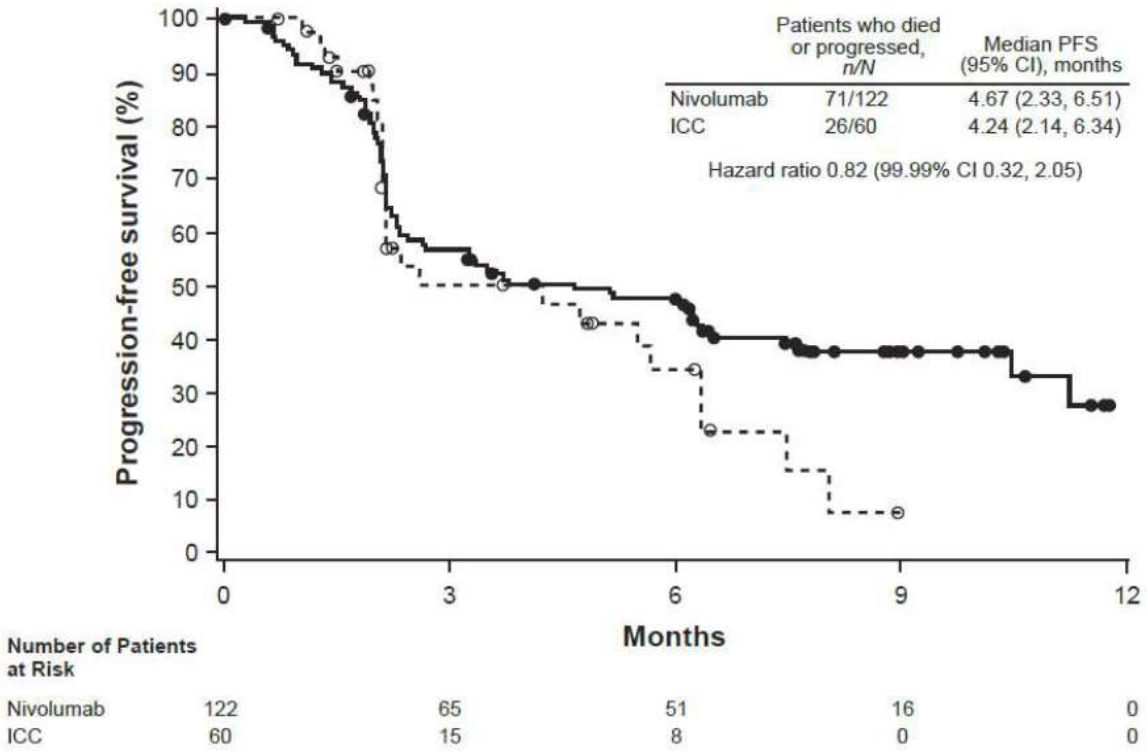


Key: ITT, intention-to-treat; PFS, progression-free survival.
Source: Larkin et al., 2015[84]

Survival analysis: CheckMate 037

In the ITT objective response population (i.e. all 182 patients who had been randomised at the point of the first planned assessment of objective response), median PFS was 4.7 months for the nivolumab group and 4.2 months for the ICC group (HR 0.82 [99.99% CI: 0.32, 2.05]).[112] Six-month PFS was 48% in the nivolumab group and 34% in the ICC group.[105, 112] The KM curve for PFS is presented in Figure 13.

Figure 13: Kaplan–Meier curves for PFS in CheckMate 037, ITT objective response analysis set



Key: CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival.
Notes: Solid line represents nivolumab; dashed line represents ICC; circles on curves represent censoring.
Source: Weber et al., 2015[112]

The descriptive PFS analysis presented has a number of factors that add uncertainty; the immaturity of the data (primarily); adverse prognostic factors in favour of the ICC group (see Section 4.5); high withdrawal rate in the ICC group (see Section 4.5); and the false-positive progression assessments in the nivolumab arm that result from the use of RECIST criteria. These issues are further discussed in Section 4.13.

Response analysis: CheckMate 066

Secondary endpoint analysis of clinical response in CheckMate 066 supports the primary survival analyses, further demonstrating the significant benefit associated with nivolumab therapy.[82, 106]

In ITT analysis, patients randomised to nivolumab demonstrated a confirmed ORR of 40.0%. This was significantly higher than the confirmed ORR in the DTIC group (13.9%; OR=4.06 [95% CI: 2.52, 6.54]; p<0.0001) and a higher proportion of patients demonstrated CR in the nivolumab group (7.6% vs 1.0%), as presented in Table 17.

In both treatment groups, the median time to response was 2.1 months (Table 17), with many patients responding by the time of the first scan (8-10 weeks). However, responses were more durable in the nivolumab group.

Median duration of response was not reached in the nivolumab group at the time of the latest August database lock (Table 17), which should be considered a further positive indicator of nivolumab's potential clinical benefit. The longest duration of response observed

to date is over 12 months, but given the number of patients with confirmed response to nivolumab still in response at the time of analysis (85.7% [72/84]) this is likely to be increased at the next data-cut.

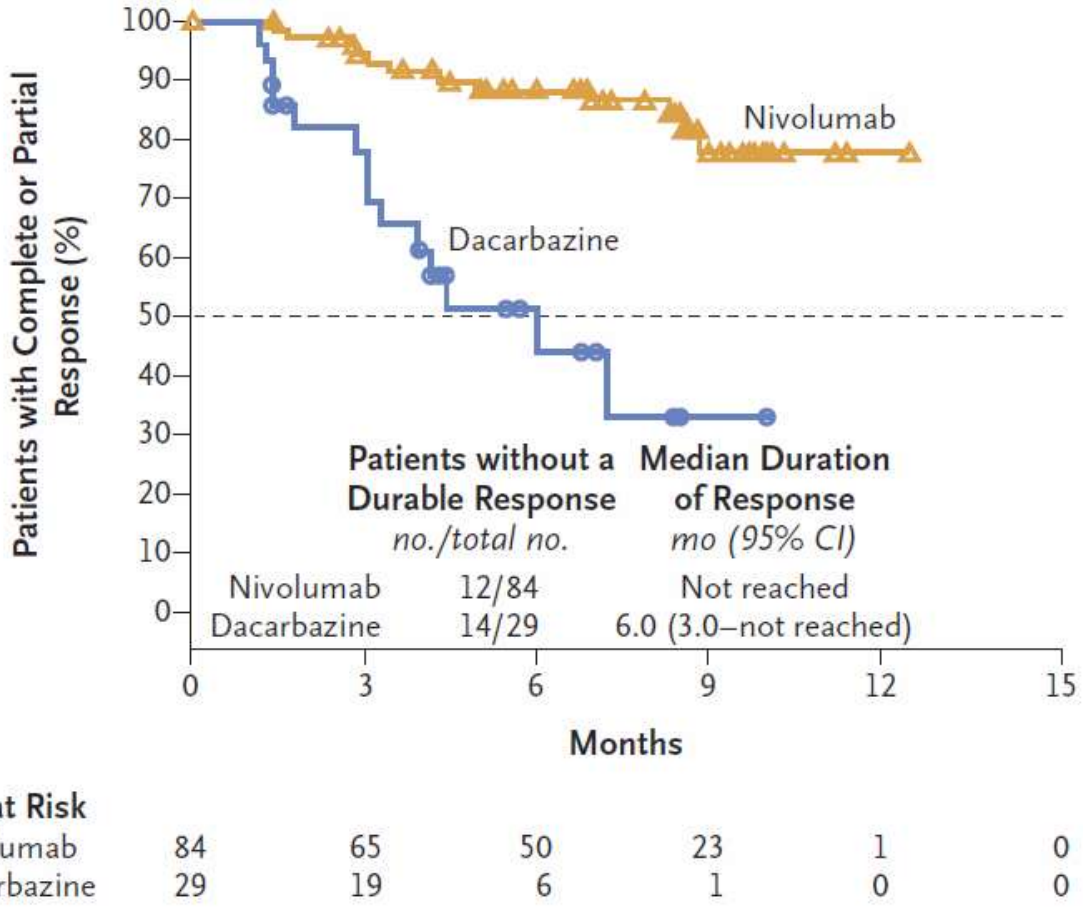
The KM curve for duration of response is presented in Figure 14.

Table 17: Summary of response in CheckMate 066, ITT analysis set

	Nivolumab (n=210)	**DTIC (n=208)**
Objective response rate (ORR)[a]		
Responders, n (%) (95% CI)	84 (40.0) (33.3, 47.0)	29 (13.9) (9.5, 19.4)
Best overall response CR, n (%) PR, n (%)	 16 (7.6) 68 (32.4)	 2 (1.0) 27 (13.0)
Unweighted ORR difference, % (95% CI)	26.1 (18.0, 34.1)	
Estimated odds ratio (95% CI)	4.06 (2.52, 6.54)	
p-value	<0.0001	
Duration of response		
Median (range), months	Not reached (0.0, 12.5)	5.98 (1.1, 10.0)
Time to treatment response		
Median (range), months	2.10 (1.2, 7.6)	2.10 (1.8, 3.6)

Key: CI, confidence interval; CR, complete response; DTIC, dacarbazine; ITT, intention-to-treat; n, number; OR, odds ratio; ORR, Objective response rate; PR, partial response.
Notes: [a], confirmed response (CR + PR) as per RECIST v1.1 criteria.
Source: CheckMate 066 CSR[106]; Robert et al., 2015[82]

Figure 14: Kaplan–Meier curves for duration of response in CheckMate 066, response-evaluable analysis set



Key: CI, confidence interval; mo, month; no., number.
Notes: Circles on the dacarbazine curve and triangles on the nivolumab curve represent censoring.
Source: Robert et al., 2015[82]

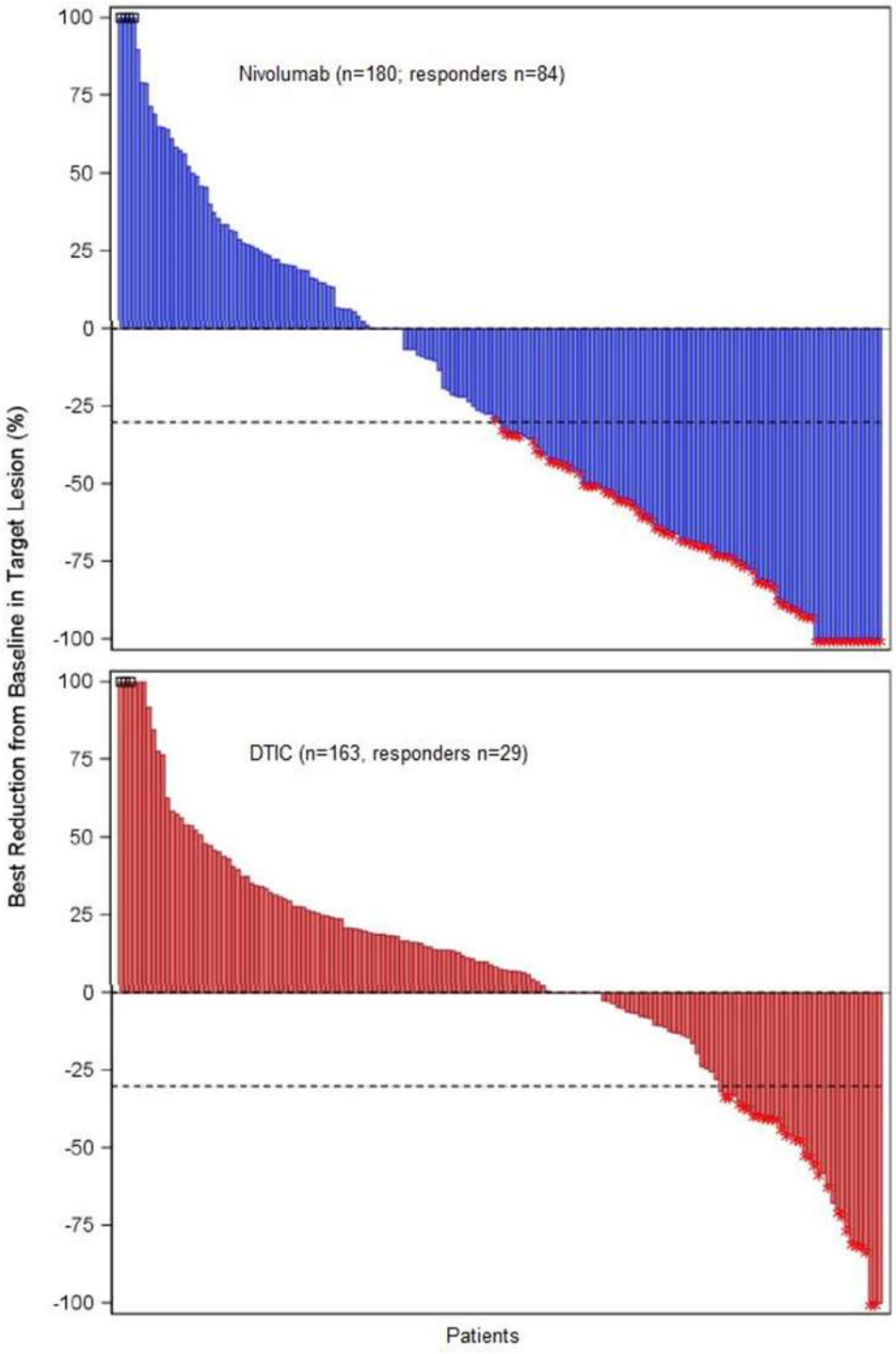
The waterfall plot of response presented in Figure 15 shows the percentage change in tumour burden from baseline for each patient of the response-evaluable analysis set, and clearly demonstrates the clinical benefit of nivolumab.

To explain the diagram:

- a positive value is indicative of an increase in tumour size and a negative value represents a reduction;
- the dotted line represents a partial response to therapy according to the RECIST criteria (30% reduction in tumour size);
- the inflection point (the point at which the curve changes from convex to concave) demonstrates the proportion of patients achieving a reduction in tumour size.

It can therefore be seen in the waterfall plot (Figure 15) that more patients in the nivolumab arm experienced a reduction in tumour size, and achieved at least a partial response to therapy, compared with the patients in the DTIC arm. Indeed, the majority of responding patients in the nivolumab group (81.0%) experienced a best reduction in target lesion burden of at least 50%.

Figure 15: Waterfall plot of best reduction from baseline in sum of diameters of target lesions in CheckMate 066, response-evaluable analysis set



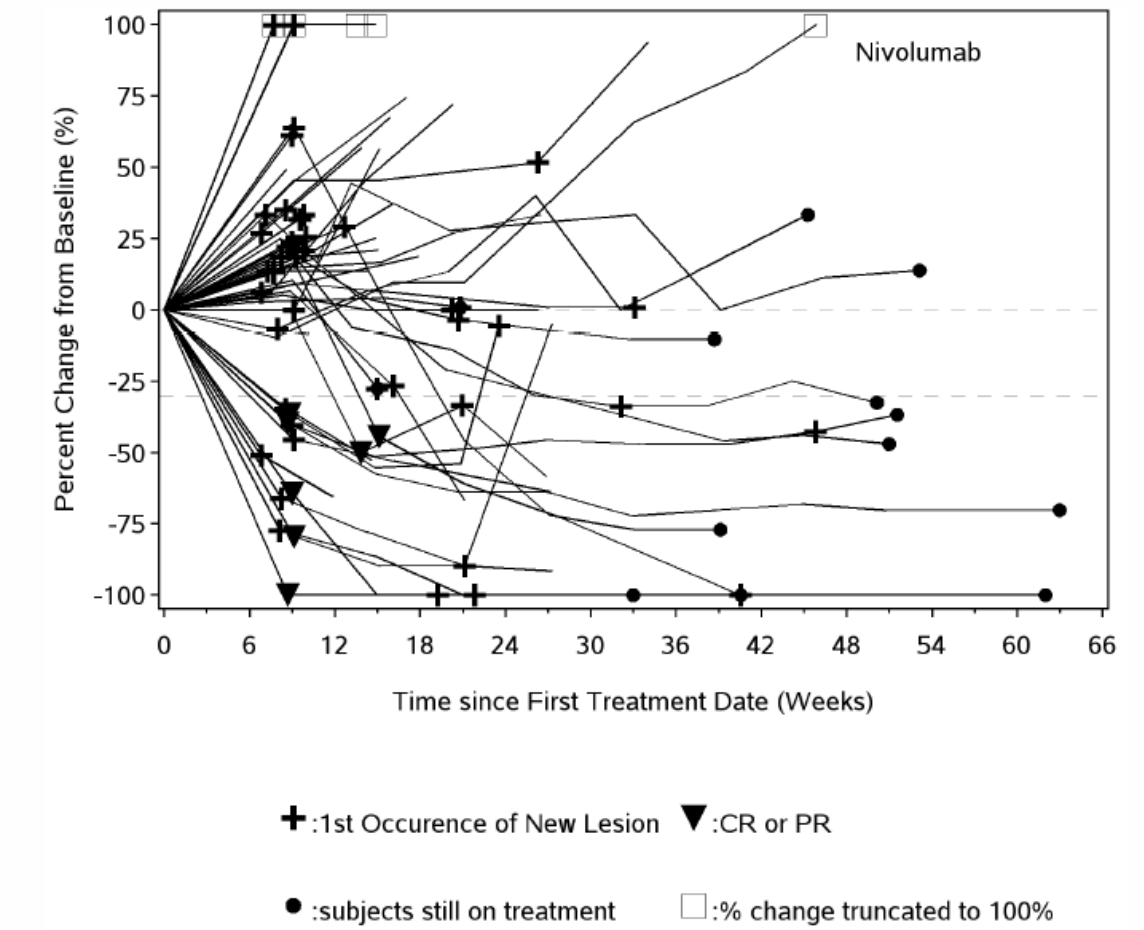
Notes: Asterisk represents responders as per RECIST criteria; square represents % change truncated to 100%.
Source: CheckMate 066 CSR[106]

Of all treated patients, 103 were treated beyond RECIST defined progression as per the study protocol (see Section 4.3), including 54 patients in the nivolumab group and 49 in the DTIC group.

Of these 103 patients, 12 treated with nivolumab (22.2%) and 2 treated with DTIC (4.1%) developed or maintained a target lesion reduction of >30% compared to baseline after initial (RECIST defined) progression. This subsequent reduction in target lesion size adds to the accumulating body of evidence demonstrating the non-conventional response associated with the immuno-oncology mechanism of action, where tumours may temporarily appear to progress (see Section 2.1).

Response patterns for response evaluable patients treated with nivolumab beyond RECIST criteria defined progression (n=51) are presented in Figure 16.

Figure 16: Response pattern in patients treated with nivolumab beyond RECIST defined progression in CheckMate 066



Key: CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.
Source: CheckMate 066 CSR[106]

Response analysis: CheckMate 067

Secondary endpoint analysis of clinical response in CheckMate 067 further demonstrates the superior benefit associated with nivolumab therapy compared with ipilimumab therapy, as observed in the PFS analysis.[84, 111]

In ITT analysis, investigator-assessed ORR was 43.7% in the nivolumab group compared with 19.0% in the ipilimumab group. Time to objective response was similar in both treatment

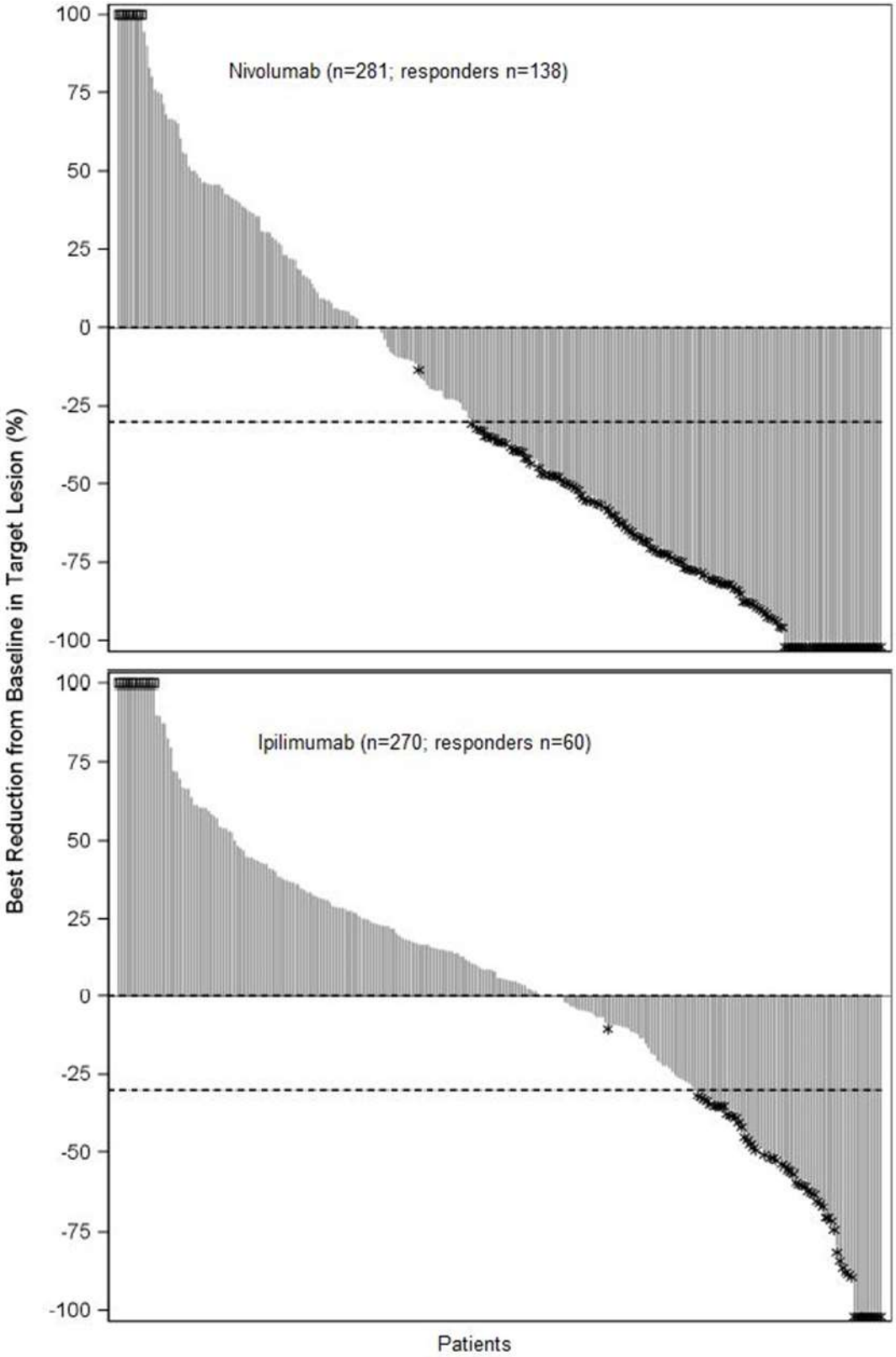
groups and, to date, median duration of response has not been reached in either treatment group. At the time of the analysis (median follow-up of approximately 12 months), 77.5% of patients continued to demonstrate response to nivolumab; 66.7% of patients responding to ipilimumab were also still responding to treatment at the time of the analysis. Response analysis from CheckMate 067 is summarised in Table 18.

Table 18: Summary of response in CheckMate 067

	Nivolumab (n=316)	**Ipilimumab (n=315)**
Objective response rate (ORR)[a]		
Responders, n (%) (95% CI)	138 (43.7) (38.1, 49.3)	60 (19.0) (14.9, 23.8)
Best overall response CR, n (%) PR, n (%)	 28 (8.9) 110 (34.8)	 7 (2.2) 53 (16.8)
Unweighted ORR difference, %	24.7	
Estimated odds ratio (95% CI)	3.40 (2.02, 5.72)	
p-value	<0.0001	
Duration of response		
Median (range), months	Not reached	Not reached
Time to treatment response		
Median (range), months	2.8 (2.3, 12.5)	2.8 (2.5, 12.4)
Key: CI, confidence interval; CR, complete response; PR, partial response; ORR, objective response rate. **Notes:** [a], confirmed response (CR + PR) as per RECIST v1.1 criteria. **Source:** CheckMate 067 CSR[111]; Larkin et al. 2015[84]		

The median change in tumour burden (assessed as the change from baseline in the sum of the longest diameters of the target tumour lesions) was -34.5% (interquartile range, -75.4, 15.4) in the nivolumab group compared with +5.9% (interquartile range, -28.0, 33.3) in the ipilimumab group, as depicted in Figure 17.

Figure 17: Waterfall plot of best reduction from baseline in sum of diameters of target lesions in CheckMate 067, response-evaluable analysis set

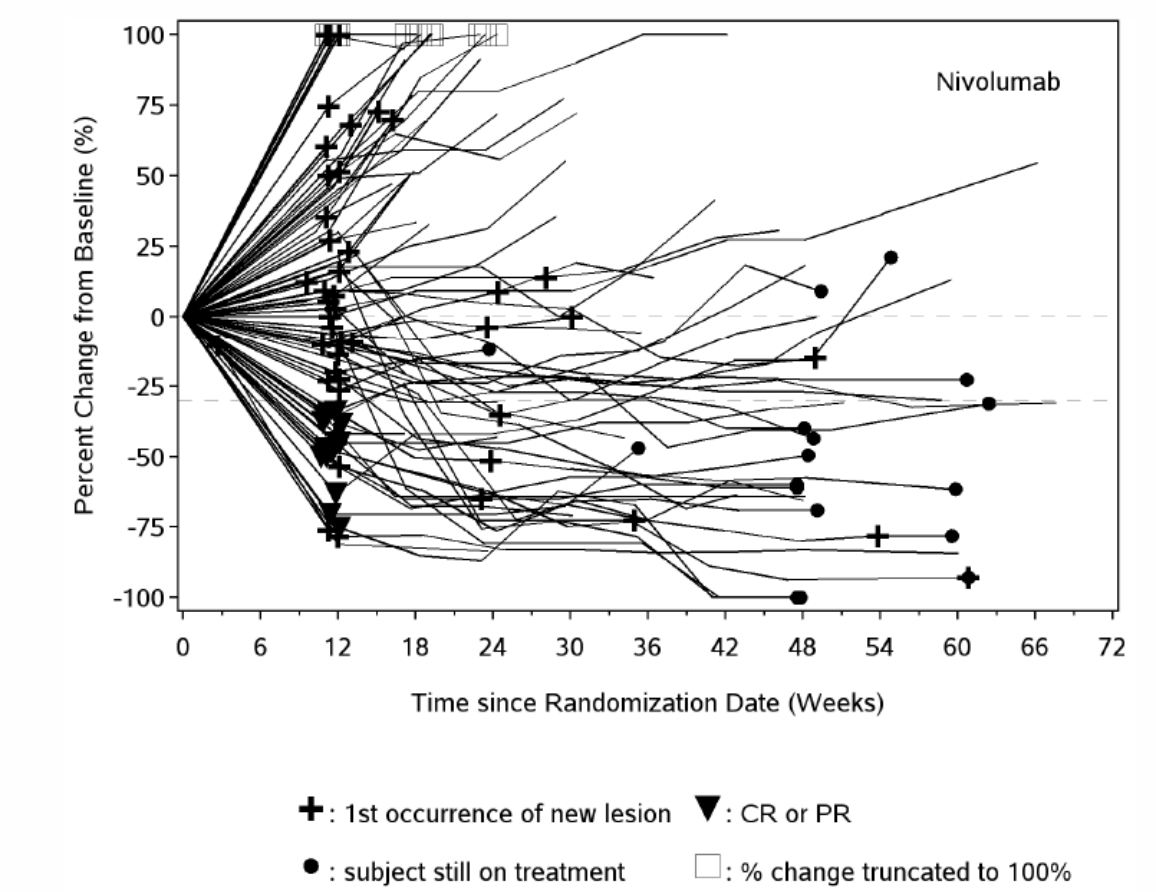


Notes: Asterisk represents responders as per RECIST criteria; square represents % change truncated to 100%.
Source: CheckMate 067 CSR[111]

Of patients with a best ORR of progressive disease, 86 patients in the nivolumab 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 nivolumab beyond RECIST criteria defined progression (n=81) are presented in Figure 18.

Figure 18: Response pattern in patients treated with nivolumab beyond RECIST defined progression in CheckMate 067



Key: CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.
Source: CheckMate 067 CSR[111]

Response analysis: CheckMate 037

Primary response analysis based on a clinical database lock date of 30 April 2014 (when median follow-up was 8.4 months) in the CheckMate 037 trial demonstrated the clear clinical benefit of nivolumab.[105, 112] In the PP objective response population (primary data set), confirmed objective responses as per IRRC were noted in 38/120 (31.7%) of patients in the nivolumab group compared with only 5/47 (10.6%) of patients in the ICC group (Table 19). Primary response analysis conclusions (IRRC assessed response in the PP objective response population) were supported by all secondary response analyses (investigator assessed response in the PP objective response population; IRRC assessed response in the ITT objective response population) (Table 19).

The majority of responses in the nivolumab group were rapid and durable. The median time to response was 2.1 months (Table 19), with many patients responding by the time of the

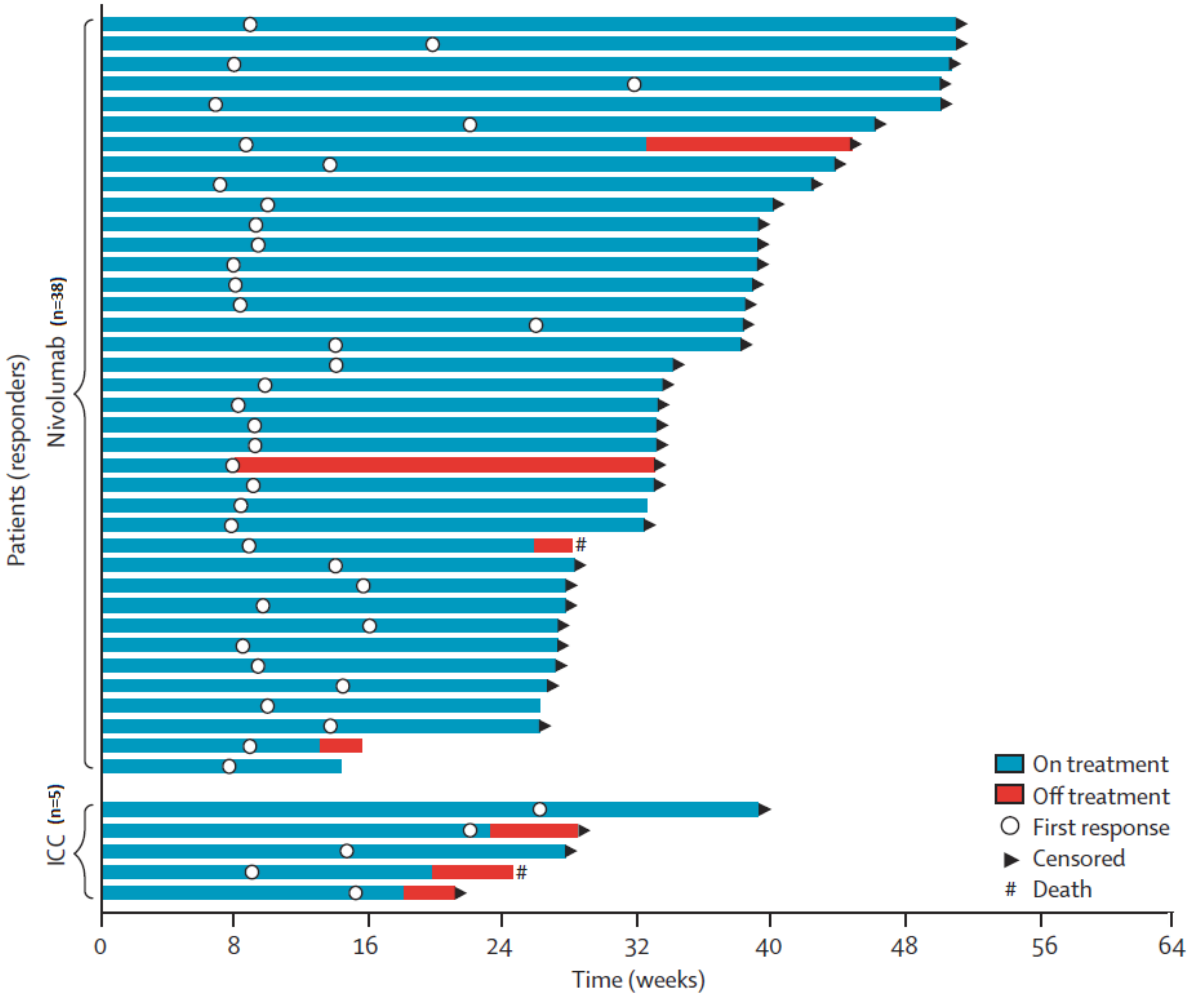
first scan (8-10 weeks), as depicted in the swimmer plot presented in Figure 19. Median duration of response was not reached in the nivolumab group at the time of the May database lock (Table 19), which should again be considered a further positive indicator of nivolumab's potential clinical benefit. The longest duration of response observed to date is over 10 months, and 87% (33/38) of patients with confirmed response to nivolumab were continuing on treatment without progression at the time of analysis (Figure 19).

Table 19: Summary of response in CheckMate 037

PP objective response analysis set, IRRC assessment		
	Nivolumab (n=120)	**ICC (n=47)**
Objective response rate (ORR)[a]		
Responders, n (%) (95% CI)	38 (31.7) (23.5, 40.8)	5 (10.6) (3.5, 23.1)
Best overall response CR, n (%) PR, n (%)	 4 (3.3) 34 (28.3)	 0 5 (10.6)
Unweighted ORR difference, % (95% CI)	21.0 (6.8, 31.7)	
Duration of response		
Median (range), months	Not reached (1.4+, 10.0+)	3.5 (1.3+, 3.5)
Time to treatment response		
Median (range), months	2.1 (1.6, 7.4)	3.5 (2.1, 6.1)
ITT objective response analysis set, IRRC assessment		
	Nivolumab (n=122)	**ICC (n=60)**
Objective response rate[a]		
Responders, n (%) (95% CI)	38 (31.1) (23.1, 40.2)	5 (8.3) (2.8, 18.4)
Best overall response CR, n (%) PR, n (%)	 4 (3.3) 34 (27.9)	 0 5 (8.3)
Unweighted ORR difference, % (95% CI)	22.8 (10.5, 32.7)	
PP objective response analysis set, investigator assessment		
	Nivolumab (n=120)	**ICC (n=47)**
Objective response rate[a]		
Responders, n (%) (95% CI)	31 (25.8) (18.3, 34.6)	5 (10.6) (3.5, 23.1)
Best overall response CR, n (%) PR, n (%)	 2 (1.7) 29 (24.2)	 0 5 (10.6)
Unweighted ORR difference, % (95% CI)	15.2 (1.3, 25.6)	
Key: CI, confidence interval; CR, complete response; ITT, intention-to-treat; n, number; ORR, objective response rate; PP, per-protocol; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.		

Notes: [a], confirmed response (CR + PR) as per RECIST v1.1 criteria.
Source: CheckMate 037[105]; Weber et al., 2015[112]

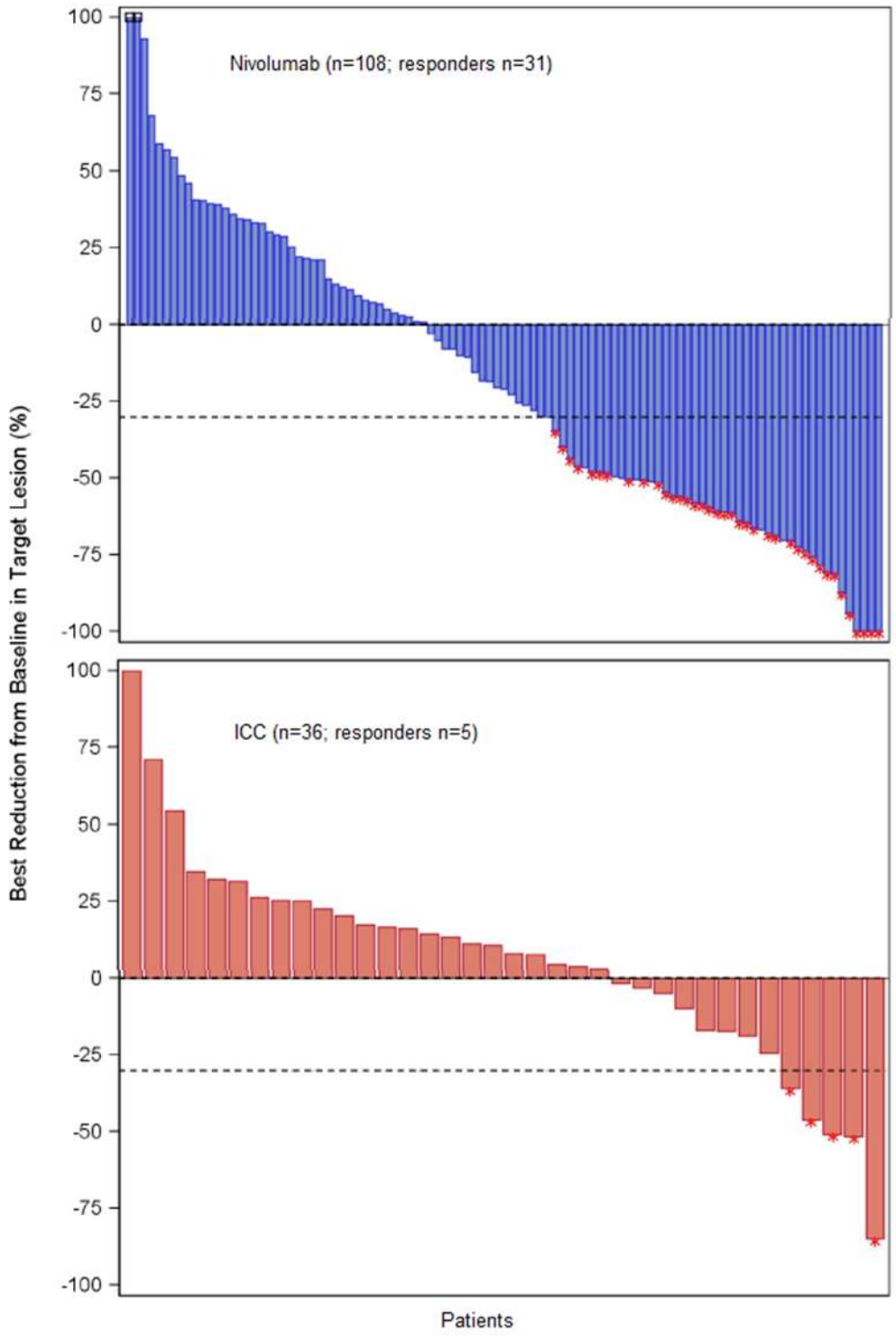
Figure 19: Swimmer plot of time to first response and duration of response in CheckMate 037, responders analysis set



Key: ICC, investigator's choice chemotherapy.
Source: Weber et al. 2015[112]

As depicted in the waterfall plot presented in Figure 20, more patients in the nivolumab arm experienced a reduction in tumour size, and achieved at least a partial response to therapy, compared with patients in the ICC arm with the majority of responding patients in the nivolumab group experiencing a best reduction in target lesion burden of at least 50%.

Figure 20: Waterfall plot of best reduction from baseline in sum of diameters of target lesions in CheckMate 037, response-evaluable analysis set

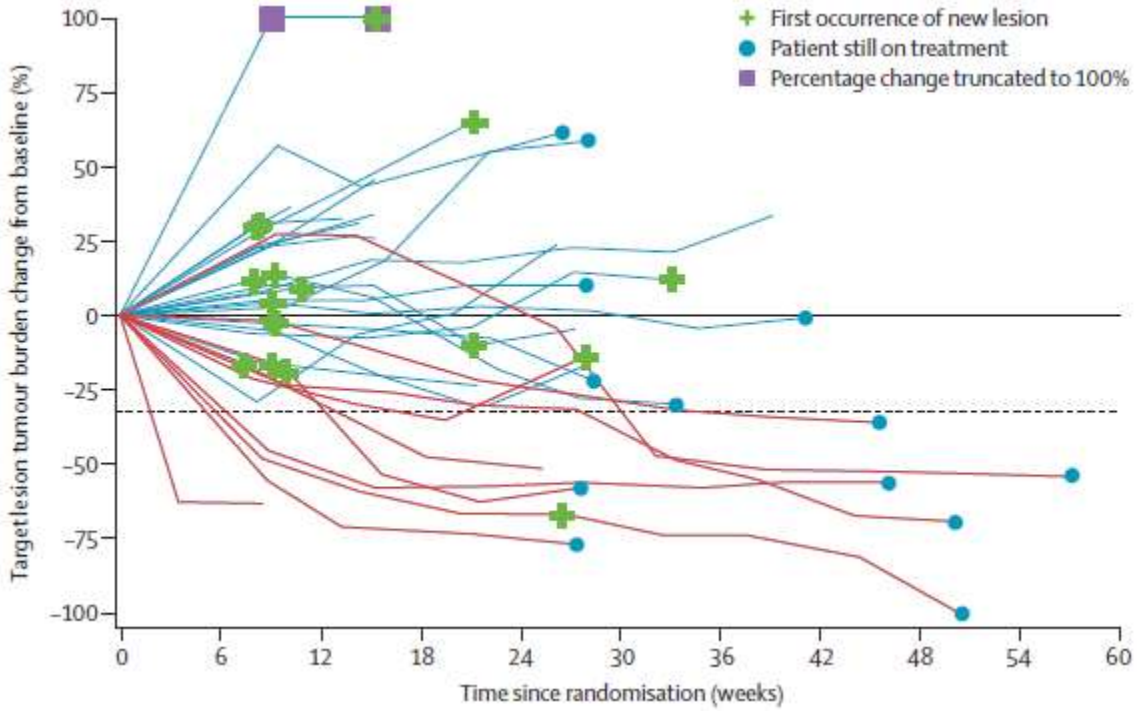


Key: ICC, investigator's choice chemotherapy.
Note: Asterisk represents responders as per RECIST criteria; square represents % change truncated to 100%.
Source: CheckMate 037[105]

Of all treated nivolumab patients at the time of interim analysis, 37 were treated beyond RECIST defined progression as per the study protocol (see Section 4.3). Of these patients, 10 (27.0%) developed or maintained a target lesion reduction of >30% compared to baseline after initial RECIST defined progression.

This is consistent with an unconventional, immune-related response as previously discussed. Response patterns for all patients treated beyond RECIST criteria defined progression (n=37) are presented in Figure 21.

Figure 21: Response pattern in patients treated with nivolumab beyond RECIST defined progression in CheckMate 037



Key: RECIST, Response Evaluation Criteria in Solid Tumors.
Notes: The red lines represent patients with an immune-related response and the blue lines represent patients who had either stable disease or progressed during continuing treatment with nivolumab.
Source: Weber et al., 2015[112]

HRQL analysis: CheckMate 066

HRQL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EuroQol-five dimension questionnaire (EQ-5D) in CheckMate 066.[106] A description of these tools is provided in Appendix 6.

EORTC QLQ-C30 questionnaire completion rate at baseline was 79% for the nivolumab group and 78.4% for the DTIC group and adjusted completion rates (proportions based on patients still participating in the study) remained at 70% or higher at each visit up to Week 73.[106] Adjusted completion rates at baseline for EQ-5D utilities were 69.5% for the nivolumab group and 64.9% for the DTIC group.[108] While adjusted completion rates remained similar throughout the study, analysis of HRQL involving DTIC after Week 13 is associated with high uncertainty due to a high attrition rate in the DTIC arm (n≤41 from week 19).

EORTC-QLQ-C30 global health status scores at baseline were similar in both treatment groups (nivolumab, 66.9; DTIC, 64.4).[106, 108] During the trial, EORTC QLQ-C30 subscale scores generally did not change over time for either treatment group, except for some clinically meaningful changes (defined as a minimally important difference of ≥10 points[186])

observed with nivolumab for emotional (Week 55, +13.0; Week 61, +12.8) and social (Week 55, +10.5) functioning scales at certain time points.

There was a small deteriorating effect on daily activities, sleep, appetite loss, diarrhoea, pain, nausea and fatigue subscales (as demonstrated by lower scores) in patients treated with DTIC, which was not observed in patients treated with nivolumab. However, overall symptom burden was generally limited and remained relatively stable over time across the two treatment groups (data not shown).[106]

EQ-5D utility scores at baseline were similar in both treatment groups at 0.778 for nivolumab and 0.711 for DTIC.[108] Improvements from baseline in EQ-5D utilities (as demonstrated by higher scores) were greater in the nivolumab versus DTIC treatment arm (p=0.045) with improvements noted from Week 7 (0.027; p=0.011 [n=132]) through Week 49 (0.045; p=0.034 [n=38]) in the nivolumab group. Clinically meaningful changes (defined as a minimally important difference of ≥0.08 points [187]) were also observed with nivolumab at some time points.

EQ-5D visual analogue scale (VAS) scores at baseline were also similar in both treatment groups at 70.9 for nivolumab and 69.1 for DTIC.[108] Significant improvements from baseline in EQ-5D VAS scores were observed at Weeks 25, 31, 37, 49 and 61 (p≤0.03) in the nivolumab group. Clinically meaningful changes (defined as a minimally important difference of ≥7 points[187]) were also observed with nivolumab at some time points.

A Cox proportional hazard regression model was used to determine the time from randomisation to first deterioration and the time from randomisation to first improvement (as defined by the minimally important difference for that scale applied at the individual patient level). Nivolumab was significantly less likely to lead to deterioration before DTIC for the following items (Table 20):

- EORTC QLQ-C30 global health (HR=066; p=0.021), physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, and constipation
- EQ-5D utility index score (HR=0.55; p=0.002)

In addition, nivolumab was significantly more likely to lead to improvement before DTIC for the following items:

- EORTC QLQ-C30 global health (HR=1.52; p=0.043), physical functioning (HR=1.92; p=0.027), fatigue (HR=1.69; p=0.008), and dyspnoea (HR=2.20; p=0.013)
- EQ-5D utility index score (HR=1.86; p=0.002)

Table 20: Cox proportional hazards model on time to first decline in HRQL, HRQL analysis set

Scale/subscale	Nivolumab vs DTIC Hazard ratio (95% CI)[a]	p-value
EORTC QLQ-C30		
Global health status	0.66 (0.47, 0.94)	0.021
Physical functioning	0.58 (0.40, 0.84)	0.004
Role functioning	0.61 (0.44, 0.87)	0.005
Emotional functioning	0.59 (0.37, 0.92)	0.019
Cognitive functioning	0.66 (0.45, 0.95)	0.024
Social functioning	0.61 (0.42, 0.87)	0.007
Fatigue	0.74 (0.55, 1.00)	Not significant
Nausea and vomiting	0.43 (0.28, 0.67)	<0.001

Scale/subscale	Nivolumab vs DTIC Hazard ratio (95% CI)[a]	p-value
Pain	0.67 (0.48, 0.92)	0.015
Dyspnoea	0.50 (0.33, 0.75)	<0.001
Insomnia	0.67 (0.45, 0.99)	0.045
Appetite loss	0.43 (0.29, 0.65)	<0.001
Constipation	0.51 (0.34, 0.76)	<0.001
Diarrhoea	0.87 (0.53, 1.43)	Not significant
Financial difficulties	0.66 (0.41, 1.05)	Not significant
EQ-5D		
EQ-5D utility index	0.55 (0.38, 0.80)	0.002
EQ-5D VAS	0.82 (0.59, 1.14)	Not significant
Key: CI, confidence interval; EQ-5D, EuroQol-five dimension questionnaire; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; VAS, visual analogue scale. **Notes:** [a], hazard ratios <1 favour nivolumab **Source:** Long et al., 2015[108]		

In summary, HRQL results from CheckMate 066 demonstrate that in the study nivolumab did not impair HRQL and in some cases, there was an improvement compared with baseline HRQL, whilst conferring survival benefits. Of note, considerable improvement is seen in the EQ-5D utility index (HR = 0.55, p=0.002) which is striking due to the rarity of demonstration of significant improvement of this magnitude with the EQ-5D.

4.8 Subgroup analysis

CheckMate 066

OS benefit was observed with nivolumab across predefined subgroups in CheckMate 066, with each unstratified HR <1 versus DTIC, as presented in Figure 22.[82, 106]

Of specific interest, in consideration of nivolumab's mechanism of action (see Section 2.1), is the fact that clinical benefit was observed not only in PD-L1-positive (≥ 5% expression) patients but also in PD-L1-negative (< 5% expression) /indeterminate patients treated with nivolumab.

Median OS is yet to be reached in either of the PD-L1 subgroups, which should be considered a positive indicator of nivolumab's potential clinical benefit irrespective of PD-L1 status. Whilst events analyses suggest the magnitude of nivolumab effect is greater in PD-L1-positive patients, the HRs for death confirm an OS benefit regardless of PD-L1 status (as summarised in Table 21).

A similar trend was observed in post-hoc analysis of ORR by PD-L1 expression status. As presented in Table 22, ORR was higher in nivolumab-treated patients with positive PD-L1 status than in nivolumab-treated patients with negative/indeterminate PD-L1 status, but both groups demonstrated numerically superior ORR compared to patients treated with DTIC therapy.

Table 21: Summary of overall survival (OS) by PD-L1 expression status in CheckMate 066, ITT analysis set

	Nivolumab (n=210)	DTIC (n=208)
PD-L1-positive patients, n (%)	74 (35.2)	74 (35.6)
Events, n (%)	11 (14.9)	29 (39.2)
Median OS (95% CI), months	Not reached	12.39 (9.17, not reached)
Unstratified hazard ratio (95% CI)	0.30 (0.15, 0.60)	
PD-L1-negative/indeterminate patients, n (%)	136 (64.8)	134 (64.4)
Events, n (%)	39 (28.7)	67 (50.0)
Median OS (95% CI), months	Not reached	10.22 (7.59, 11.83)
Unstratified hazard ratio 95% CI	0.48 (0.32, 0.71)	
Key: CI, confidence interval; DTIC, dacarbazine; ITT, intention-to-treat; n, number; OS, overall survival; PD-L1, programmed death-ligand-1. **Source:** CheckMate 066 CSR[106]; Robert et al., 2015[82]		

Table 22: Summary of response by PD-L1 expression status in CheckMate 066, ITT analysis set

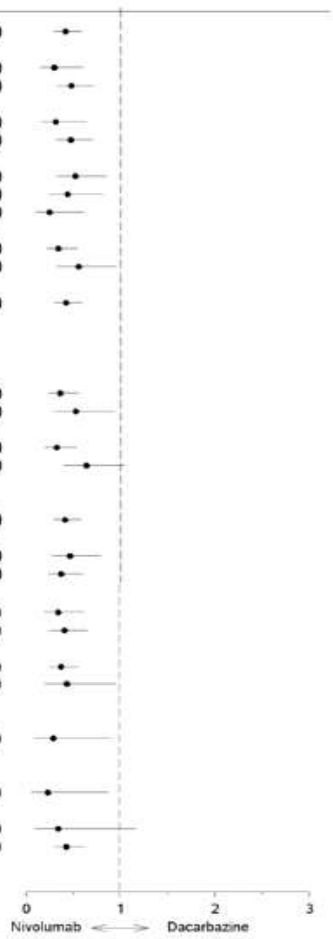
	Nivolumab (n=210)	DTIC (n=208)
Objective response rate (ORR)[a]		
PD-L1-positive patients, n (%)	74 (35.2)	74 (35.6)
Responders, n (%) (95% CI)	39 (52.7) (40.8, 64.3)	8 (10.8) (4.8, 20.2)
PD-L1-negative/indeterminate patients, n (%)	136 (64.8)	134 (64.4)
Responders, n (%) (95% CI)	45 (33.1) (25.2, 41.7)	21 (15.7) (10.0, 23.0)
Key: CI, confidence interval; CR, complete response; n, number; ORR, objective response rate; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors. **Notes:** [a], confirmed response (CR + PR) as per RECIST v1.1 criteria. **Source:** CheckMate 066 CSR[106]; Robert et al., 2015[82]		

CheckMate 067 and 037

Subgroup analysis for CheckMate 067 and 037 is presented in Appendix 7. Results were consistent with the CheckMate 066 trial.

Figure 22: Forest plot of treatment effect on OS in pre-defined subgroups of CheckMate 066; ITT analysis set

	N	Nivolumab N of Events (N of subjects)	Nivolumab mOS (95% CI)		Dacarbazine N of Events (N of subjects)	Dacarbazine mOS (95% CI)		Unstratified Hazard Ratio	(95% CI)
Overall	418	50(210)	N.A.		96(208)	10.84	(9.33, 12.09)	0.42	(0.30, 0.59)
PD-L1 Status									
Positive	148	11(74)	N.A.		29(74)	12.39	(9.17, N.A.)	0.30	(0.15, 0.60)
Negative/Indeterminate	270	39(136)	N.A.		67(134)	10.22	(7.59, 11.83)	0.48	(0.32, 0.71)
M Stage at Study Entry									
M0/M1A/M1B	163	11(82)	N.A.		29(81)	12.39	(9.56, N.A.)	0.31	(0.16, 0.63)
M1C	255	39(128)	N.A.		67(127)	9.33	(6.64, 11.17)	0.47	(0.32, 0.71)
Age Category									
< 65	200	28(106)	N.A.		40(94)	11.17	(9.17, N.A.)	0.52	(0.32, 0.85)
>= 65 and < 75	151	16(77)	N.A.		30(74)	11.70	(9.33, 15.18)	0.44	(0.24, 0.81)
>= 75	67	6(27)	N.A.		26(40)	6.64	(4.86, 9.33)	0.25	(0.10, 0.61)
Gender									
Male	246	27(121)	N.A.		62(125)	9.92	(8.38, 11.70)	0.34	(0.22, 0.54)
Female	172	23(89)	N.A.		34(83)	12.39	(7.59, N.A.)	0.56	(0.33, 0.95)
Race									
White	416	50(209)	N.A.		95(207)	10.41	(9.26, 12.39)	0.42	(0.30, 0.60)
Black	0	0(0)	N.A.		0(0)	N.A.			
Asian	1	0(0)	N.A.		1(1)	12.09	(N.A., N.A.)		
Other	1	0(1)	N.A.		0(0)	N.A.			
Region									
W.Europe+Canada	290	29(145)	N.A.		66(145)	9.92	(8.34, 13.96)	0.36	(0.23, 0.56)
Rest of World	128	21(65)	N.A.	(12.68, N.A.)	30(63)	11.17	(7.59, 14.85)	0.53	(0.30, 0.93)
Baseline ECOG Performance Status									
0	269	23(148)	N.A.		48(121)	11.83	(9.59, 15.18)	0.32	(0.20, 0.53)
1	144	26(60)	12.68	(7.46, N.A.)	46(84)	7.43	(5.16, 11.70)	0.64	(0.40, 1.04)
History of Brain Metastases									
Yes	15	1(7)	N.A.	(0.59, N.A.)	2(8)	N.A.	(3.35, N.A.)		
No	403	49(203)	N.A.		94(200)	10.41	(9.26, 12.09)	0.41	(0.29, 0.58)
Smoking Status									
Yes	163	24(90)	N.A.	(12.68, N.A.)	33(73)	10.22	(9.33, 15.18)	0.46	(0.27, 0.79)
No	232	25(111)	N.A.		58(121)	10.41	(7.39, 12.09)	0.37	(0.23, 0.60)
Baseline LDH 1									
<= ULN	245	16(120)	N.A.		38(125)	14.85	(11.17, N.A.)	0.35	(0.19, 0.62)
> ULN	153	29(79)	N.A.	(8.51, N.A.)	53(74)	6.31	(4.21, 8.38)	0.41	(0.26, 0.65)
Baseline LDH 2									
<= 2*ULN	355	35(178)	N.A.		73(177)	11.17	(9.56, 14.85)	0.38	(0.25, 0.57)
> 2*ULN	43	10(21)	10.28	(1.84, N.A.)	18(22)	2.58	(0.95, 4.21)	0.44	(0.20, 0.96)
Prior Neo-adjuvant or Adjuvant Therapy									
Neo-adjuvant	2	0(1)	N.A.		1(1)	7.43	(N.A., N.A.)		
Adjuvant	68	4(32)	N.A.		13(36)	12.09	(8.34, N.A.)	0.29	(0.10, 0.91)
Time from Completion of Prior Adjuvant Therapy to Randomization									
< 6 Months	19	1(7)	N.A.	(7.26, N.A.)	3(12)	11.60	(4.17, N.A.)		
>= 6 Months	49	3(25)	N.A.		10(24)	12.09	(5.16, N.A.)	0.24	(0.07, 0.88)
AJCC Stage at Study Entry									
Stage III	49	4(27)	N.A.		9(22)	11.60	(7.13, 15.18)	0.35	(0.10, 1.16)
Stage IV	369	46(183)	N.A.		87(186)	10.22	(8.38, 12.39)	0.44	(0.30, 0.62)



Key: AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; LDH, lactate dehydrogenase; n, number; NA, not available; OS, overall survival; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.
Source: CheckMate 066 CSR[106]

4.9 Meta-analysis

Meta-analysis has not been conducted for the three RCTs available for nivolumab monotherapy as, although these studies all provide relevant information relating to the decision problem, the studies themselves are too clinically diverse to be combined. The key reasons why meta-analysis would be inappropriate include differences in control arms (DTIC, ICC and ipilimumab) and differences in patient populations enrolled (treatment naïve BRAF mutation-negative, previously treated and treatment naïve across all patients regardless of BRAF mutation status). Furthermore, the key efficacy endpoint of interest in melanoma (OS) is only available from one trial (CheckMate 066) at this time.

4.10 Indirect and mixed treatment comparisons

Summary

- Many of the treatment comparators of interest have not been compared in head to head clinical trials; therefore, indirect treatment comparisons were required
- To achieve this, 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 nivolumab with all comparators of interest within one analysis to form indirect treatment comparisons, was not possible for a variety of reasons, including:
    - Non-proportional hazards between BRAF inhibitors, palliative chemotherapy and immunotherapies due to their differing mechanisms of action
    - High levels of crossover in the BRAF inhibitor trials and subsequent ipilimumab use
    - Lack of homogeneity of trial designs in the evidence base
- Patient level data have been used where possible to inform indirect treatment comparisons in order to account for differences in patient characteristics
- Comparison to ipilimumab was performed using data from the MDX010-20 clinical trial requiring the following assumptions, which were accepted during previous NICE appraisals:
    - Equivalence of DTIC and gp100
    - Line of treatment is not an independent prognostic factor and does not independently affect treatment effectiveness
    - No difference between treatment effects by BRAF mutation status
    - Equivalence of ipilimumab 3mg/kg+gp100 and ipilimumab 3mg/kg
- Indirect treatment comparison results versus ipilimumab indicated a significant difference in PFS (HR=0.58; 95% CI: 0.42, 0.80) and OS (HR=0.55; 95% CI: 0.36, 0.84)
- Estimates are in line with observed PFS data from the 067 clinical trial (HR=0.57 [95% CI: 0.43, 0.76]; p<0.001)
- The vast majority of the benefit for nivolumab compared to ipilimumab was derived from reduction in the time to progression
- Post-progression survival (PPS) was similar for ipilimumab compared to nivolumab providing validity to the assumption and clinical expectation that immunotherapies like nivolumab and ipilimumab, which target immuno-regulatory signalling pathways, will provide a similar long-term survival benefit profile
- 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 TA321
- 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 0.5 years versus more than 2 years, which is consistent with the increased speed of response and magnitude of survival benefit observed with nivolumab

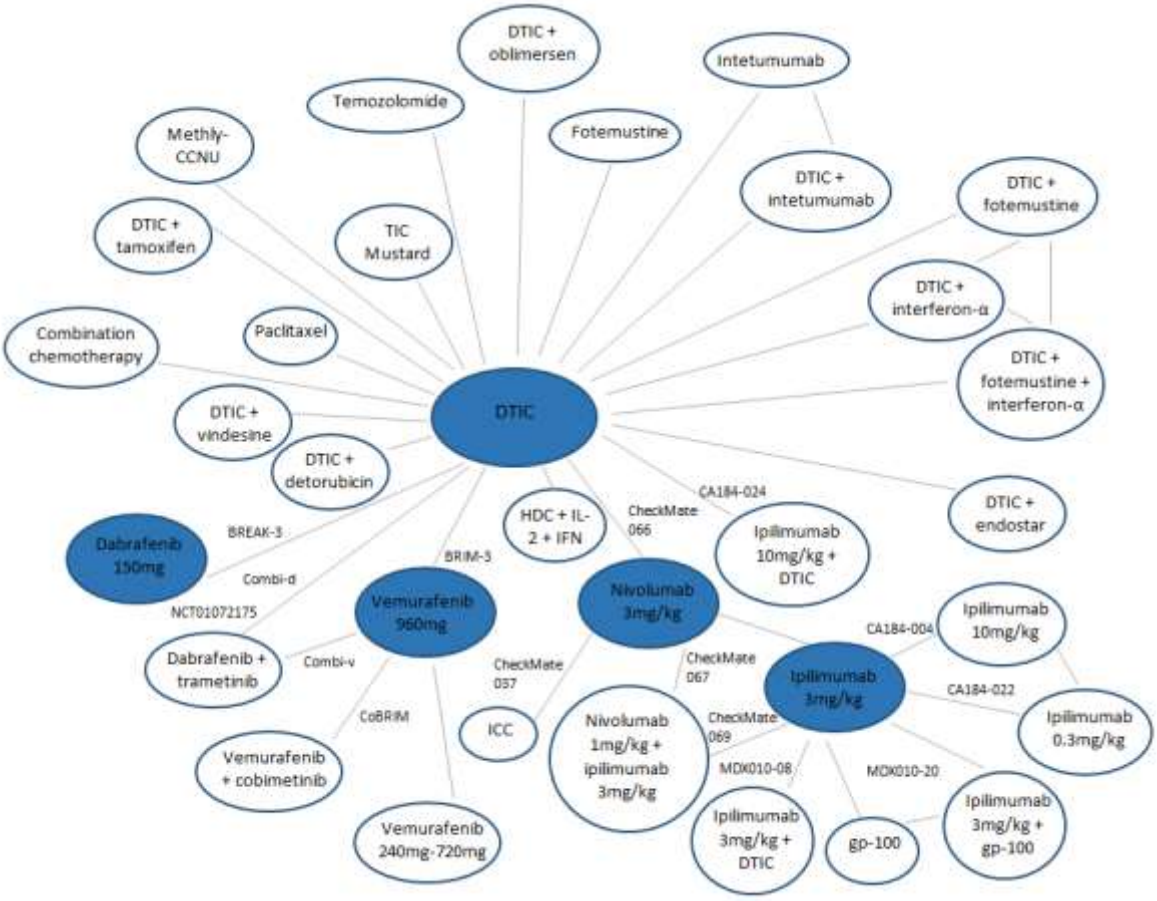
Many of the treatment comparators of interest have not been compared in head to head clinical trials; therefore, indirect treatment comparisons are required. Additionally, for the purposes of economic modelling, it is important that the relative efficacy (OS and PFS) between treatments allows for long-term extrapolation of treatment effects. To achieve this, 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, and the assumptions required to form indirect comparisons between nivolumab and the treatment comparators of interest also differ by comparison. Given these issues, the strategy for estimating treatment efficacy and relative treatment effects differs by treatment comparison. 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
- Indirect treatment comparison strategy
- Comparison of nivolumab to ipilimumab and palliative chemotherapy
    - Evidence base
    - Methods
    - Results
- Comparison of nivolumab 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 10. The broad network of evidence identified is shown in Figure 23. The treatments/comparators of interest are identified in the blue ovals. It is clear that there are many trials in this network that do not contribute information to comparisons on nivolumab with the other comparators of interest. Many of these are ‘spider arms’ in the network that were included due to the inclusion of DTIC in the trials. The nivolumab trial CheckMate 067 includes a direct comparison of nivolumab and ipilimumab; however, at the time of submission, OS data were not available for this trial, and therefore, CheckMate 067 was not included in the estimation of treatment effects (direct or indirect).

Figure 23: Broad evidence base network



Key: CCNU, lomustine; DTIC, dacarbazine; gp-100, glycoprotein-100; HDC, histamine dihydrochloride; ICC, investigator's choice chemotherapy; IFN, interferon; IL-2, interleukin-2; kg, kilogram; mg, milligram; TIC, triazeno imidazole carboxamide.

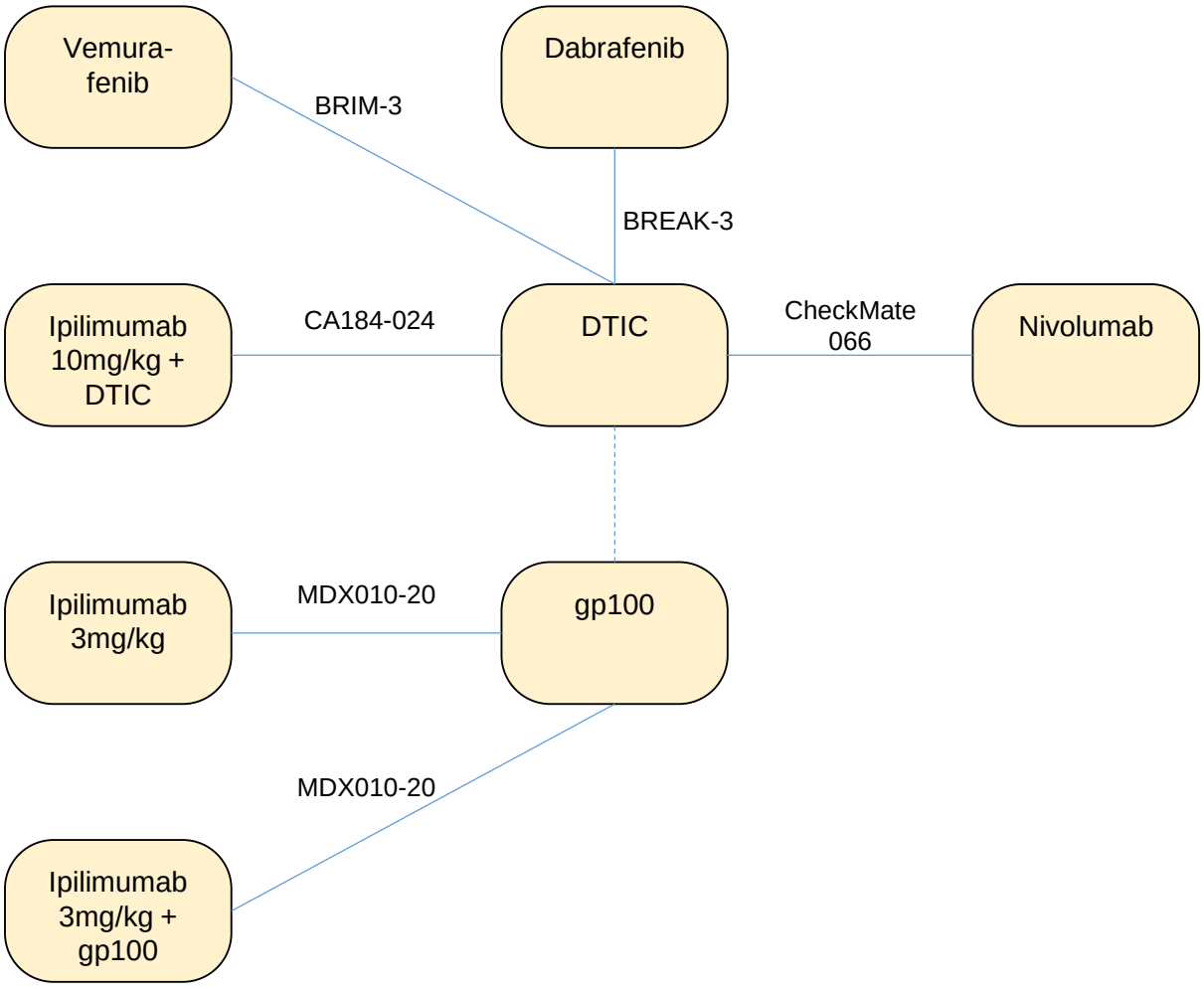
The treatment comparators of interest for nivolumab, by BRAF status and treatment experience, are shown in Table 23. As OS is the most important outcome for patients with advanced melanoma, and as there are some issues with response and progression assessments of immuno-oncology therapies against RECIST criteria (see Section 4.3), only trials that report OS were included within the indirect comparison.

Table 23: Comparators considered for indirect comparison, relevant to final scope

Population	Comparators, treatment naïve	Comparators, previously treated
BRAF mutation positive	Ipilimumab 3mg/kg Vemurafenib (960mg BID) Dabrafenib (150mg BID)	Either ipilimumab or vemurafenib/dabrafenib dependent upon first-line therapy Palliative chemotherapy (including DTIC)
BRAF mutation negative	Ipilimumab 3mg/kg DTIC (where ipilimumab cannot be tolerated)	Palliative chemotherapy (including DTIC)

The relevant trials identified for these treatments, which report OS, and are not 'spider arms' within the network, are shown in the network diagram in Figure 24.

Figure 24: Network diagram



Key: DTIC, dacarbazine; gp100, gp100 melanoma peptide vaccine.
Notes: The dotted line between DTIC and gp100 does not indicate a trial, but rather indicates that if DTIC and gp100 are considered equivalent, it allows for MDX010-20 to be linked within this network of treatments.

Indirect treatment comparison strategy

Head to head evidence for nivolumab versus palliative chemotherapy is available from the CheckMate 066 trial. Therefore, the required treatment comparisons are formed as follows:

- Head to head comparison (CheckMate 066):
    - Nivolumab versus palliative chemotherapy (DTIC)
- Indirect treatment comparison:
    - Nivolumab versus ipilimumab
    - Nivolumab versus BRAF inhibitors

The key trial design features to consider within this evidence base are shown in Table 24. Quality assessment of these trials is presented in Appendix 3.

Table 24: Key trial design features for selected evidence base

Trial	Treatments	BRAF status	Previously treated?	Patient level data available?	Subsequent therapy / crossover
CheckMate 066	• Nivolumab • Dacarbazine	BRAF mutation negative	No	Yes	Subsequent ipilimumab in either arm and crossover (from dacarbazine to nivolumab) has been allowed since July 2014, but none observed in the current data-cut
CA184-024	• Ipilimumab 10mg/kg + dacarbazine • Dacarbazine	Unknown	No	Yes	No subsequent ipilimumab or BRAF inhibitors
MDX010-20	• Ipilimumab 3mg/kg • gp100 • Ipilimumab 3mg/kg + gp100	Unknown	Yes	Yes	No subsequent ipilimumab or BRAF inhibitors
BRIM-3	• Vemurafenib • Dacarbazine	BRAF mutation positive	No	No	Crossover & subsequent ipilimumab
BREAK-3	• Dabrafenib • Dacarbazine	BRAF mutation positive	No	No	Crossover & subsequent ipilimumab

A mixed treatment comparison, combining nivolumab with all comparators of interest within one analysis to form indirect treatment comparisons, is not possible 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 5.3.3, Figure 36 and Figure 37)
    - 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 are problematic, for example when trying to use DTIC as the common comparator, given that CheckMate 066 did not have patients that crossed over from DTIC to nivolumab prior to analysis.
- Lack of homogeneity of trial designs in the evidence base, including:
    - Line of therapy (at the treatment doses of interest); i.e. lack of data for ipilimumab 3mg/kg at first-line, requiring the use of similar approaches to those used in TA319, which led to the NICE recommendation (i.e. utilising

available evidence of ipilimumab 3mg/kg in second-line and/or evidence at 10mg/kg + dacarbazine in first-line)

- Differences in BRAF status

As previously stated, OS data for nivolumab are only available from CheckMate 066, which enrolled BRAF mutation-negative patients; this evidence is assumed to be equally applicable to BRAF mutation-positive patients as, similar to ipilimumab, the efficacy of nivolumab is not dependent upon BRAF mutation status (see Section 4.13). Moreover, the indirect comparison is only possible for treatment naïve patients as no evidence is available for BRAF inhibitors in previously treated patients.

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 with ipilimumab and palliative chemotherapy 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 25.

Table 25: Treatment comparison strategy

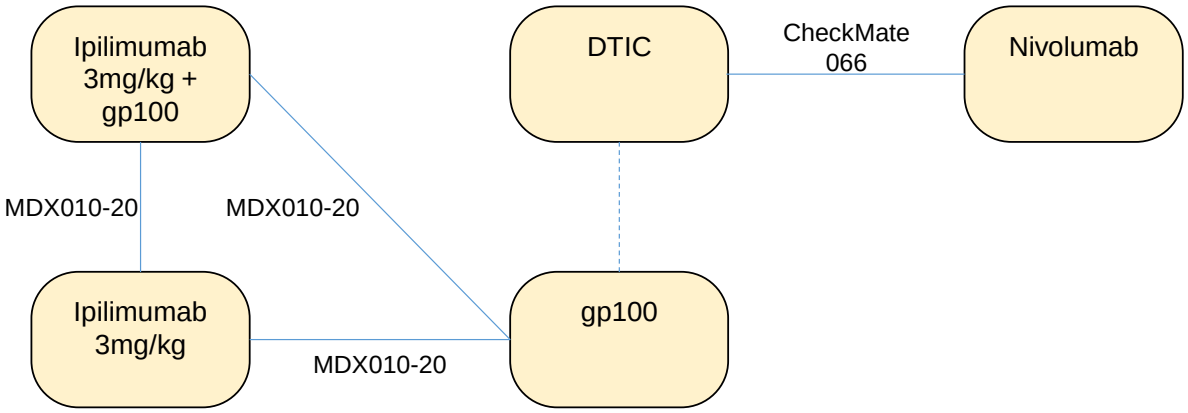
Comparison	Treatments
Nivolumab vs palliative chemotherapy such as DTIC	Use head to head patient level data from CheckMate 066
Nivolumab vs ipilimumab	Use patient level data from CheckMate 066 and MDX010-20 / CA184-024 to form an indirect comparison
Nivolumab vs vemurafenib	Use patient level data from CheckMate 066 and aggregate/summary data from BRIM-3 to form an indirect comparison
Nivolumab vs dabrafenib	Use patient level data from CheckMate 066 and aggregate/summary data from BREAK-3 to form an indirect comparison

Comparison of nivolumab to ipilimumab and palliative chemotherapy

Evidence base

It might be considered natural to form an indirect comparison with ipilimumab using CheckMate 066 and CA184-024 with DTIC as the common comparator; however, CA184-024 studies ipilimumab at a higher dose (10mg/kg) than is required in this decision problem (3mg/kg) and is given in combination with DTIC. It has been previously established in TA319 that assuming equivalence of ipilimumab 3mg/kg and ipilimumab 10mg/kg plus DTIC is not a reasonable assumption, therefore we do not use CA184-024 (ipilimumab 10mg/kg) in our base case analyses, but have presented these as a sensitivity/scenario analysis for completeness. We have therefore formed indirect treatment comparisons of nivolumab versus ipilimumab 3mg/kg using CheckMate 066 and MDX010-20, which was used as the primary evidence base for recommendation of ipilimumab in treatment naïve patients in TA319. The network diagram for this comparison is shown in Figure 25.

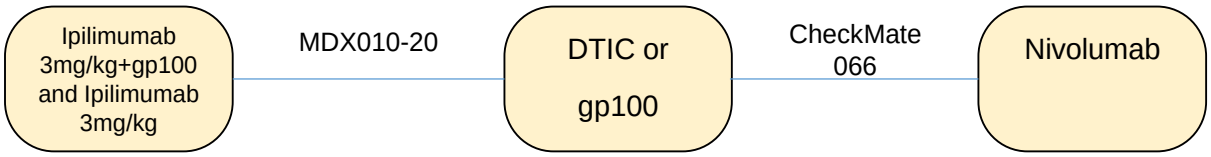
Figure 25: Network diagram for CheckMate 066 and MDX010-20



Key: DTIC, dacarbazine; gp100, gp100 melanoma peptide vaccine.

To maximise the patient level data used in this analysis and to make the indirect comparison feasible, this network is consolidated and simplified to the network shown in Figure 26.

Figure 26: Network diagram for the comparison of Nivolumab with Ipilimumab



Key: DTIC, dacarbazine; gp100, gp100 melanoma peptide vaccine.

For this network to be used in a viable/robust analysis, the following assumptions have been made:

Equivalence of DTIC and gp100

All published meta-analyses have shown that there are no discernible differences between the chemotherapies and gp100 with respect to OS and PFS.[4, 23, 75, 188, 189] The following evidence is available for the equivalence of gp100 to palliative chemotherapy (such as DTIC), some of which was presented during the appraisal of ipilimumab in previously treated patients (TA268) as part of which the assumption of equivalence of gp100 to palliative chemotherapy was accepted:

- Meta-analysis of KM OS curves from selected RCTs in advanced melanoma, which demonstrated that, when corrected for prognostic factors, these curves are indistinguishable from historical melanoma survival curves[189]
- A systematic review and meta-analysis of RCTs containing OS for previously treated patients based upon summary statistics, which showed that gp100 is similar to existing treatments for the management of pre-treated patients with unresectable Stage III/IV melanoma[188]
- A meta-analysis of Phase II Cooperative Group trials in metastatic Stage IV melanoma which concluded that no treatments at that point had a significant effect on OS and identified key prognostic variables in melanoma[23]

This is in line with clinical expert evidence at the appraisal committee meeting for ipilimumab in treatment naïve patients (TA319), where the clinical expert stated that DTIC, similar to gp100, has never been shown to have survival benefit.[4] Indeed, in the subsequent text

within this section and in the statistical models, the equivalence of DTIC and gp100 is denoted in places by broad use of the term 'palliative chemotherapy' (the specific treatment comparator per the final scope). We recognise that gp100 is not palliative chemotherapy, but the outcomes on gp100 have been used as a proxy for outcomes on palliative chemotherapy in order to form indirect treatment comparisons with ipilimumab, as discussed above.

Line of treatment is not independently prognostic and does not independently impact treatment effectiveness

This assumption is required as CheckMate 066 is in first line patients, whilst MDX010-20 studies previously treated patients. Based upon available information for ipilimumab and nivolumab, no difference in efficacy has been seen over different lines of treatment (see Section 4.13).[23, 51, 190, 191] This assumption was previously accepted in TA319 in the context of the MDX010-20 study and its applicability to first-line therapy with ipilimumab.[4]

No difference between treatment effects by BRAF mutation status

This is required as CheckMate 066 is in BRAF mutation-negative patients, whilst MDX010-20 did not capture the BRAF status of the patients. This is a reasonable assumption as demonstrated by Larkin et al. (2015), which presents a pooled analysis of nivolumab data and concludes that nivolumab has similar efficacy and safety outcomes in BRAF mutation positive and negative patients (regardless of prior BRAF inhibitor or ipilimumab treatment).[83] Likewise, ipilimumab demonstrated similar efficacy in both BRAF mutation-positive and -negative patients in CA184-004.[117]

Equivalence of ipilimumab 3mg/kg+gp100 and ipilimumab 3mg/kg

This is 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.[75]

The primary baseline characteristics (i.e. those with known prognostic effects on outcomes) in CheckMate 066 and MDX010-20 are shown in Table 26. Prognostic factors were selected 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.[4, 23] In addition to adjusting for baseline demographic characteristics that impact prognosis, subsequent ipilimumab use is adjusted for within the analysis, as this is also known to be prognostic. The list of potentially prognostic covariates was validated with UK clinicians during an advisory board in March 2015.[12]

The use of the covariate-adjusted indirect comparison for comparing ipilimumab and nivolumab allows the differences between the trials with respect to these important prognostic factors to be controlled for when estimating the comparable treatment effect between ipilimumab and nivolumab. In addition to controlling for known prognostic factors, a covariate is included in the model to test for any study level effects from unknown prognostic factors. This covariate also acts as a test of the validity of the assumptions noted previously with a small, non-significant study effect indicating that the prognostic models should be controlling for the differences between trials.

Table 26: Prognostic characteristics of CheckMate 066 and MDX010-20

	CheckMate 066		**MDX010-20**	
Characteristic	DTIC (n=208)	Nivolumab (n=210)	gp100 (n=136)	Ipilimumab & ipilimumab+gp100 (n=540)
ECOG = 0	58.2%	70.5% (unknown= 0.5%)	52.9% (unknown= 0.7%)	58.3%
LDH (>ULN)	35.6% (4.3% not reported)	37.6% (5.2% not reported)	39.7%	37.2%
M stage = M1c	61.1%	61.0%	72.1%	71.3%
History of Brain Metastases	3.8%	3.3%	15.4%	11.3%
Age (under 65)	45.2%	50.5%	69.1%	71.5%
Gender (males)	60.1%	57.6%	53.7%	60.7%
Subsequent ipilimumab	38.0%	21.4%	NA (0%)	NA (0%)
Key: DTIC, dacarbazine; ECOG, Eastern Cooperative Oncology Group score; gp100, gp100 melanoma peptide vaccine; LDH, lactate dehydrogenase; NA, not applicable, ULN, upper limit of normal range.				

Methods

As described in Section 4.7, OS data for nivolumab in study CheckMate 066 are relatively immature (i.e. they do not reach the median survival point). The validity and robustness of survival extrapolations of OS (needed for long-term estimation of treatment effects in the economic model) are therefore likely to be limited if parametric curves are fitted directly to trial OS data due to high levels of uncertainty around long-term estimates.

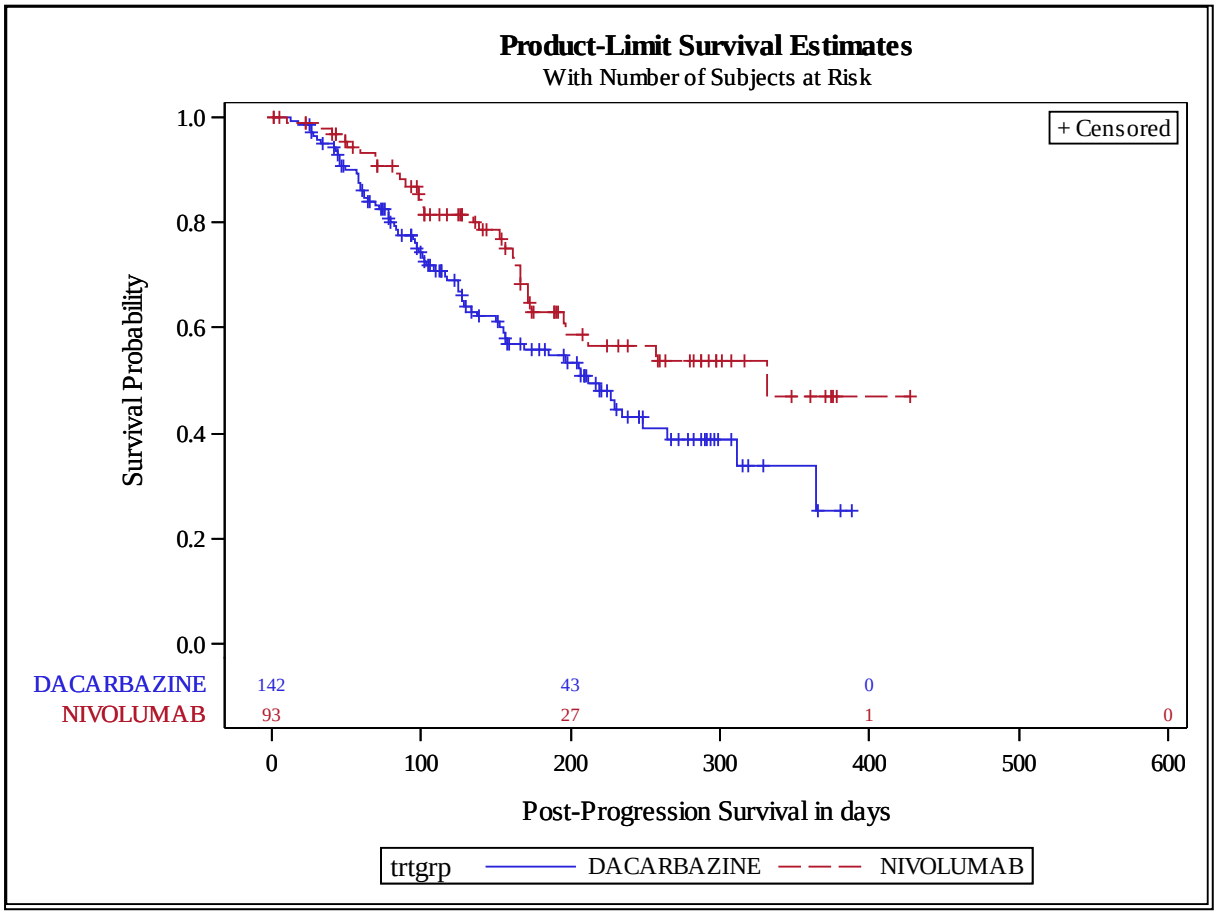
An alternative approach (to allow more robust estimation of long-term survival extrapolations) is to use time to progression (TTP), pre-progression survival (PrePS) and post-progression survival (PPS) instead of OS and PFS; TTP and PrePS are used to inform the long-term extrapolation of PFS, and TTP, PrePS and PPS are used to inform the long-term extrapolation of OS.

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. PrePS is defined the same way as OS; however, patients that progress are censored at the time of progression. PPS only includes patients that have progressed and follows time to death, or censoring, from the point of progression.

The KM plot for PPS for nivolumab and DTIC in CheckMate 066 is presented in Figure 27. The PPS data are much more mature compared to OS for nivolumab, and therefore, long-term extrapolations based upon parametric curves fitted to PPS are likely to be more valid and robust than extrapolations based on curves fitted to OS data. As a result, the economic model has been designed to adopt a Markov-based state-transition approach using TTP,

PrePS, and PPS for modelling survival, rather than an area under the curve (AUC) partitioned survival method using PFS and OS.

Figure 27: Kaplan–Meier curve for post-progression survival in CheckMate 066



Parametric survival curves have been fitted to TTP, PrePS and PPS separately in the statistical software R[192]. In line with Decision Support Unit (DSU) guidance (technical support document [TSD] 14)[193], 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 27. By assuming equivalence of gp100 (MDX010-20) and DTIC (CheckMate 066), the adjustment for the trial indicator covariate (i.e. CheckMate 066or MDX010-20) in the survival models helps form the indirect comparison of nivolumab and ipilimumab; i.e. the treatment effect estimates can be considered relative treatment effects controlling for the study effect (indirect comparison). This is analogous to using summary-level relative treatment effects and a common comparator in the adjusted indirect comparator approach.

Table 27: Prognostic factors included within the covariate-adjusted model for nivolumab versus ipilimumab and palliative chemotherapy

Covariate	Levels
Treatment	3 levels: nivolumab, ipilimumab and palliative chemotherapy
Trial	2 levels: CheckMate 066 and MDX010-20
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
Use of subsequent ipilimumab (for the PPS outcome only)	2 levels: yes vs no
Key: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; NA, not applicable, 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 sensitivity of these results have been explored in the following ways:

- Performing the indirect comparison to ipilimumab using CA184-024 instead of MDX010-20
- Assuming common PPS response for ipilimumab and nivolumab
- Producing parsimonious models, using backwards selection of covariates

The results from these sensitivity analyses are presented in Appendix 8.

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 99% of patients [714 out of 718 pooled across groups] 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 sensitivity analyses looking into parsimonious models also support this conclusion.

The number of events by outcome are shown in Table 28 for both the full trial population and the group of patients with complete covariate information that are used for fitting survival models:

Table 28: 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						
MDX010-20	gp100	119 / 136 (87.5%)	127 / 136 (93.4%)	100 / 136 (73.5%)	27 / 136 (19.9%)	92 / 100 (92.0%)
	Ipilimumab pooled	406 / 540 (75.2%)	493 / 540 (91.3%)	383 / 540 (70.9%)	110 / 540 (20.4%)	296 / 383 (77.3%)
CheckMate 066	DTIC	96 / 208 (46.2%)	163 / 208 (78.4%)	145 / 208 (69.7%)	18 / 208 (8.7%)	66 / 142 (46.5%)
	Nivolumab	50 / 210 (23.8%)	108 / 210 (51.4%)	96 / 210 (45.7%)	12 / 210 (5.7%)	31 / 93 (33.3%)
Population of patients with complete covariate information						
MDX010-20	gp100	118 / 135 (87.4%)	126 / 135 (93.3%)	100 / 135 (74.1%)	26 / 135 (19.3%)	92 / 100 (92.0%)
	Ipilimumab pooled	406 / 540 (75.2%)	493 / 540 (91.3%)	383 / 540 (70.9%)	110 / 540 (20.4%)	296 / 383 (77.3%)
CheckMate 066	DTIC	91 / 199 (45.7%)	158 / 199 (79.4%)	141 / 199 (70.9%)	17 / 199 (8.5%)	62 / 138 (44.9%)
	Nivolumab	45 / 199 (22.6%)	105 / 199 (52.8%)	96 / 199 (48.2%)	9 / 199 (4.5%)	31 / 93 (33.3%)

Key: DTIC, dacarbazine; gp100, gp100 melanoma peptide vaccine; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival; TTP, time to progression.

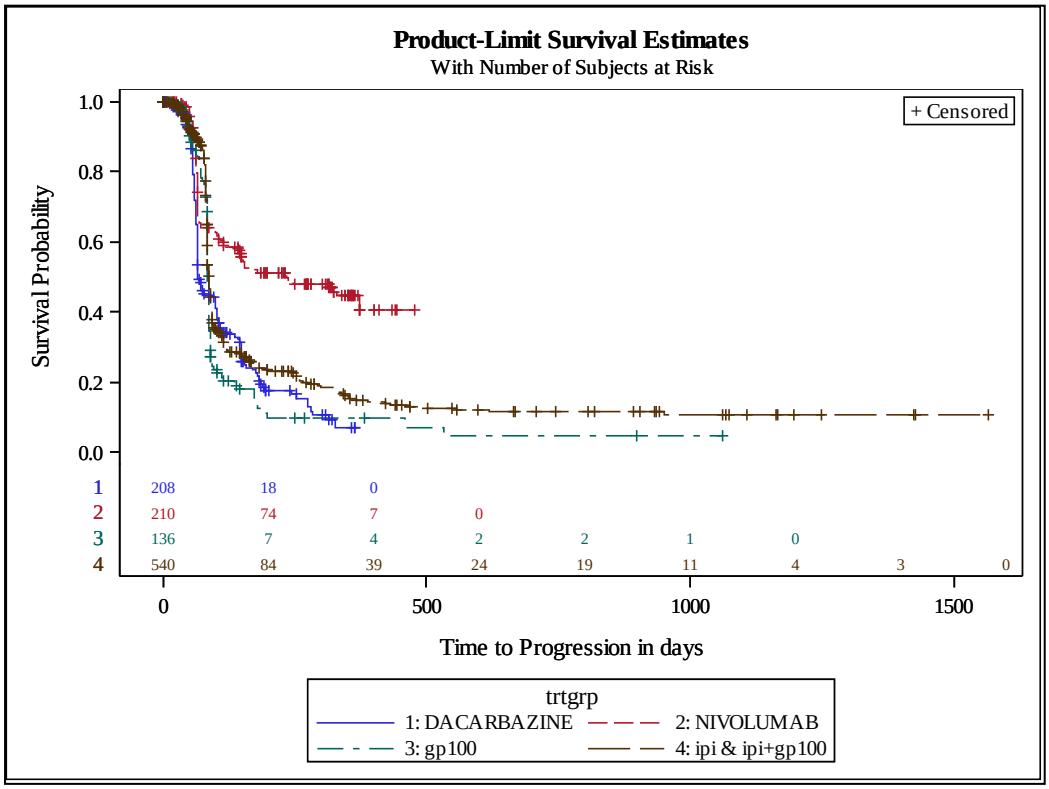
Results – TTP

Unadjusted KM curves for CheckMate 066 and MDX010-20 for TTP are shown in Figure 28.

There are steep drops in the KM curves for both trials near to the start of the curves. This is because the timing of progression assessment relies on protocol-specified tumour assessment times. For CheckMate 066, the first scheduled time at which tumour assessment occurred was 9 weeks, meaning that there was a large number of patients seen to progress at or shortly after the 2 month time point; in reality, some of these patients will have progressed at a time earlier than 2 months, but this information cannot be captured. Similarly for MDX010-20, there are a cluster of patients who have progressed at around 3 months, because the protocol defined first assessment of tumour at 12 weeks. 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, the data were cut at Day 100 to allow a more clinically and statistically plausible shape and continuous flow to the occurrence of progression in the data from Day 100 onwards. Day 100 was selected as a common study day to ensure that, in both studies, patients surviving to that point will have had their first tumour assessment, i.e. the 12 week scheduled time in MDX010-20 (selected as it was longer than that for CheckMate 066), incorporating a time/visit-window for patient assessments around that.

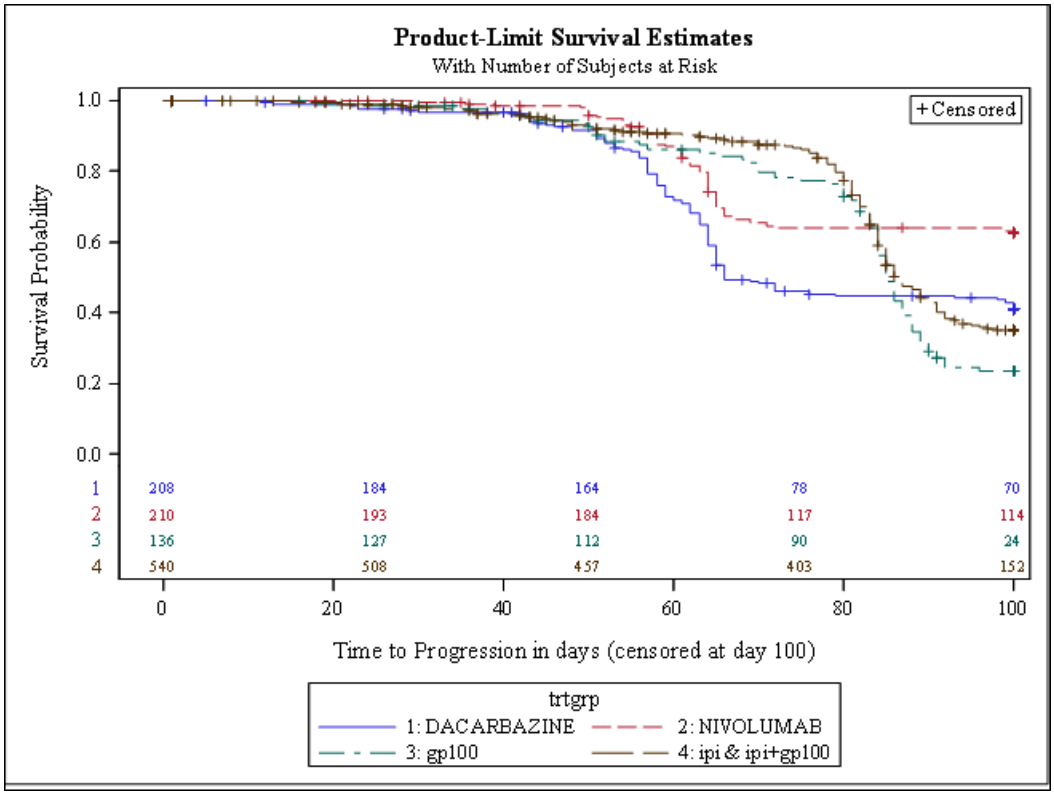
The KM curves for TTP split at Day 100 are shown in Figure 29 (KM censored at Day 100) and Figure 30 (KM from Day 100 onwards and rebased at Day 100). The TTP events prior to and after Day 100 are shown in Table 29.

Figure 28: Kaplan–Meier curves for time to progression



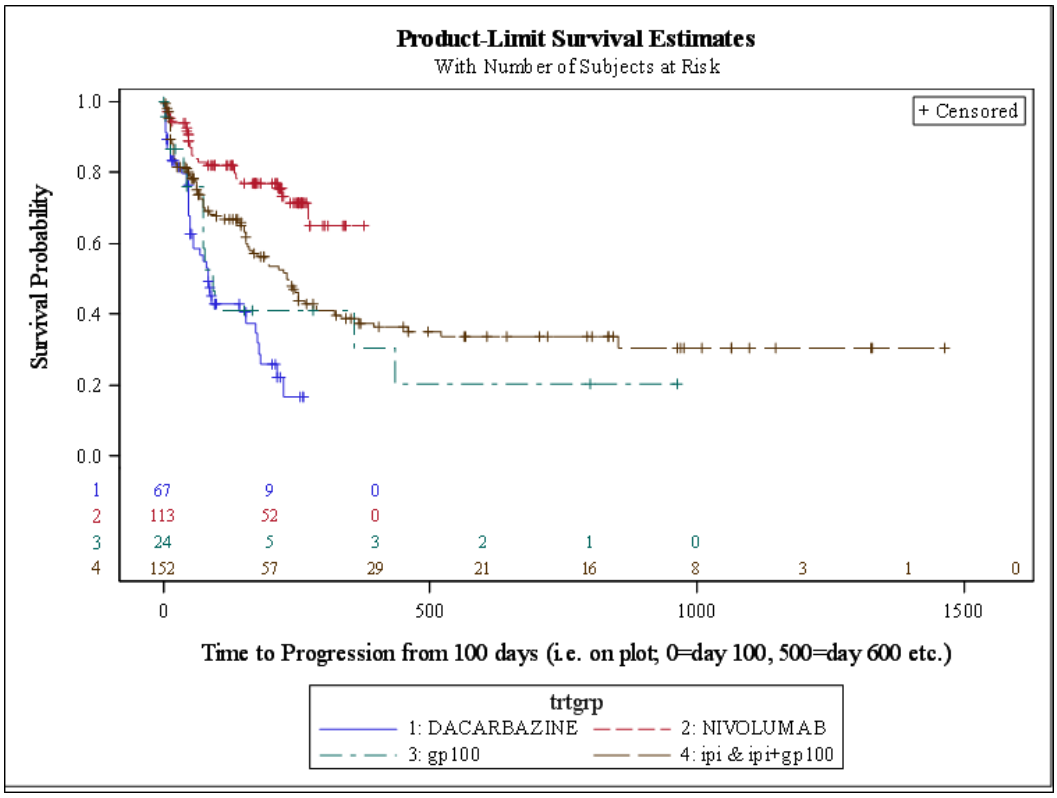
Notes: Dacarbazine and nivolumab are from CheckMate 066, and gp100 and 'ipi & ipi+gp100' are from MDX010-20. The different lengths of Kaplan–Meier curves for the two trials are due to the stage of the trial at the point of data cut used in these analyses.

Figure 29: Kaplan–Meier curves for time to progression (patients censored at Day 100)



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

Figure 30: Kaplan–Meier curves for time to progression (measured from Day 100)



Notes: Dacarbazine and nivolumab are from CheckMate 066, and gp100 and 'ipi & ipi+gp100' are from MDX010-20. Time zero on the plot equates to day 100 of the trial.

Table 29: Events by trial and treatment for TTP before and after Day 100

Study	Treatment group	TTP ≤100 days Events n/N(%)	TTP >100 days Events n/N(%)
Full population			
MDX010-20	gp100	87 / 136 (64.0%)	13 / 24 (54.2%)
	Ipilimumab pooled	301 / 540 (55.7%)	82 / 152 (53.9%)
CheckMate 066	DTIC	104 / 208 (50.0%)	41 / 67 (61.2%)
	Nivolumab	69 / 210 (32.9%)	27 / 113 (23.9%)
Population of patients with complete covariate information			
MDX010-20	gp100	87 / 135 (64.4%)	13 / 23 (56.5%)
	Ipilimumab pooled	301 / 540 (55.7%)	82 / 152 (53.9%)
CheckMate 066	DTIC	101 / 199 (50.8%)	40 / 66 (60.6%)
	Nivolumab	69 / 199 (34.7%)	27 / 108 (25.0%)
Key: DTIC, dacarbazine; gp100, gp100 melanoma peptide vaccine; TTP, time to progression.			

TTP pre-100 days was estimated within the economic model based on the observed KM data up to 100 days (as shown in Figure 29). To estimate relative efficacy and to control for differences of patient prognostic factors between trials and treatment arms, the KM data for TTP pre-100 days were adjusted by applying HRs estimated from a Cox proportional hazards model for the same covariates used for fitting survival curves (Table 30). This method assumes proportionality of the effects of the prognostic factors and use these for adjusting the observed TTP pre-100 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-100 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 30: Cox proportional hazards model; TTP pre-100 days

Model parameter	Parameter estimate	Standard error	P-value	Hazard ratio
Study (CheckMate 066 vs MDX010-20)	-0.10053	0.14838	0.4981	0.904
Treatment (ipilimumab vs palliative chemotherapy)	-0.27502	0.12212	0.0243	0.760
Treatment (nivolumab vs palliative chemotherapy)	-0.69219	0.15662	<.0001	0.500
Sex (male vs female)	0.10456	0.08729	0.2310	1.110
Age group (under 65 vs 65 and over)	0.07851	0.09196	0.3933	1.082
ECOG (ECOG=0 vs ECOG ≥1)	0.03920	0.09223	0.6708	1.040
Elevated LDH (>ULN vs ≤ULN)	0.34677	0.09647	0.0003	1.414

Model parameter	Parameter estimate	Standard error	P-value	Hazard ratio
M stage (M1c vs M0 or M1a or M1b)	-0.00651	0.09874	0.9474	0.994
History of brain metastases (yes vs no)	-0.06095	0.15250	0.6894	0.941
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 100 days, and the fitted curves are shown against the KM curves by trial and treatment in Figure 31. Note, the amount of missing covariate data was minimal (e.g. more than 98% of patients [349 out of 356 pooled across groups] are included in the TTP post 100 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 31 are predicted curves from the estimated parametric equations; i.e. the 4 shown curves (by treatment) are all estimated from each parametric equation using summary covariate information observed in the data for the given treatment group.

The model fits were assessed using AIC/BIC, as shown in Table 31, where lower values represent better fitting models. The fits of the parametric curves according to visual fit to KM data and AIC/BIC indicate that the generalised gamma, Gompertz, log-logistic and log-normal models are all reasonable fits to the data.

The Gompertz curve provided the best statistical fit and long-term extrapolations for Gompertz were judged to be clinically plausible and the most in line with long-term data available for ipilimumab; therefore, Gompertz 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 32. Parameters for alternative model fits are supplied in Appendix 8.

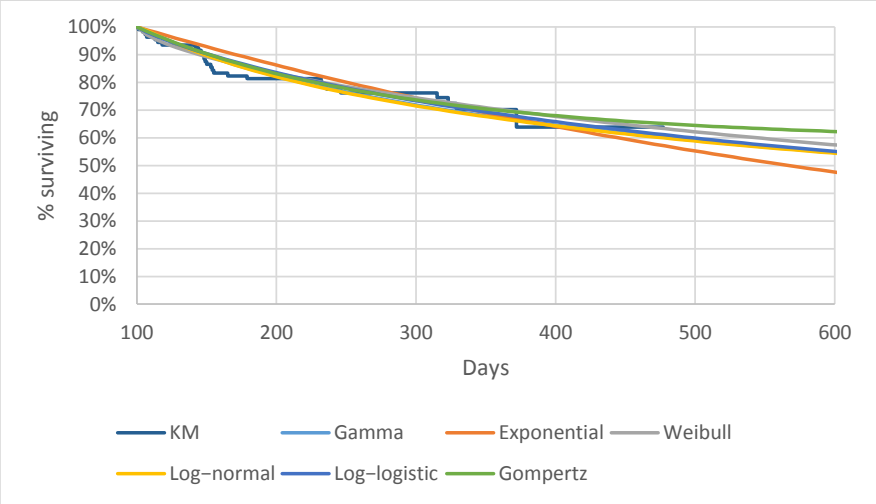
Fitted curves are constructed using the “Shape” value together with the linear combination of the intercept and covariate estimates. For the Gompertz distribution, the exponential of the covariate estimates can be interpreted as HRs. Using this, we observe a strong positive effect in favour of both nivolumab and ipilimumab versus palliative chemotherapy.

Using the same parametric model, setting ipilimumab as the reference treatment, we estimated an indirect treatment comparison effect of nivolumab vs ipilimumab, in favour of nivolumab, of: HR=0.356, 95% confidence interval (0.165, 0.771).

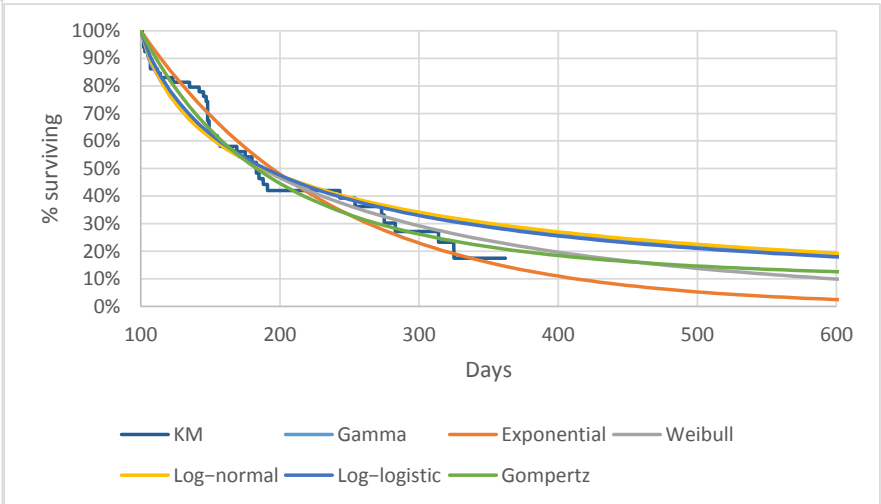
Although many of the covariates individually had modest effects on the outcome and were not statistically significant, we felt it important to retain these in the model to fully adjust for prognostic factors and to allow more flexibility within the economic model for different patient populations.

Figure 31: Parametric model fits for time to progression post 100 days

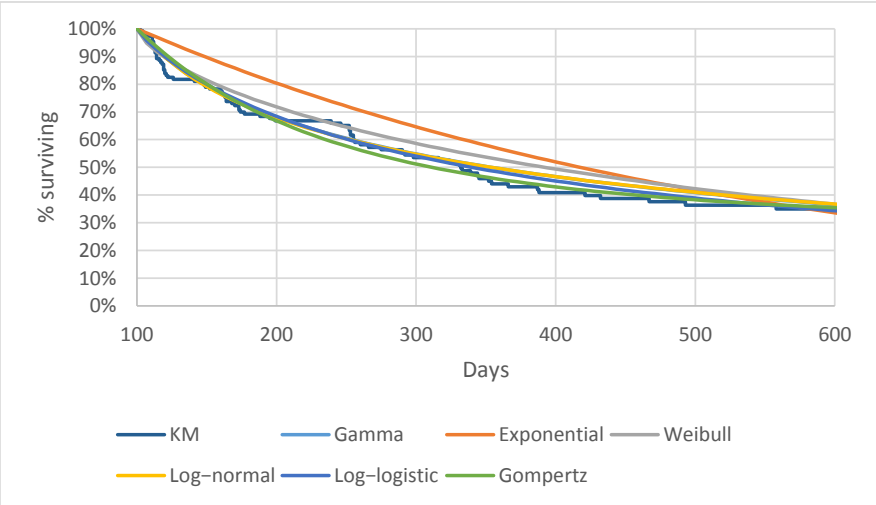
CheckMate 066: nivolumab



CheckMate 066: DTIC



MDX010-20: ipilimumab



MDX010-20: gp100

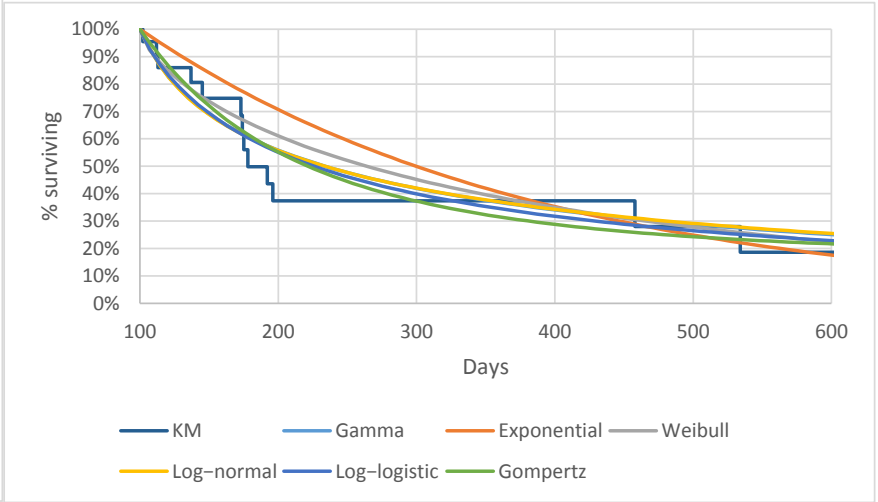


Table 31: Model fit estimates for TTP post 100 days

Model	AIC	BIC
Exponential	2232.96	2271.51
Generalised Gamma	2186.23	2232.49
Gompertz	2176.14	2218.55
Log-logistic	2185.59	2228.00
Log-normal	2184.28	2226.69
Weibull	2195.53	2237.94
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; TTP, time to progression.		

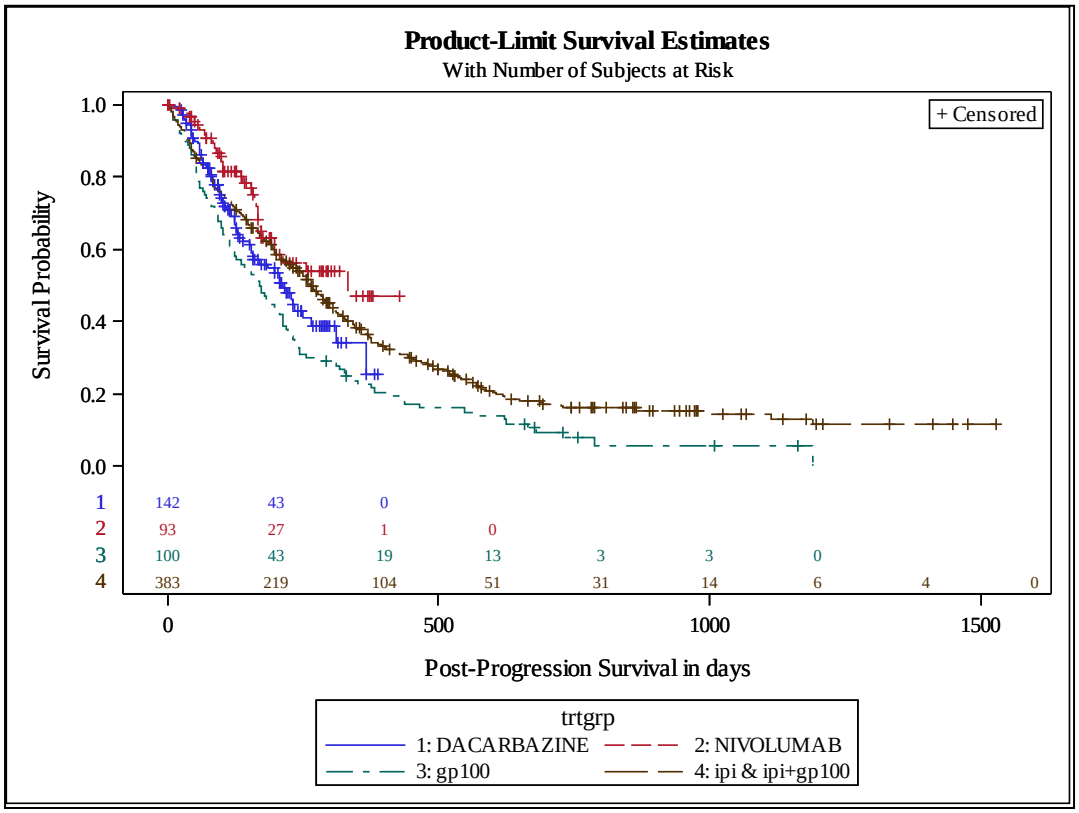
Table 32: Gompertz model parameter estimates for TTP post 100 days

Model Parameter	Estimate	Lower 95% CL	Upper 95% CL
Shape	-0.004	-0.005	-0.003
Rate (intercept)	0.006	0.003	0.013
Treatment: ipilimumab vs palliative chemotherapy	-0.395	-0.986	0.197
Treatment: nivolumab vs palliative chemotherapy	-1.430	-1.920	-0.933
Study: CheckMate 066 vs MDX010-20	0.342	-0.297	0.980
Sex: male vs female	-0.152	-0.475	0.172
Aged under 65: YES vs No	0.180	-0.160	0.521
High LDH: Yes vs No	-0.195	-0.604	0.215
ECOG: 0 vs ≥1	-0.057	-0.406	0.292
M stage: M1c vs 'M0 or M1a or M1b'	0.290	-0.055	0.635
History of brain metastases: Yes vs No	0.111	-0.469	0.692
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 32.

Figure 32: Kaplan–Meier curves for post-progression survival



Notes: Dacarbazine and nivolumab are from CheckMate 066, and gp100 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.

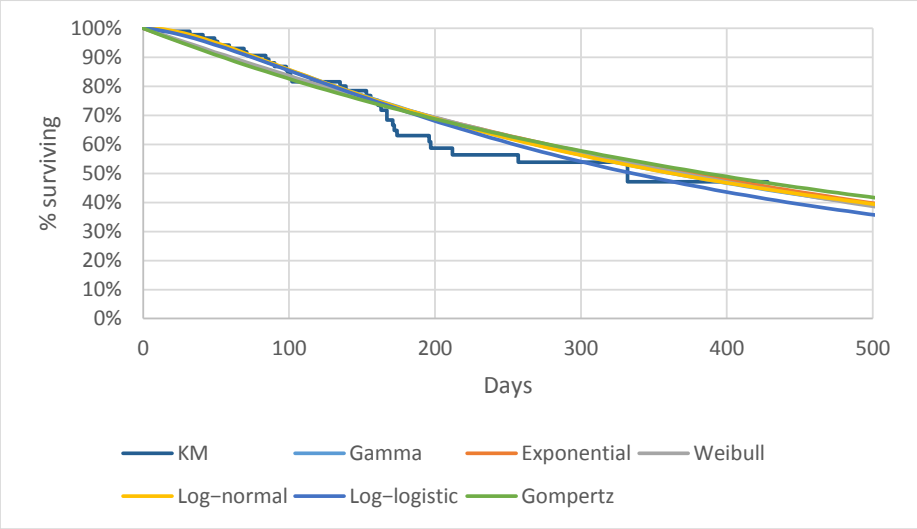
The six covariate-adjusted parametric curves were fitted to the PPS data, and the fitted curves are shown with the KM curves by trial and treatment in Figure 33. The model fits were assessed using AIC/BIC in Table 33, where lower values represent better fitting models.

Table 33: Model fit estimates for PPS

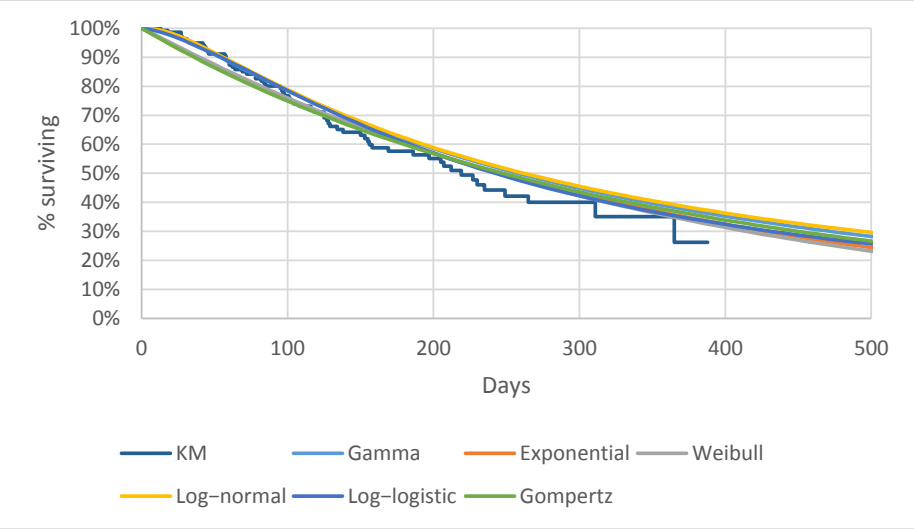
Model	AIC	BIC
Exponential	6574.76	6625.04
Generalised Gamma	6543.75	6603.17
Gompertz	6572.27	6627.12
Log-logistic	6543.14	6597.99
Log-normal	6543.57	6598.42
Weibull	6575.76	6630.61
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; PPS, post-progression survival.		

Figure 33: Parametric model fits for post-progression survival

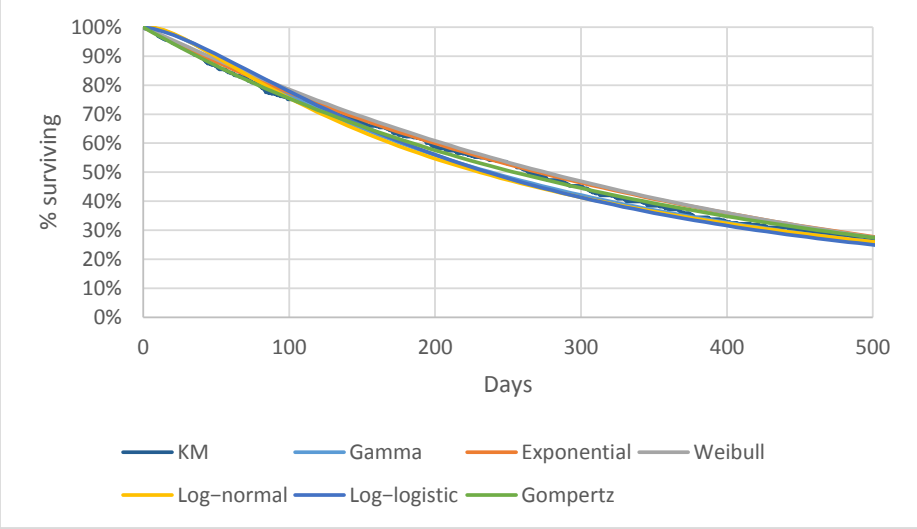
CheckMate 066: nivolumab



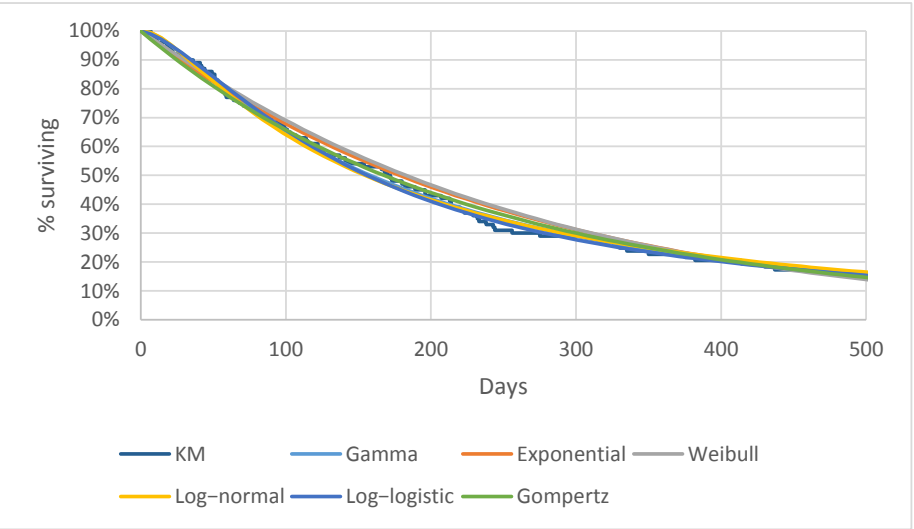
CheckMate 066: DTIC



MDX010-20: ipilimumab



MDX010-20: gp100



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. 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 clinical validation of the expected survival for ipilimumab and DTIC. The parameter estimates for this selected model are shown in Table 34. Parameters for alternative model fits are supplied in Appendix 8.

Table 34: Log-logistic model parameter estimates for PPS

Model Parameter	Estimate	Standard Error	p-value
Scale[a]	0.683 (0.381[a])	0.026	
Intercept	5.152	0.178	<0.0001
Treatment: ipilimumab vs palliative chemotherapy	0.403	0.135	0.003
Treatment: nivolumab vs palliative chemotherapy	0.381	0.197	0.054
Study: CheckMate 066 vs MDX010-20	0.137	0.188	0.468
Sex: male vs female	-0.132	0.098	0.178
Aged under 65: Yes vs No	0.168	0.105	0.111
High LDH: Yes vs No	-0.897	0.111	<0.001
ECOG: 0 vs ≥1	0.349	0.103	0.001
M stage: M1c vs 'M0 or M1a or M1b'	-0.099	0.112	0.375
History of brain metastases: Yes vs No	-0.075	0.164	0.650
Subsequent ipilimumab: Yes vs No	0.667	0.189	<0.001

Key: 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.

Using the same parametric model, setting ipilimumab as the reference treatment, we estimated an indirect treatment comparison effect of nivolumab vs ipilimumab of: estimate=-0.023, standard error=0.238, p-value=0.924; thus implying there is little to no difference between nivolumab and ipilimumab with respect to PPS. As the log-logistic parametric curve is an accelerated failure time model, this can be interpreted as a mean PPS ratio (nivolumab/ipilimumab) of 0.98 (i.e. exp(-0.023)).

This result provides further validity to the assumption and clinical expectation that immunotherapies like nivolumab and ipilimumab, which target immuno-regulatory signalling pathways, will provide a similar long-term survival benefit profile.

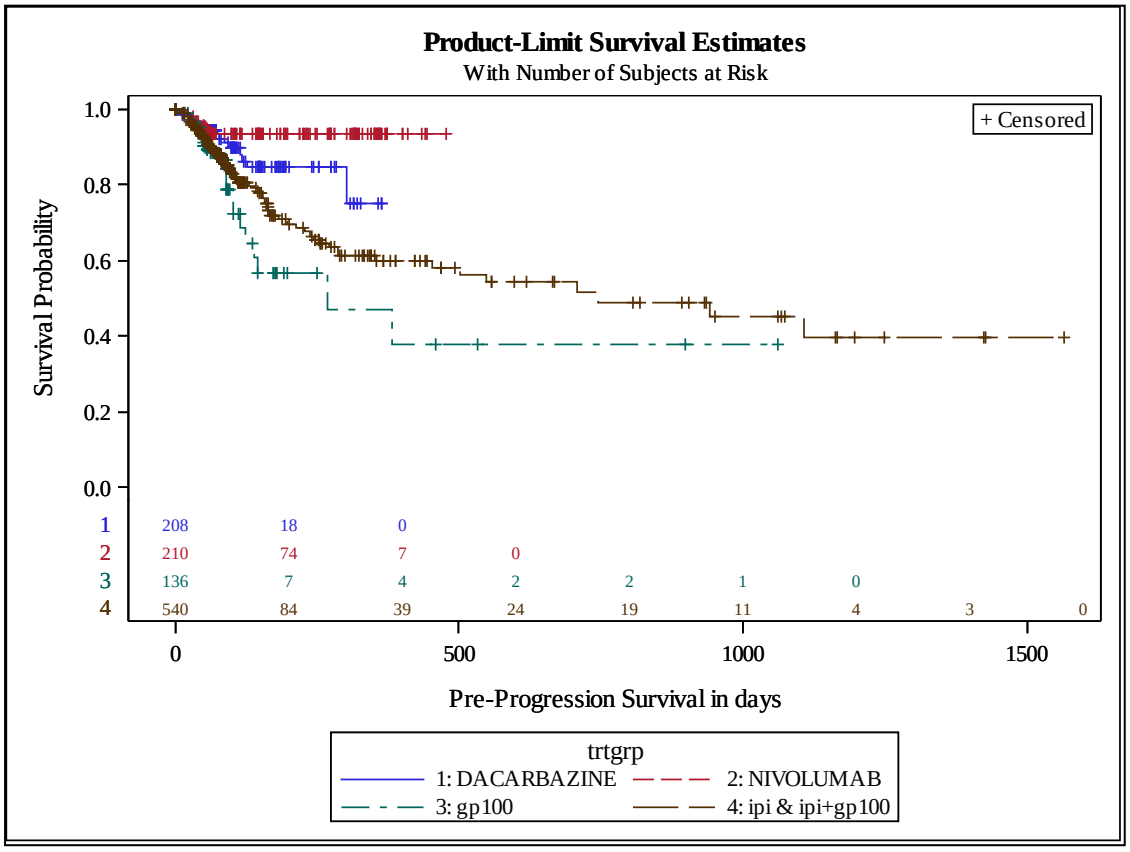
Although some of the covariates individually had modest effects on the outcome and were not statistically significant, we felt it was important to retain these in the model to fully adjust for prognostic factors and to allow more flexibility within the economic model for different patient populations.

Results – PrePS

The KM curves for CheckMate 066 and MDX010-20 for PrePS are shown in Figure 34. Only a small amount of data is available for PrePS for both DTIC and nivolumab. Curve fits were attempted for PrePS; however, none of the standard parametric curves provided an acceptable visual fit to all 4 treatment arms included in the model (Appendix 8). 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 34: Kaplan–Meier curves for pre-progression survival



Similarly, for the adjustment of KM data for TTP pre-100 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 35).

Table 35: Cox proportional hazards model; PrePS

Model parameter	Parameter estimate	Standard error	P-value	Hazard ratio
Study (CheckMate 066 vs MDX010-20)	-0.77439	0.32147	0.0160	0.461
Treatment (ipilimumab vs palliative chemotherapy)	-0.17910	0.22646	0.4290	0.836
Treatment (nivolumab vs palliative chemotherapy)	-1.06624	0.41501	0.0102	0.344
Sex (male vs female)	0.31757	0.16339	0.0519	1.374
Age group (under 65 vs 65 and over)	-0.06347	0.16934	0.7078	0.939
ECOG (ECOG=0 vs ECOG ≥1)	-0.97366	0.17286	<.0001	0.378

Model parameter	Parameter estimate	Standard error	P-value	Hazard ratio
Elevated LDH (>ULN vs ≤ULN)	1.24471	0.18430	<.0001	3.472
M stage (M1c vs M0 or M1a or M1b)	0.58809	0.24684	0.0172	1.801
History of brain metastases (yes vs no)	0.01643	0.24329	0.9462	1.017
Key: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; PrePS, pre-progression survival; ULN, upper limit of normal range.				

Results – adjusted indirect comparisons

To examine the validity of the results of the indirect treatment comparison between nivolumab and ipilimumab using the patient level data and covariate-adjusted parametric survival curve approach, we also used a traditional approach, adjusted indirect comparisons[194], to obtain a relative treatment effect between nivolumab and ipilimumab. We constructed adjusted indirect comparisons between nivolumab and ipilimumab for the endpoints TTP post 100 days, PPS, OS, and PFS. To do this for each endpoint, we first performed a Cox proportional hazards regression separately for CheckMate 066 and MDX010-20, to estimate HRs for nivolumab versus DTIC and for ipilimumab versus gp100. The HRs were adjusted for the same covariates as used in the parametric survival models. The HRs were then used to construct the adjusted indirect comparisons between nivolumab and ipilimumab, assuming equivalence of DTIC and gp100 to form the common comparator. The results of the adjusted indirect comparisons are shown in Table 36.

The relative treatment effects between nivolumab and ipilimumab cannot be directly compared as they represent different quantities; i.e. HRs from Cox regression models or treatment effects in an accelerated failure time parametric model. However, in order to compare treatment effect estimates based purely upon clinical trial with those produced via the fitted Weibull parametric models HRs have been produced using both the Weibull parametric models and Cox regression informed adjusted indirect comparisons. We can see by comparing the HRs produced that adjusted indirect comparison (Cox regression models) and the Weibull model produce very similar results for nivolumab versus ipilimumab (see last two columns in Table 36).

Overall, we can conclude that nivolumab outperforms ipilimumab with respect to OS and PFS and that upon further exploration of these outcomes, i.e. by analysing TTP post 100 days and PPS, we see that the main nivolumab relative treatment benefit compared to ipilimumab is in delaying time to progression (i.e., significantly lower hazards for TTP post-100 days).

Table 36: Adjusted indirect comparisons of nivolumab versus ipilimumab

	Hazard ratio (95% confidence interval)			
Outcome	**CheckMate 066: nivolumab vs DTIC**	**MDX010-20: ipilimumab vs gp100**	**Adjusted indirect comparison: nivolumab vs ipilimumab**	**Weibull parametric model: nivolumab vs ipilimumab**
TTP Post 100 days	0.24 (0.14, 0.41)	0.66 (0.36, 1.19)	0.37 (0.17, 0.81)	0.38 (0.18, 0.84)
PPS	0.63 (0.41, 0.99)	0.69 (0.54, 0.87)	0.92 (0.56, 1.53)	0.95 (0.58, 1.55)

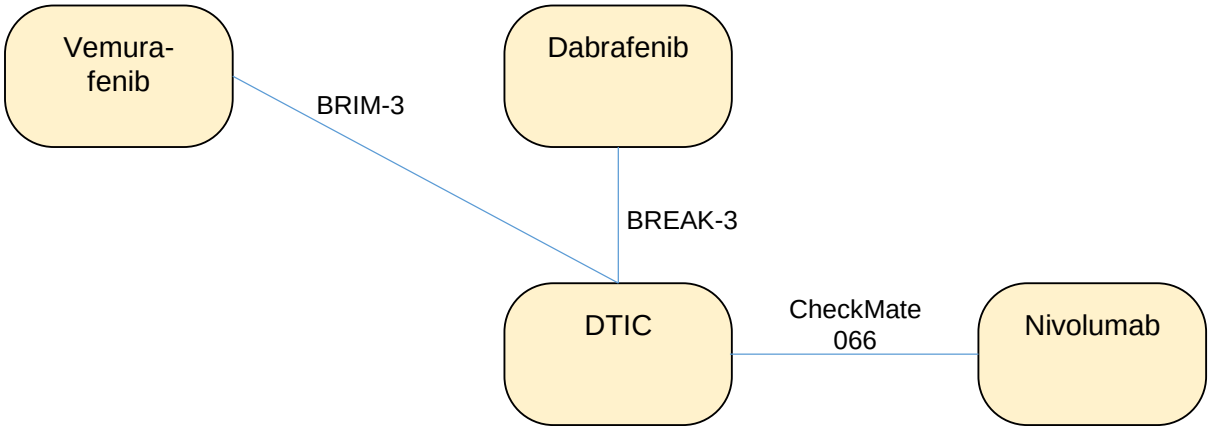
	Hazard ratio (95% confidence interval)			
Outcome	**CheckMate 066: nivolumab vs DTIC**	**MDX010-20: ipilimumab vs gp100**	**Adjusted indirect comparison: nivolumab vs ipilimumab**	**Weibull parametric model: nivolumab vs ipilimumab**
OS	0.37 (0.26, 0.54)	0.68 (0.55, 0.84)	0.55 (0.36, 0.84)	0.62 (0.41, 0.94)
PFS	0.44 (0.34, 0.56)	0.75 (0.61, 0.91)	0.58 (0.42, 0.80)	0.59 (0.43, 0.80)
Key: DTIC, dacarbazine; gp100, gp100 melanoma peptide vaccine; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; TTP, time to progression.				

Comparison of nivolumab to BRAF inhibitors

Evidence base

The network of evidence linking nivolumab with vemurafenib and dabrafenib is in Figure 35.

Figure 35: Network diagram for nivolumab and BRAF inhibitors



Key: DTIC, Dacarbazine.

Although patient level data are available for CheckMate 066, only summary data 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 066, BRIM-3 and BREAK-3 are shown in Table 37. There are some differences between the trials with respect to baseline characteristics of prognostic factors.

In TA321, the committee determined that vemurafenib and dabrafenib have approximately equal efficacy, and a meta-analysis was carried out by the 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 37: Baseline characteristics of CheckMate 066, BRIM-3, and BREAK-3

	CheckMate 066		BRIM-3		BREAK-3	
Characteristic	DTIC (n=208)	Nivolumab (n=210)	DTIC (n=338)	Vemurafenib (n=337)	DTIC (n=63)	Dabrafenib (n=187)
ECOG = 0	58.2%	70.5% (unknown= 0.5%)	68%	68%	70%	66%
LDH (>ULN)	35.6% (4.3% not reported)	37.6% (5.2% not reported)	58%	58%	30% (2% unknown)	36% (<1% unknown)
M stage = M1c	61.1%	61.0%	65%	66%	63%	66%
History of brain metastases	3.8%	3.3%	NR	NR	NR	NR
Age (under 65)	45.2% Median=66 years	50.5% Median=64 years	100% Median=52 years	100% Median=56 years	NR% Median=50 years	78.6% Median=53 years
Gender (males)	60.1%	57.6%	54%	59%	59%	60%

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 between CheckMate 066 and BRIM-3 invalid given that there was no cross-over in this data-cut of CheckMate 066, and the true effects of DTIC would be hard to estimate from BRIM-3.
- The proportional hazards assumption of relative treatment effects does not appear to hold within BRIM-3 (Figure 36 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.[195]

For these reasons, it was not appropriate to simply apply HRs estimated from BRIM-3 to the parametric curves estimated in CheckMate 066.

Instead, to form indirect comparisons between nivolumab 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[196]
- 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 nivolumab, the nivolumab 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 nivolumab in the BRAF mutation-positive patient population, keeping the efficacy observed for vemurafenib within BRIM-3 unaltered.

Source KM data for vemurafenib

The OS data for vemurafenib from the BRIM-3 trial were taken from Figure 4 in Hauschild 2013 and are presented in Figure 36.[103] The PFS data for vemurafenib from the BRIM-3 trial were taken from Figure 3 in McArthur 2014 and are presented in Figure 37.[139] These two publications were selected as the most up to date information on OS and PFS for vemurafenib at the time of submission.

Figure 36: Overall survival Kaplan–Meier plot for BRIM-3 (vemurafenib versus DTIC censored at crossover)

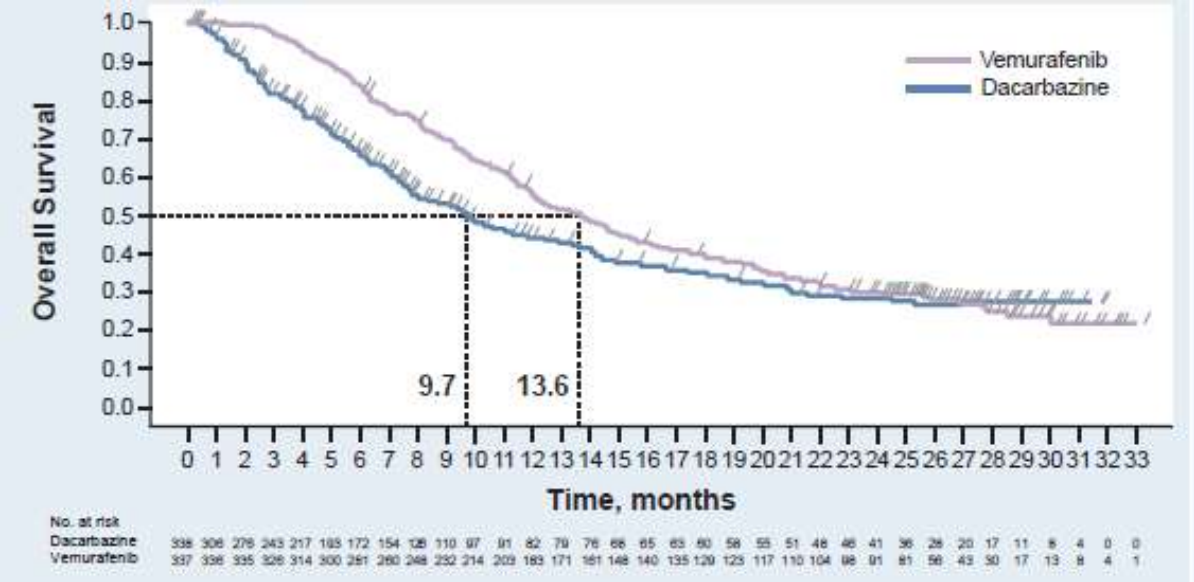
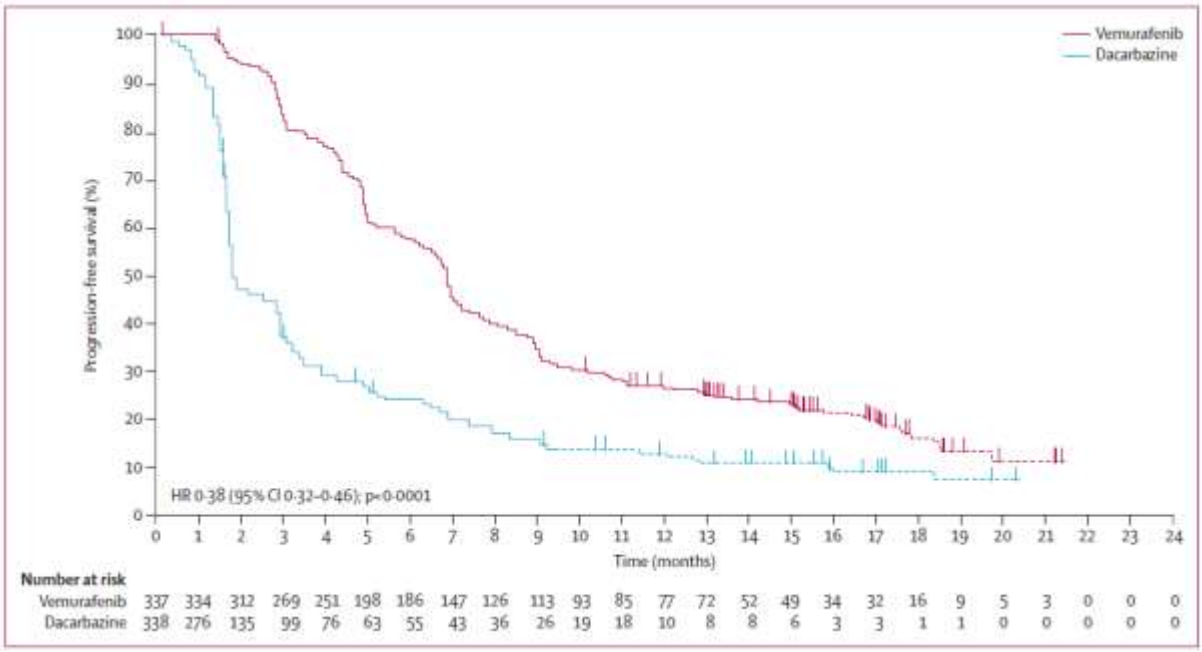


Figure 37: Progression-free survival Kaplan–Meier plot for BRIM-3 (vemurafenib versus DTIC)

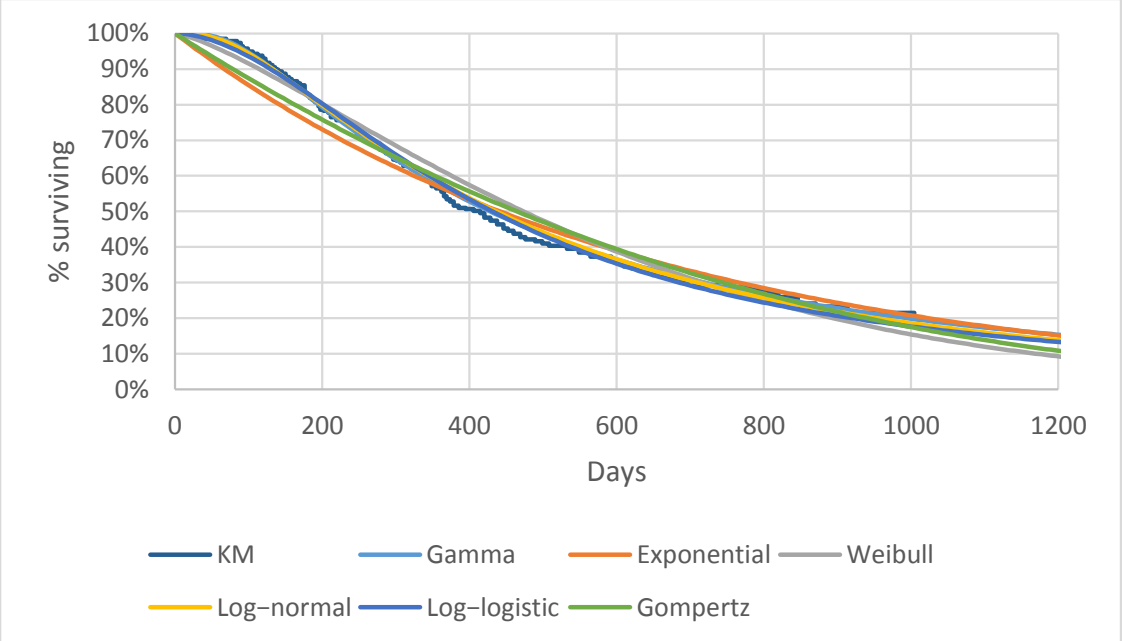


Results

Figure 38 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 38, 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 38: Parametric survival curves fitted to BRIM-3 vemurafenib OS data



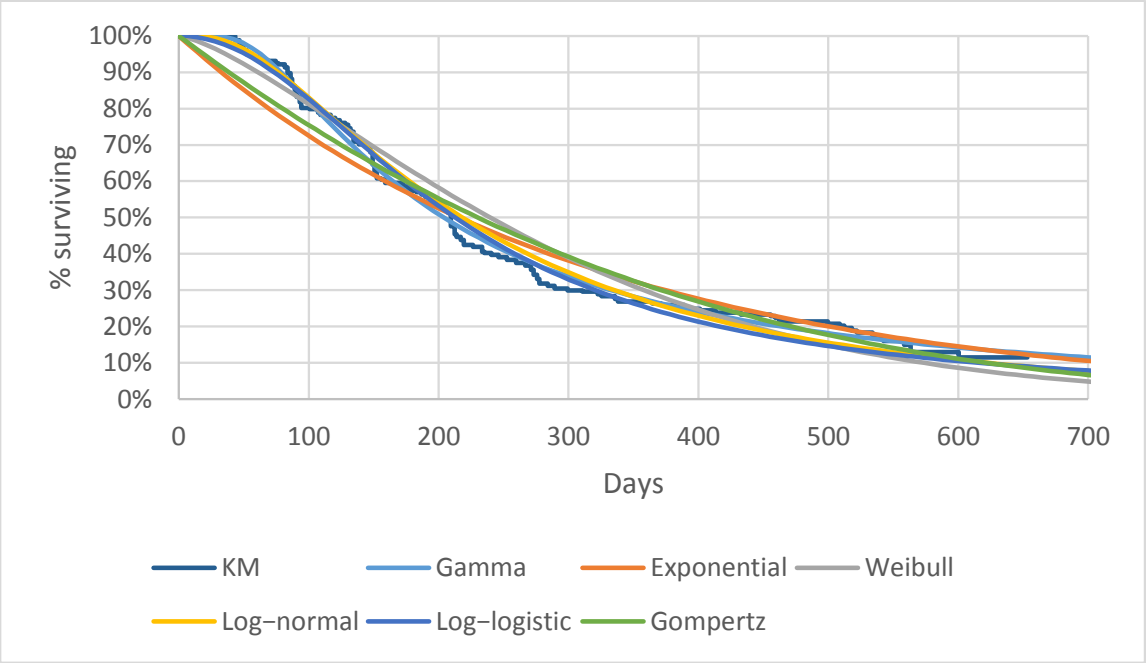
Key: OS, overall survival.

Table 38: Model fit estimates for OS (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 39 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 39, 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 39: Parametric survival curves fitted to BRIM-3 vemurafenib PFS data



Key: PFS, progression-free survival.

Table 39: Model fit estimates for PFS (BRIM-3)

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
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; PFS, progression-free survival.		

Results – BRAF inhibitors – selected model estimates

Table 40: 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
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.			

A comparison of the survival outcomes for BRAF inhibitors versus nivolumab is presented within Section 5.3.4 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 nivolumab as an immunotherapy will result in increased survival. 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 0.5 years versus more than 2 years, which is consistent with the increased speed of response and magnitude of survival benefit observed with nivolumab.

4.11 Non-randomised and non-controlled evidence

List of relevant non-randomised and non-controlled evidence

Systematic reviews were carried out to identify non-RCT evidence in adults with advanced melanoma in the first-line and subsequent-line setting. Both reviews used similar methodologies to those presented in Section 4.1. Details of the review methodologies and search strategies used are provided in Appendix 2.

Only one non-RCT (CheckMate 003) was identified that is considered relevant to the decision problem as it provides long-term survival data to support the use of nivolumab and included a 96-week treatment discontinuation rule aligned with that proposed in this submission (see Section 3.2).

CheckMate 003

CheckMate 003 investigated the efficacy and safety of nivolumab in patients with selected advanced solid tumours[197, 198]; a number of patients had advanced melanoma. Results for the advanced melanoma subgroup of interest to the decision problem are presented alongside results of the total population.[81, 197, 199]

A summary of the CheckMate 003 trial is presented in Table 41.

Table 41: List of relevant non-randomised and non-controlled evidence

Study number (acronym)	Objective	Population	Intervention	Primary study reference	Justification for inclusion
CheckMate 003	To assess the safety, anti-tumour activity and pharmacokinetics of nivolumab	Patients with advanced solid tumours; advanced melanoma subgroup	Nivolumab 0.1-10mg/kg q2w	Topalian et al., 2012[198]	Provides long-term survival data to support the use of nivolumab. Trial design included treatment discontinuation at 96 weeks
Key: kg, kilogram; mg, milligram; q2w, every 2 weeks.					

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

CheckMate 003 was a Phase I, dose-escalation study designed to assess the safety, anti-tumour activity and pharmacokinetics of multiple doses of nivolumab in patients with selected advanced or recurrent and progressing solid tumours, specifically melanoma, NSCLC, renal-cell cancer, castration-resistant prostate cancer or colorectal cancer. All patients enrolled had received previous treatment for advanced malignancies, but patients with prior antibody therapy that targeted T-cell function were excluded.

Small cohorts of patients were initially enrolled and sequentially assigned to nivolumab treatment at doses of 1.0, 3.0 or 10.0mg/kg q2w. A maximum tolerated dose (MTD) was not reached, resulting in expansion cohorts in each of the disease indications being enrolled and treated with nivolumab 3mg/kg or 10mg/kg q2w. Additionally, on the basis of initial signals of activity in melanoma, expansion cohorts of melanoma patients were enrolled and randomly assigned to nivolumab treatment at doses of 0.1, 0.3 or 1.0mg/kg q2w. No dose escalations or de-escalations were permitted within each patient's treatment, with the exception of melanoma patients enrolled in the 0.1 or 0.3mg/kg additional expansion cohorts who could escalate to the 1mg/kg dose level upon confirmed and worsening progressive disease within the first two treatment cycles.

Initial treatment was administered for a maximum duration of 96 weeks. Treatment was discontinued before 96 weeks in the event of: confirmed complete response; progressive disease; unacceptable toxicity; or withdrawn consent. In clinically stable patients, study treatment could be continued beyond apparent initial disease progression (RECIST v1.0 criteria assessed) until progression was confirmed. During the 46 week follow-up period, treatment could be re-initiated at the previous dose for patients who entered follow-up with ongoing disease control and subsequently demonstrated confirmed disease progression.

The primary endpoint of the CheckMate 003 study was safety and tolerability. This included assessment of AEs and fatalities. Secondary and exploratory endpoints included efficacy analyses of response and survival as well as pharmacokinetic outcomes.

The CheckMate 003 trial design is summarised in Table 42.

Table 42: Summary of CheckMate 003 methodology

Location	Patients were treated across 13 sites in North America
Trial design	Phase I, open-label, multi-centre, multidose, dose-escalation study The study consisted of 3 periods: • screening – up to 28 days • treatment – up to 96 weeks initial treatment, divided into 8 week treatment cycles comprised of 4 doses of study drug administered on Days 1, 15, 29 and 43. Re-initiation of treatment could occur in the follow-up period and continued for up to 1 year • follow-up – up to 46 weeks Patients were sequentially assigned to dose cohorts with dose escalation proceeding when a minimum of 3 patients in a dose cohort had received treatment for a full cycle (8 weeks) and not experienced a dose-limiting toxicity Patients enrolled in additional melanoma expansion cohorts were randomly assigned to one of 3 dose levels (0.1, 0.3 or 1.0mg/kg) according to a computer-generated randomisation schema
Eligibility criteria for participants	Men and women aged ≥18 years with previously treated, advanced solid tumour who signed informed consent and met the following key target disease and other criteria were enrolled: • untreated, histologically confirmed advanced or recurrent and progressing melanoma, NSCLC, renal-cell cancer, castration-resistant prostate cancer or colorectal cancer • measurable disease by RECIST v1.0 criteria with modification • ECOG PS of 0 or 1 • life expectancy ≥12 weeks • at least 1 and up to 5 prior systemic therapies for advanced/ recurrent and progressing disease • prior chemotherapy, immunotherapy or radiotherapy must have been completed at least 4 weeks before study drug administration • prior treated brain or meningeal metastases must be without MRI evidence of progression for at least 8 weeks and off immunosuppressive doses of systemic steroids for at least 2 weeks before study drug administration Patients who met any of the following key criteria were excluded from the study eligibility criteria: • history of severe hypersensitivity reactions to other mAbs • prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured • active, known or suspected autoimmune disease • prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody or any other antibody targeting T-cell co-stimulation pathways • underlying medical conditions that (in the investigators opinion) will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or AEs • concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic or absorbable topical corticosteroids

Settings and locations where the data were collected	Assessments were conducted on site, but all data for each patient were recorded in a case report form that was made available to BMS Medical Monitors and government inspectors as required
Trial drugs	Nivolumab 0.1 – 10mg/kg administered as an IV infusion Initial treatment was administered for a maximum duration of 96 weeks. Treatment continued until there was confirmed complete response, disease progression, an unacceptable level of toxic effects or patient withdrew consent before 2 years. Treatment after RECIST v1.0 criteria assessed progression was permitted for clinically stable patients Patients entering the follow-up period with ongoing disease control (ongoing CR, PR, or stable disease) may be permitted to reinitiate study therapy upon confirmed disease progression, within the 46 week follow-up period, after discussion and agreement with the BMS Medical Monitor. Patients that resume study therapy in this setting may receive study therapy for a total of 3 years (including the initial treatment period). Patients who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy Intra-patient dose escalation was not permitted in original cohorts and expansion cohorts of MTD. Patients in the 0.1 or 0.3mg/kg melanoma group could escalate to the 1mg/kg dose level upon confirmed and worsening progressive disease within the first 2 treatment cycles and in consultation and agreement by the BMS Medical Monitor
Permitted and disallowed concomitant medication	Prophylactic premedication was permitted if indicated by previous experience with nivolumab Inhaled or intranasal corticosteroids were permitted if the patient was on a stable dose. New herbal remedies, other marketed anti-cancer chemo/ immunotherapy drugs, investigational drugs (drugs not marketed for any indication) or live vaccines were prohibited Palliative/therapeutic therapies could be administered after consultation with the BMS Medical Monitor
Primary outcomes	Safety and tolerability Adverse events were graded using the CTEP CTCAE, Version 3.0 Assessments were performed at the end of each treatment cycle (8 weeks). Follow-up assessments were planned at 0-7 days post treatment discontinuation and 56 days later with further follow-up visits scheduled depending on the status of the patient at the end of treatment
Secondary outcomes	Immunogenicity; pharmacokinetics; preliminary efficacy; characterisation of dose-response relationship in melanoma and NSCLC Assessments for secondary outcomes were performed as per the assessment schedule for primary outcomes Primary efficacy outcome was ORR, using RECISTv1.0 criteria with modifications. Tumour measurements were collected by investigators and centrally assessed by the sponsor Secondary efficacy outcomes included PFS, DOR and TTR

Key exploratory outcomes	Overall survival Following completion of treatment and follow-up periods, all patients were followed for survival approximately every 3 months. Assessment of OS was conducted retrospectively
Pre-planned subgroups	Subgroup analyses assessing the safety and efficacy of nivolumab in melanoma, NSCLC and renal-cell cancer patients were pre-planned
Key: AE, adverse event; BMS, Bristol-Myers Squibb; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CTEP, Cancer Therapy Evaluation Programme; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; kg, kilogram; mg, milligram; mAbs, monoclonal antibodies; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; NSCLC, non-small-cell lung cancer; ORR; objective response rate; OS, overall survival; PD-1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; PD-L2, programmed death receptor ligand 2; PFS, progression-free survival; PR, partial response; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response. **Source:** CheckMate 003 CSR[197]; Topalian et al., 2012[198]	

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

Participant flow is reported for the CSR data set, based on a database lock of 4 February 2013.[197] The primary data set is based on an earlier database lock date of 24 February 2012 and efficacy analysis is based on patients who began treatment by 1 July 2011 who could be evaluated for a response.[198] For the advanced melanoma subgroup, additional data presented in this submission are based on a database lock of 5 March 2013[199] with further follow-up analysis based on a database lock of September 2014 also presented.[81] Efficacy analysis is based on all treated patients with standard censoring methods used to account for missing data.

Objective response and stable disease rates with CIs were estimated by using the Clopper–Pearson method. Time-to-event end points, including PFS, OS, survival rates, and duration of response were estimated by using the KM method, with CIs based on Greenwood's formula. Survival data were collected retrospectively. AEs were coded by using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1. Categories of Select AEs with potential immunologic aetiologies, defined as AEs that require more frequent monitoring or intervention with immune suppression or hormone replacement, were based on a prespecified list of MedDRA terms.

Participant flow in the studies

A total of 107 melanoma patients were enrolled and began treatment with nivolumab in CheckMate 003; 17 of whom were initially treated at the licensed dose of 3mg/kg.[197] At the time of database lock for CSR analysis (4 February 2013), 97 (82.9%) of these patients had discontinued treatment including all 17 patients in the nivolumab 3mg/kg monotherapy group. As was the case in the Phase III trials (see Section 4.5), the most common reason for discontinuation was disease progression (61.7% of all melanoma patients; 64.7% of melanoma patients treated with nivolumab 3mg/kg). However, it is also important to note that a proportion of patients discontinued due to complete response (11.8% of melanoma patients treated with nivolumab 3mg/kg) or completion of maximum cycles, demonstrating continuing response (5.9% of melanoma patients treated with nivolumab 3mg/kg).

In line with the study protocol, treatment was re-initiated in 4 patients; one who was re-treated with nivolumab 3mg/kg as per their original assignment.

Participant flow for the melanoma cohort of patients in CheckMate 003 is presented in Table 43.

Table 43: Patient disposition in CheckMate 003, melanoma analysis set

	Nivolumab dose, mg/kg				
	0.1	**0.3**	**1**	**3**	**10**
All enrolled population	17	18	35	17	20
All treated population	17	18	35	17	20
Patient status					
Discontinued treatment, n (%)	15 (88.2)	13 (72.2)	32 (91.4)	17 (100.0)	20 (100.0)
Discontinued study, n (%)	14 (82.4)	13 (72.2)	28 (80.0)	17 (100.0)	20 (100.0)
Initiated retreatment, n (%)	0	0	3 (8.6)	1 (5.9)	0
In survival follow-up phase, n (%)	8 (47.1)	8 (44.4)	20 (57.1)	7 (41.2)	4 (20.0)
Key reasons for discontinuation					
Complete response, n (%)	0	0	1 (2.9)	2 (11.8)	0
Completion of maximum cycles, n (%)	0	0	8 (22.9)	1 (5.9)	1 (5.0)
Disease progression, n (%)	12 (70.6)	13 (72.2)	16 (45.7)	11 (64.7)	14 (70.0)
Adverse event, n (%)	3 (17.6)	0	3 (8.6)	1 (5.9)	4 (20.0)
Death (any cause), n (%)	0	0	0	0	0
Other, n (%)	0	0	4 (11.4)	2 (11.8)	1 (5.0)

Key: kg, kilogram; mg, milligram; n, number.
Source: CheckMate 003 CSR[197]

Participant characteristics

In the subgroup of patients with advanced melanoma, the majority of patients were heavily pre-treated; 61% had received at least two prior regimens.[199] In addition, a number of patients in this subgroup presented with adverse prognostic factors of visceral disease (78%) and increased LDH (36%).

Key baseline demographics and disease characteristics of patients in the advanced melanoma cohort of CheckMate 003 are presented in Table 44.

Table 44: Characteristics of participants in CheckMate 003, melanoma analysis set

Baseline characteristic	**Melanoma subgroup (n=107)**
Age, median years (range)	61 (29-85)
Gender, male n (%)	72 (67)
ECOG PS, n (%)	0: 68 (64) 1: 36 (34) 2: 3 (3)

Baseline characteristic	Melanoma subgroup (n=107)
Number of prior therapies, n (%)	1: 40 (37) 2: 39 (36) 3: 18 (17) ≥4: 9 (8)
Nature of prior therapy, n (%)	Chemotherapy: 70 (65) Radiotherapy: 46 (43) Hormonal, immunological or biological: 69 (65) Other: 15 (14)
Lesions at baseline, n (%)	Bone: 14 (13) Liver: 37 (35) Lung: 64 (60) Lymph node: 73 (68) Previous brain metastases: 3 (3) Any visceral site: 83 (78)
Elevated LDH, n (%)	37 (36)
Key: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; n, number; NSCLC, non-small-cell lung cancer; PS, performance status. **Source**: Topalian et al., 2014[199]	

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

Quality assessment of CheckMate 003 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 45; the complete quality assessment is provided in Appendix 3.

Table 45: Quality assessment results for CheckMate 003

Were attempts made to minimise selection bias?	Yes
Do the selected patients represent the eligible population for the intervention?	Melanoma subgroup
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?	Yes
Are the study results internally valid?	Yes
Are the study results externally valid?	Yes
Key: UK, United Kingdom.	

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

Response analysis

Primary dataset (24 February 2012 database lock)

In the all treated patients population (primary data set), confirmed objective responses were observed in a substantial proportion of patients with melanoma, NSCLC or renal-cell cancer.[198]

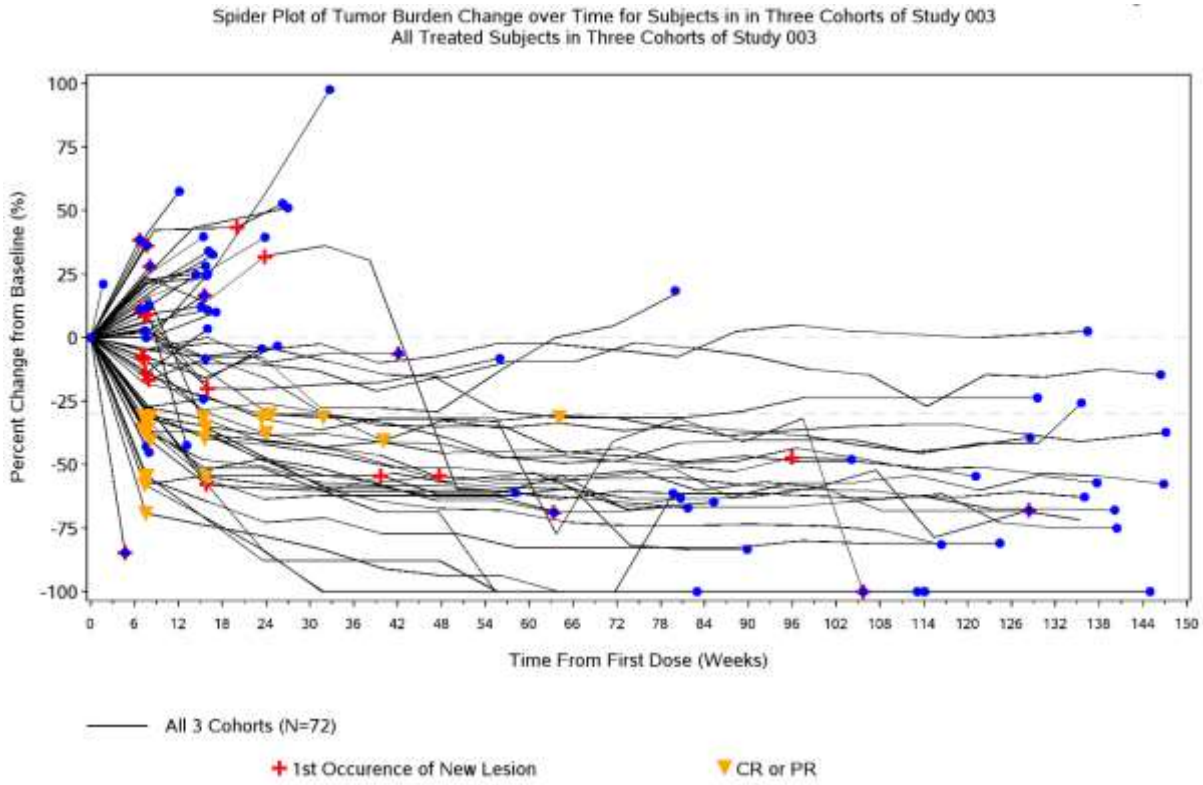
In primary analysis, objective responses were observed in 26/94 (27.7%) of melanoma patients in the efficacy analysis set.[198] At the licensed dose of nivolumab 3mg/kg, objective responses were observed in 7/17 (41.2%) of melanoma patients in the efficacy analysis set.

Of all melanoma patients who demonstrated an objective response, 18/26 (69.2%) had started treatment at least 1 year before the database lock and of these, 13/18 (72.2%) had a response that lasted 1 year or more. The remaining 8 melanoma patients with objective responses had received study medication for less than 1 year and had responses ranging from 1.9 to 5.6 months. Stable disease lasting 24 weeks or more was observed in an additional 6/94 (6.4%) of melanoma patients in the efficacy analysis set.

Advanced melanoma subgroup analysis (5 March 2013 database lock)

In pre-specified subgroup analysis, objective responses were observed in 33/107 (30.8%) of melanoma patients in the efficacy analysis set.[199] The median duration of response with nivolumab was 2 years, and 57.6% (19/33) of patients with confirmed response were still in response at the time of analysis. An additional 7/107 (6.5%) of melanoma patients experienced stable disease lasting 24 weeks or more. Responses occurred rapidly with almost half of all responses (45.5%) documented at the first tumour assessment (8 weeks). Response patterns analysis shows that for most patients with complete or partial response before 96 weeks, treatment discontinuation has little effect on continuing response. In melanoma patients treated at 1mg/kg (n=35), 3mg/kg (n=17) and 10mg/kg (n=20), ongoing responses are clearly visible beyond 96 weeks for the majority of patients who were still on study at the 96 week time point and subsequently stopped therapy, as presented in Figure 40.

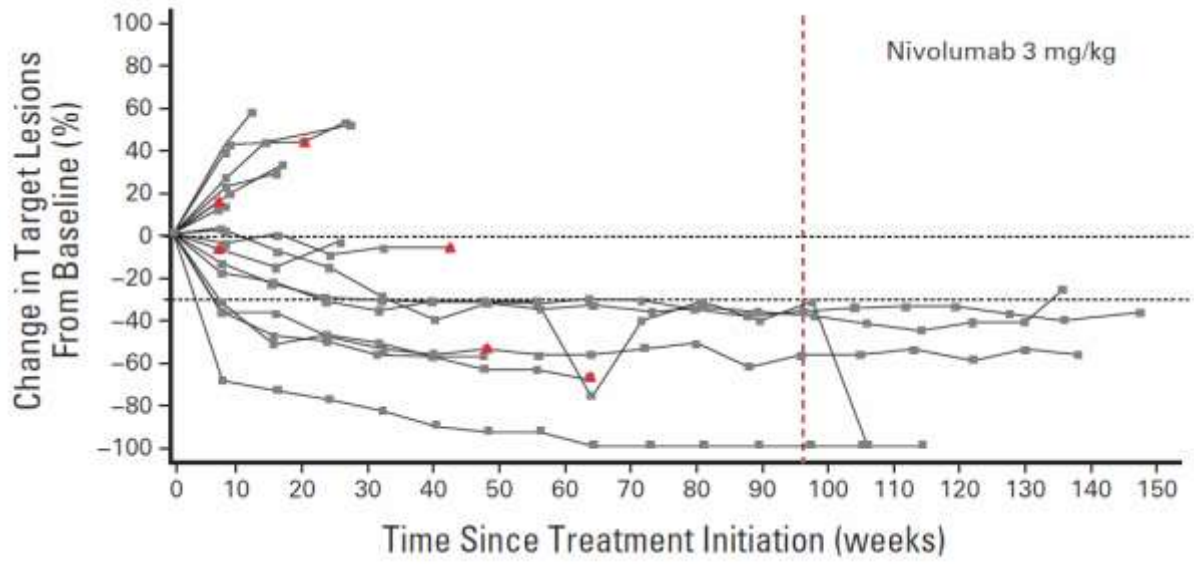
Figure 40: Response patterns in melanoma patients treated with nivolumab 1mg/kg, 3mg/kg or 10mg/kg in CheckMate 003



Key: kg, kilogram; mg. milligram; RECIST, Response Evaluation Criteria in Solid Tumours.
Notes: Horizontal reference line indicates the 30% reduction in tumour burden consistent with RECIST 1.0 criteria. Data includes patients from 3 melanoma cohorts in study CA209-003 – 1mg/kg, 3mg/kg and 10mg/kg
Source: CheckMate 003 CSR[197]

Response patterns for melanoma patients treated at the licensed dose of nivolumab 3mg/kg are presented in Figure 41. The majority (12/17 [70.6%]) of responding patients who discontinued treatment for reasons other than progressive disease maintained responses for at least 16 weeks off-treatment (16 to 56+ weeks) with 8/17 (47.1%) demonstrating ongoing response at the time of analysis. More specifically, five of the seven patients with complete or partial response before 96 weeks have completed therapy and continued to maintain their response. This can be observed in Figure 41.

Figure 41: Response patterns in melanoma patients treated with nivolumab 3mg/kg in CheckMate 003



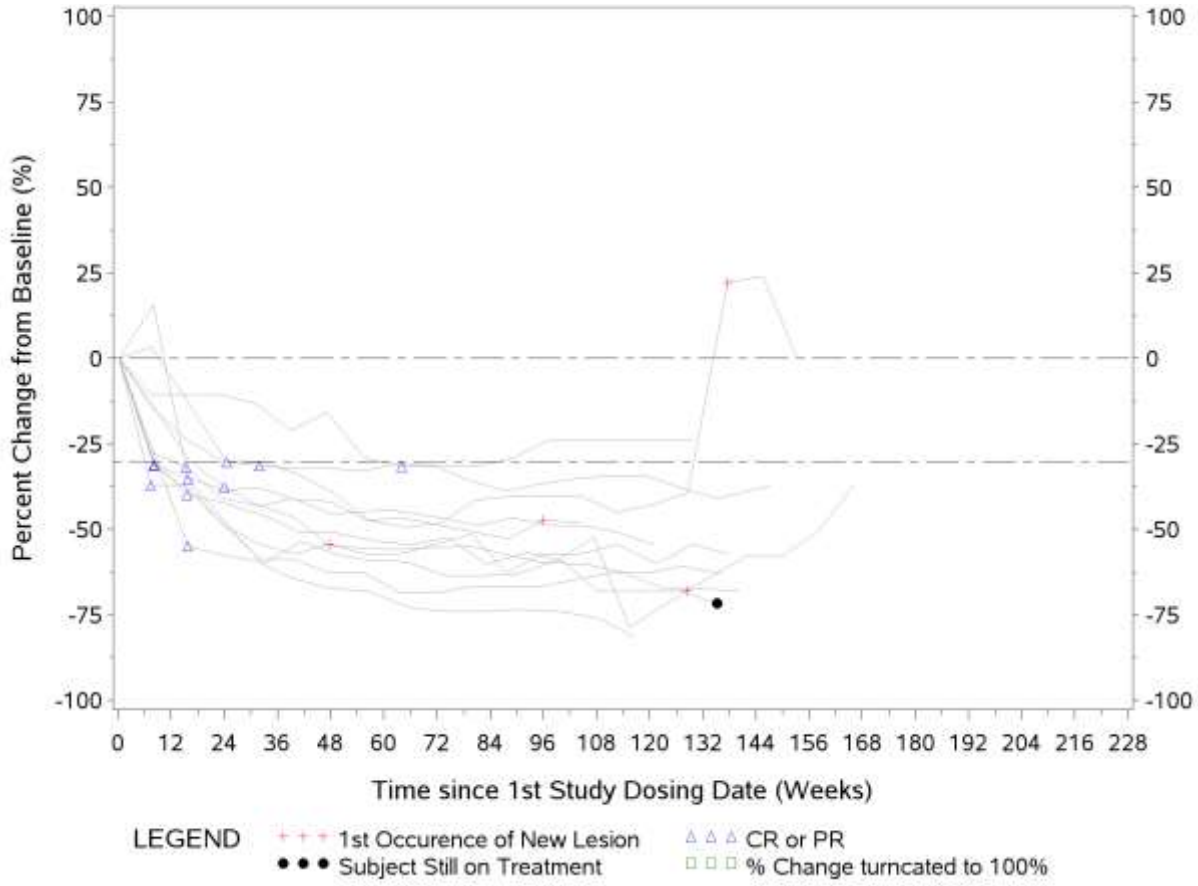
Key: kg, kilogram; mg. milligram; RECIST, Response Evaluation Criteria in Solid Tumours.
Notes: triangles indicate first occurrence of a new lesion; vertical line at 96 weeks indicates the protocol-defined maximum duration of continuous nivolumab therapy; horizontal line at -30% marks the threshold for defining partial response according to RECIST v1.0 criteria.
Source: Topalian et al., 2014[199]

Advanced melanoma subgroup follow-up analysis (September 2014 database lock)

In a follow-up analysis based on a database lock of September 2014, objective responses were observed in 34/107 (31.8%) of melanoma patients in the efficacy analysis set.[81] Median follow-up at this time was 55 months (range 32-70) and confirmed a median duration of response with nivolumab of approximately 2 years with responses ongoing in 41.2% (14/34) of patients with confirmed response at the time of analysis. The median duration of response in patients who discontinued nivolumab for reasons other than progressive disease was 11 months.

Ongoing responses are clearly visible beyond 96 weeks for the majority of patients who were still on study at the 96 week time point and subsequently stopped therapy, as presented in Figure 42.

Figure 42: Response patterns in melanoma patients treated with nivolumab 1mg/kg, 3mg/kg or 10mg/kg in CheckMate 003 still on treatment at week 96 with a BORR of either PR or CR



Key: kg, kilogram; mg. milligram; RECIST, Response Evaluation Criteria in Solid Tumours.
Notes: vertical line at 96 weeks indicates the protocol-defined maximum duration of continuous nivolumab therapy; horizontal line at -30% marks the threshold for defining partial response according to RECIST v1.0 criteria.
Source: Patient level data analysis from CHECKMATE 003

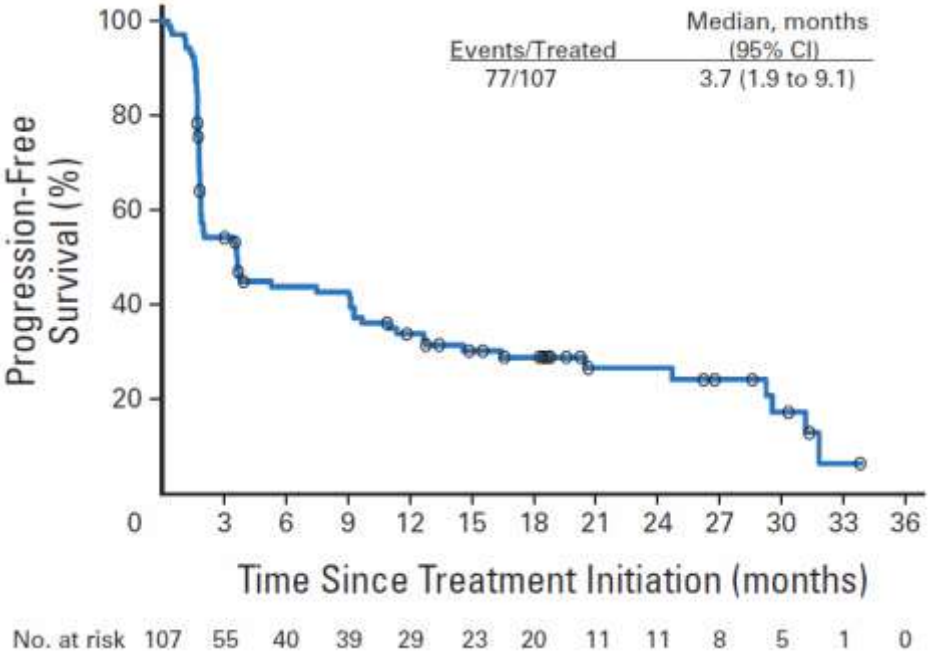
Survival analysis

Advanced melanoma subgroup analysis (5 March 2013 database lock)

Median PFS in the melanoma subgroup of patients in CheckMate 003 was 3.7 months (95% CI: 1.9 to 9.1 months), with 1- and 2-year PFS rates of 36% and 27%, respectively.[199]
Median PFS in the melanoma subgroup of patients treated at the licensed dose of nivolumab 3mg/kg was markedly higher at 9.7 months.

The KM curve for PFS in the melanoma subgroup of patients is presented in Figure 43.

Figure 43: Kaplan–Meier curve for progression-free survival in CheckMate 003, melanoma analysis set



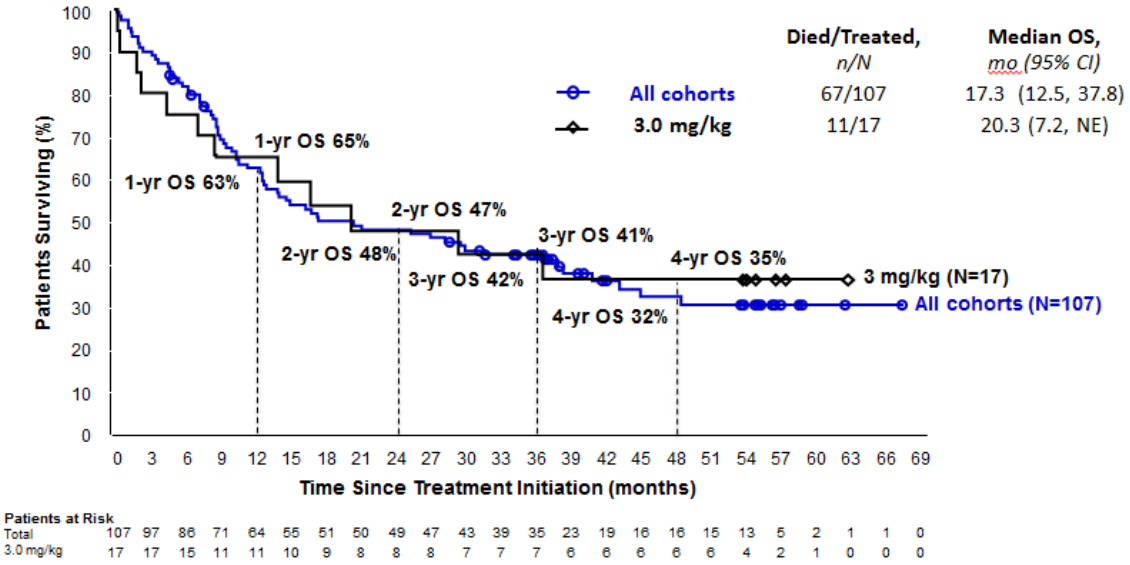
Key: CI, confidence interval.
Notes: Circles indicate censored events.
Source: Topalian et al., 2014[199]

Advanced melanoma subgroup follow-up analysis (September 2014 database lock)

Retrospective analysis of survival in patients with advanced melanoma treated with nivolumab in CheckMate 003 confirmed a median OS of 17.3 months (95% CI: 12.5 to 37.8 months).[81] As was observed in PFS analysis, median OS in the melanoma subgroup of patients treated at the licensed dose of nivolumab 3mg/kg was markedly higher at 20.3 months and 1- to 4-year survival rates of 65%, 47%, 41% and 35% were observed in patients treated at the licensed nivolumab dose of 3mg/kg.

The KM curve for OS in the melanoma subgroup of patients is presented in Figure 44.

Figure 44: Kaplan–Meier curve for overall survival in CheckMate 003, melanoma analysis set



Key: CI, confidence interval; kg, kilogram; mg, milligram; mo, month; n, number; NE, not estimable; OS, overall survival; yr, year.
Notes: Circles and diamonds indicate censored events.
Source: Hodi et al., 2014[81]

Conclusion

Although based on small patient numbers, these data confirm the validity of the assumptions made in the cost-effectiveness model and support UK clinician guidance on the implementation of a 2 year maximum duration of therapy recommendation.

4.12 Adverse reactions

Summary

- Nivolumab has a well-characterised safety profile, commonly defined by select AEs with a potential immunological cause
    - Frequently reported AEs considered related to nivolumab across trials were the common AEs of fatigue, pruritus, nausea, diarrhoea and rash
- Nivolumab was generally well tolerated with low rates of discontinuations due to reasons other than progressive disease or specifically due to study drug toxicity, in any of the CheckMate trials
    - Median duration of nivolumab 3mg/kg monotherapy ranged from 5.3 to 6.6 months
    - Relative dose intensity ≥90% in the majority (84.0 to 91.3%) of patients treated with nivolumab
    - Discontinuation due to AEs considered related to nivolumab rates did not exceed 8% in a single trial
- Serious complications associated with nivolumab therapy were rare
    - A single death suspected to be related to an AE caused by nivolumab therapy (neutropenia) across all Phase III trials
- Nivolumab was associated with reduced rates of TRAEs compared with palliative chemotherapy
    - CheckMate 066: lower rates of Grade 3-4 AEs considered related to study drug compared with DTIC (11.7% vs 17.6%)
    - CheckMate 037: lower rates of Grade 3-4 AEs considered related to study drug compared with ICC (9.0% vs 31.4%)
- Nivolumab monotherapy was associated with a favourable safety profiled compared to ipilimumab monotherapy in CheckMate 067
    - Reduced rates of Grade 3-4 AEs (43.5% vs 55.6%)
    - Reduced rates of Grade 3-4 TRAEs (16.3% vs 27.3%)
    - Reduced rates of SAEs (36.1% vs 52.1%) and Grade 3-4 SAEs (28.1% vs 38.3%)
    - Reduced rates of TRSAEs (8.0% vs 22.2%) and Grade 3-4 TRSAEs (5.8% vs 16.4%)
    - Reduced rates of discontinuation due to AEs (13.7% vs 22.5%), Grade 3-4 AEs (8.6% vs 19.9%), TRAEs (7.7% vs 14.8%) and Grade 3-4 TRAEs (5.1% vs 13.2%
    - Reduced rates of common immune related AEs overall, particularly gastrointestinal events considered related to study drug (19.5% vs 36.7%) and skin events considered related to study drug (41.9% vs 54.0%)
- Select AEs mild and transient in the majority, quickly resolved with corticosteroids or other immunosuppressant medication
- Safety profile consistent regardless of treatment history with no association found between ipilimumab-related and nivolumab-related toxic effects

Nivolumab was generally well tolerated with low rates of discontinuations due to reasons other than progressive disease or specifically due to study drug toxicity, in any of the CheckMate trials.

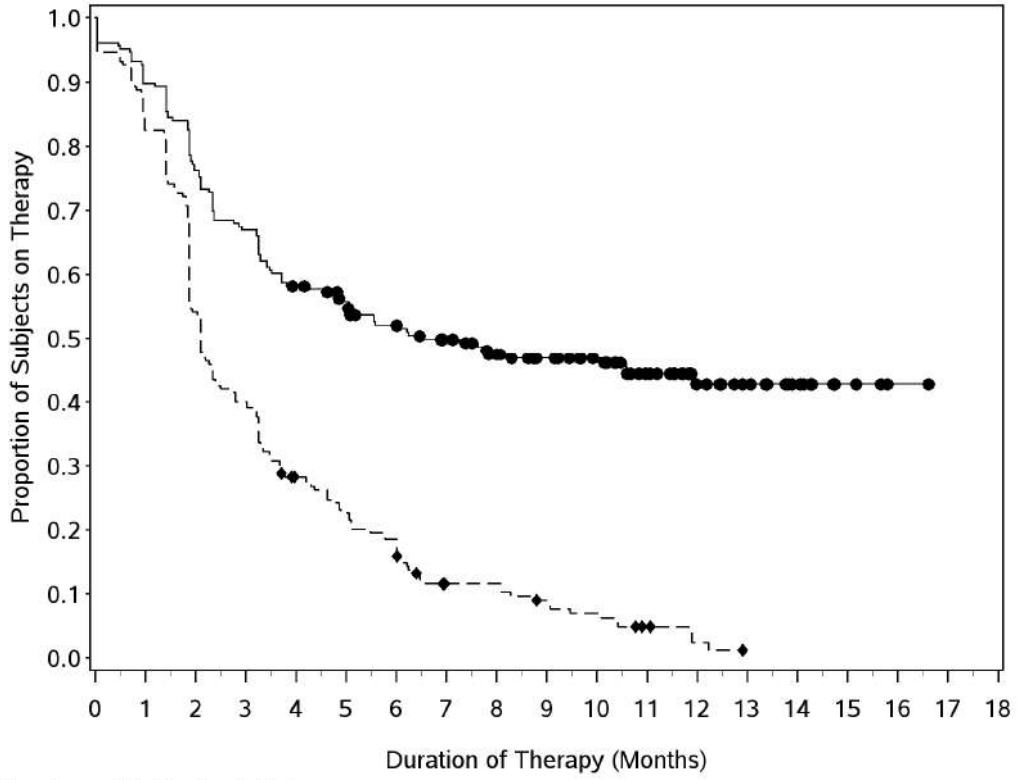
Treatment exposure: CheckMate 066

In CheckMate 066, 206 patients received at least 1 infusion of nivolumab and 205 patients received at least 1 infusion of DTIC.[82, 106] The majority of patients (91.3%) in the nivolumab group and 52.2% of patients in the dacarbazine group received ≥90% of the intended dose.

The median number of nivolumab doses received was 12, and the median duration of nivolumab therapy was 6.5 months. The median number of DTIC doses received was 4, and the median duration of DTIC therapy was 2.1 months.

The KM curve for time-on-treatment is presented in Figure 45.

Figure 45: Kaplan–Meier curve for time-on-treatment in CheckMate 066, safety analysis set



Notes: solid line represents nivolumab group; dashed line represents DTIC group.
Source: CheckMate 066 CSR[106]

Safety profile: CheckMate 066

The majority of patients in both treatment groups experienced at least one AE of any grade.[82, 106] Likewise, a similar proportion of patients in each treatment arm experienced an AE of Grade 3 or 4.

The incidence of treatment-related adverse events (TRAEs) of any grade was also similar in the nivolumab group and the DTIC group. However, TRAEs of Grade 3 or 4 were reported less frequently in the nivolumab group.

Importantly, no deaths were reported by the investigators as being due to study drug toxicity.

Summary safety data are presented in Table 46.

Table 46: Summary of safety data from CheckMate 066, safety analysis set

	Nivolumab (n=206)		DTIC (n=205)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All AEs, n (%)	192 (93.2)	70 (34.0)	194 (94.6)	78 (38.0)
TRAEs, n (%)	153 (74.3)	24 (11.7)	155 (75.6)	36 (17.6)
All SAEs, n (%)	64 (31.1)	43 (20.9)	78 (38.0)	54 (26.3)
TRSAEs, n (%)	19 (9.2)	12 (5.8)	18 (8.8)	12 (5.9)
DC due to AEs, n (%)	14 (6.8)	12 (5.8)	24 (11.7)	19 (9.3)
DC due to TRAEs, n (%)	5 (2.4)	4 (1.9)	7 (3.4)	5 (2.4)
Deaths relating to study drug, n (%)	0		0	
Key: AEs, adverse events; DC, discontinuation; DTIC, dacarbazine; n, number; SAEs, serious adverse events; TRAEs, treatment-related adverse events; TRSAEs, treatment related serious adverse events. **Source:** CheckMate 066 CSR[106]; Robert et al., 2015[82]				

The most frequently reported TRAEs (reported in ≥15% of patients) in the nivolumab group of CheckMate 066 were: fatigue (19.9%); pruritus (17.0%); nausea (16.5%); diarrhoea (16.0%); and rash (15.0%). The most frequently reported TRAEs in the DTIC group were: nausea (41.5%); vomiting (21.0%); and diarrhoea (15.6%).

Serious TRAEs (TRSAEs) reported by more than 1 patient in the nivolumab group were: vomiting; hyperglycaemia; pyrexia; infusion-related reaction; and pneumonitis (each reported by 2 patients). TRSAEs reported by more than 1 patient in the DTIC group were: pancytopenia; thrombocytopenia (both reported by 3 patients); and neutropenia (2 patients).

No TRSAE leading to the discontinuation of the study drug were reported in more than 1 patient in either treatment group.

Select AEs, defined as AEs with a potential immunological cause that need frequent monitoring and potential intervention, were analysed according to organ category (skin, gastrointestinal, endocrine, pulmonary, hepatic, and renal). The majority of Select AEs were mostly low-grade (Grade 1-2), while Select AEs of at least Grade 3 that were considered to be related to study treatment were uncommon. Select TRAEs of Grade 3 or 4 were not reported by more than 3 patients in any single organ category.

In the nivolumab group, the majority of Select AEs were resolved the exception being for some events in the endocrine Select AE category. While most of these AEs were well controlled with hormone replacement therapy, they were not considered resolved due to the need for continuing hormone replacement therapy.

Aside from the endocrine Select AE category, the AEs with the longest median times to resolution were those belonging to the skin (15.7 weeks) and hepatic (8.0 weeks) Select AE

categories. Median time to resolution for all other Select AE categories ranged from 0.14 to 6.14 weeks, depending on organ category.

Immunosuppressive medication (usually systemic corticosteroids) was administered for the management of a proportion of AEs in each Select AE category in both treatment groups. The exception was for the skin AEs where dermatological corticosteroid preparations were also used. The median time to resolution of Select AEs in patients who received immunosuppressive medication did not exceed 6.43 weeks.

Select AE data are presented in Table 47.

Table 47: Select AE data from CheckMate 066, safety analysis set

	Nivolumab (n=206)		DTIC (n=205)	
	All causality	**Drug related**	**All causality**	**Drug related**
Endocrine category				
All AEs, n (%)	19 (9.2)	15 (7.3)	3 (1.5)	1 (0.5)
Grade 3-4 AEs, n (%)	2 (1.0)	2 (1.0)	0	0
Time to onset, median weeks	12.14	12.14	6.00	12.14
Time to resolution, median weeks	Not reached	Not reached	Not reached	17.71
Gastrointestinal category				
All AEs, n (%)	53 (25.7)	35 (17.0)	44 (21.5)	32 (15.6)
Grade 3-4 AEs, n (%)	5 (2.4)	3 (1.5)	1 (0.5)	1 (0.5)
Time to onset, median weeks	7.71	8.29	4.29	3.07
Time to resolution, median weeks	0.57	0.43	0.71	0.29
Hepatic category				
All AEs, n (%)	19 (9.2)	7 (3.4)	14 (6.8)	8 (3.9)
Grade 3-4 AEs, n (%)	11 (5.3)	3 (1.5)	5 (2.4)	2 (1.0)
Time to onset, median weeks	6.00	14.00	2.93	2.71
Time to resolution, median weeks	8.00	2.00	21.29	8.57
Pulmonary category				
All AEs, n (%)	3 (1.5)	3 (1.5)	0	0
Grade 3-4 AEs, n (%)	0	0	0	0
Time to onset, median weeks	12.14	12.14	-	-
Time to resolution, median weeks	6.14	6.14	-	-
Renal category				
All AEs, n (%)	9 (4.4)	4 (1.9)	6 (2.9)	1 (0.5)
Grade 3-4 AEs, n (%)	1 (0.5)	1 (0.5)	3 (1.5)	0
Time to onset, median	15.00	10.79	3.71	29.86

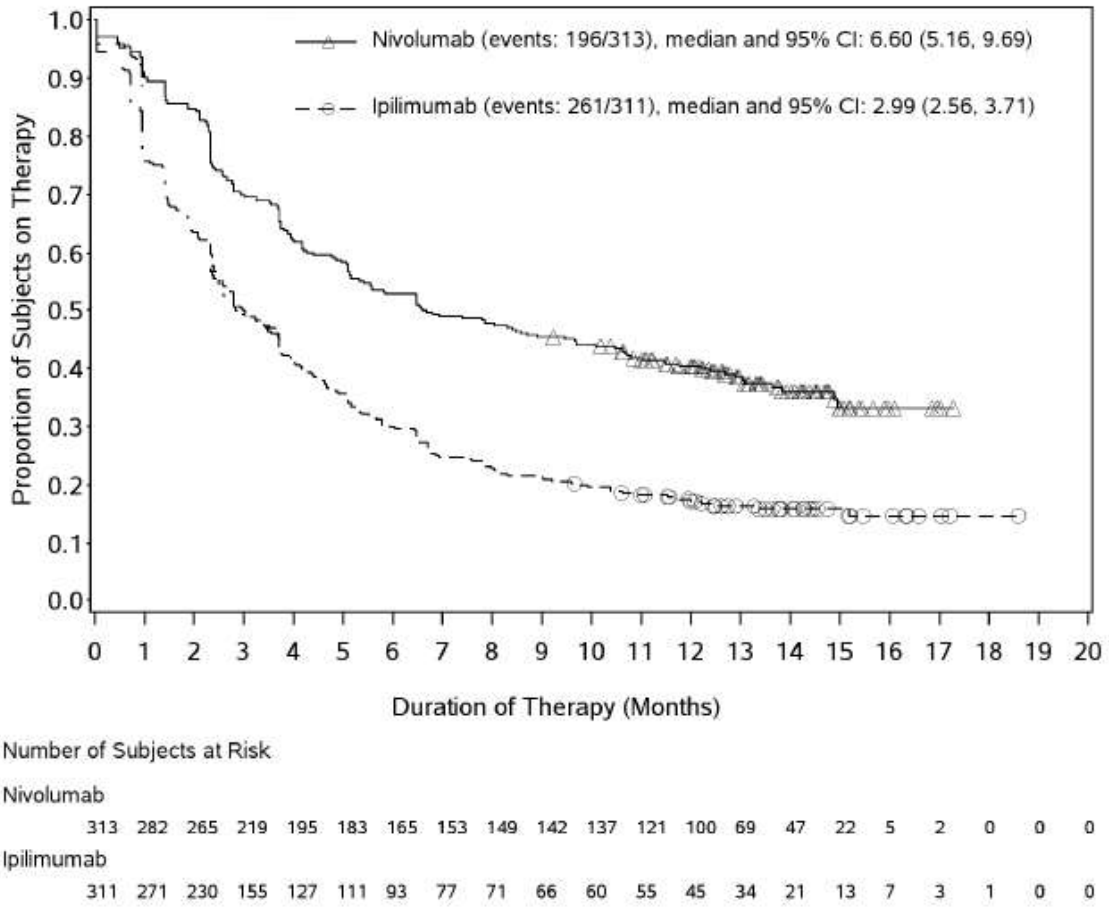
	Nivolumab (n=206)		DTIC (n=205)	
	All causality	**Drug related**	**All causality**	**Drug related**
weeks				
Time to resolution, median weeks	4.71	5.43	7.57	0.43
Skin category				
All AEs, n (%)	98 (47.6)	77 (37.4)	51 (24.9)	29 (14.1)
Grade 3-4 AEs, n (%)	4 (1.9)	3 (1.5)	0	0
Time to onset, median weeks	6.50	6.14	6.57	6.14
Time to resolution, median weeks	15.71	17.43	4.29	1.71
Hypersensitivity/infusion reactions category				
All AEs, n (%)	16 (7.8)	15 (7.3)	13 (6.3)	13 (6.3)
Grade 3-4 AEs, n (%)	0	0	0	0
Time to onset, median weeks	2.21	2.14	0.14	0.14
Time to resolution, median weeks	0.14	0.14	0.14	0.14
Key: AEs, adverse events; DTIC, dacarbazine. **Source:** CheckMate 066 CSR[106]; Robert et al., 2015[82]				

Treatment exposure: CheckMate 067

In CheckMate 067, 313 patients received at least 1 infusion of nivolumab, and 311 patients received at least 1 infusion of ipilimumab.[84, 111] In both the nivolumab and the ipilimumab group, approximately 88% of patients had a relative dose intensity of 90 to <110%. The median number of nivolumab doses was 15, and the median duration of nivolumab therapy was 6.6 months; 147/313 patients (47.0%) received more than 4 doses of nivolumab monotherapy. The median number of ipilimumab doses was 4, and the median duration of ipilimumab therapy was 3.0 months.

The KM curve for time-on-treatment is presented in Figure 46.

Figure 46: Kaplan–Meier curve for time-on-treatment in CheckMate 067, safety analysis set



Key: CI, confidence interval
Source: CheckMate 067 CSR[111]

Safety profile: CheckMate 067

The majority of patients treated with nivolumab or ipilimumab monotherapy experienced at least one AE of any grade, and a slightly higher proportion of patients experienced an AE of Grade 3 or 4 in the ipilimumab group.[84, 111]

The incidence of TRAEs of any grade were again similar across immuno-oncology monotherapy groups, but TRAEs of Grade 3 or 4 were experienced by more patients treated with ipilimumab compared with nivolumab therapy. The overall frequency of SAEs and TRSAEs (any grade and Grade 3 or 4) was also higher in the ipilimumab monotherapy group.

One death due to toxic effects of the study drug was reported in the nivolumab group (neutropenia) and one in the ipilimumab group (cardiac arrest).

Summary safety data are presented in Table 48.

Table 48: Summary of safety data from CheckMate 067, safety analysis set

	Nivolumab (n=313)		Ipilimumab (n=311)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All AEs, n (%)	311 (99.4)	136 (43.5)	308 (99.0)	173 (55.6)
TRAEs, n (%)	257 (82.1)	51 (16.3)	268 (86.2)	85 (27.3)
All SAEs, n (%)	113 (36.1)	88 (28.1)	162 (52.1)	119 (38.3)
TRSAEs, n (%)	25 (8.0)	18 (5.8)	69 (22.2)	51 (16.4)
DC due to AEs, n (%)	43 (13.7)	27 (8.6)	70 (22.5)	62 (19.9)
DC due to TRAEs, n (%)	24 (7.7)	16 (5.1)	46 (14.8)	41 (13.2)
Deaths relating to study drug, n (%)	1		1	
Key: AEs, adverse events; DC, discontinuation; n, number; SAEs, serious adverse events; TRAEs, treatment-related adverse events; TRSAEs, treatment related serious adverse events. **Source:** CheckMate 067 CSR[111]; Larkin et al., 2015[84]				

The most frequently reported TRAEs in both the nivolumab and the ipilimumab groups were fatigue (nivolumab, 34.2%; ipilimumab, 28.0%), rash (nivolumab, 25.9%; ipilimumab, 32.8%), diarrhoea (nivolumab, 19.2%; ipilimumab, 33.1%) and pruritus (nivolumab, 18.8%; ipilimumab, 35.4%), all reported by a higher proportion of patients treated with ipilimumab with the exception of fatigue.

No individual TRSAE was reported with a frequency ≥2% in the nivolumab monotherapy group. In the ipilimumab monotherapy group: colitis (9.0%); diarrhoea (7.1%); and hypophysitis (2.6%) were reported in ≥2% of patients. Similarly, no TRSAE leading to the discontinuation of the study drug were reported by ≥2% of patients in the nivolumab group but treatment-related gastrointestinal disorders of Grade 3 or 4 led to study drug discontinuation in 10.6% of patients in the ipilimumab group.

Select AEs were again mostly low-grade. Select AEs of Grade 3 or 4 considered to be related to study drug were more common in the ipilimumab group compared with the nivolumab group for the endocrine, gastrointestinal and skin categories. The biggest difference between groups was observed in the gastrointestinal category where 36.7% of patients treated with ipilimumab experienced a drug-related event compared with 19.5% of patients treated with nivolumab and 11.6% versus 2.2% of patients treated with ipilimumab and nivolumab, respectively, experienced a drug-related event of Grade 3 or 4. Slightly more patients in the nivolumab group (2.6%) had a Select AE of Grade 3 or 4 considered to be related to study drug belonging to the hepatic category.

As was observed in CheckMate 066, Select AEs in the nivolumab group were resolved quickly (in less than 8 weeks) in the majority. The exception was again in the case of Select AEs in the endocrine and skin category where median time to resolution was over 18 weeks. A similar trend was observed in the ipilimumab group. Select AE data are presented in Table 49.

Table 49: Select AE data from CheckMate 067, safety analysis set

	Nivolumab (n=313)		Ipilimumab (n=311)	
	All causality	**Drug related**	**All causality**	**Drug related**
Endocrine category				
All AEs, n (%)	54 (17.3)	45 (14.4)	38 (12.2)	34 (10.9)
Grade 3-4 AEs, n (%)	2 (0.6)	2 (0.6)	7 (2.3)	7 (2.3)

	Nivolumab (n=313)		Ipilimumab (n=311)	
	All causality	**Drug related**	**All causality**	**Drug related**
Time to onset, median weeks	9.1	12.0	9.0	8.9
Time to resolution, median weeks	Not reached	16.1	Not reached	Not reached
Gastrointestinal category				
All AEs, n (%)	99 (31.6)	61 (19.5)	150 (48.2)	114 (36.7)
Grade 3-4 AEs, n (%)	12 (3.8)	7 (2.2)	40 (12.9)	36 (11.6)
Time to onset, median weeks	8.7	8.9	4.6	4.4
Time to resolution, median weeks	0.7	1.6	2.4	2.9
Hepatic category				
All AEs, n (%)	40 (12.8)	22 (7.0)	34 (10.9)	22 (7.1)
Grade 3-4 AEs, n (%)	16 (5.1)	8 (2.6)	14 (4.5)	5 (1.6)
Time to onset, median weeks	7.8	14.1	8.1	9.1
Time to resolution, median weeks	7.1	5.4	4.3	4.2
Pulmonary category				
All AEs, n (%)	7 (2.2)	5 (1.6)	10 (3.2)	6 (1.9)
Grade 3-4 AEs, n (%)	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
Time to onset, median weeks	8.7	9.0	10.1	10.1
Time to resolution, median weeks	2.4	4.1	4.6	6.3
Renal category				
All AEs, n (%)	10 (3.2)	3 (1.0)	14 (4.5)	8 (2.6)
Grade 3-4 AEs, n (%)	2 (0.6)	1 (0.3)	4 (1.3)	1 (0.3)
Time to onset, median weeks	7.1	4.1	9.6	10.0
Time to resolution, median weeks	2.0	Not reached	2.5	2.5
Skin category				
All AEs, n (%)	167 (53.4)	131 (41.9)	194 (62.4)	168 (54.0)
Grade 3-4 AEs, n (%)	6 (1.9)	5 (1.6)	12 (3.9)	9 (2.9)
Time to onset, median weeks	5.6	4.3	3.4	3.4
Time to resolution, median weeks	18.4	25.7	12.1	11.0
Hypersensitivity/infusion reactions category				
All AEs, n (%)	16 (5.1)	13 (4.2)	9 (2.9)	8 (2.6)
Grade 3-4 AEs, n (%)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Time to onset, median weeks	2.3	2.1	2.3	2.2
Time to resolution, median weeks	0.1	0.1	0.1	0.1

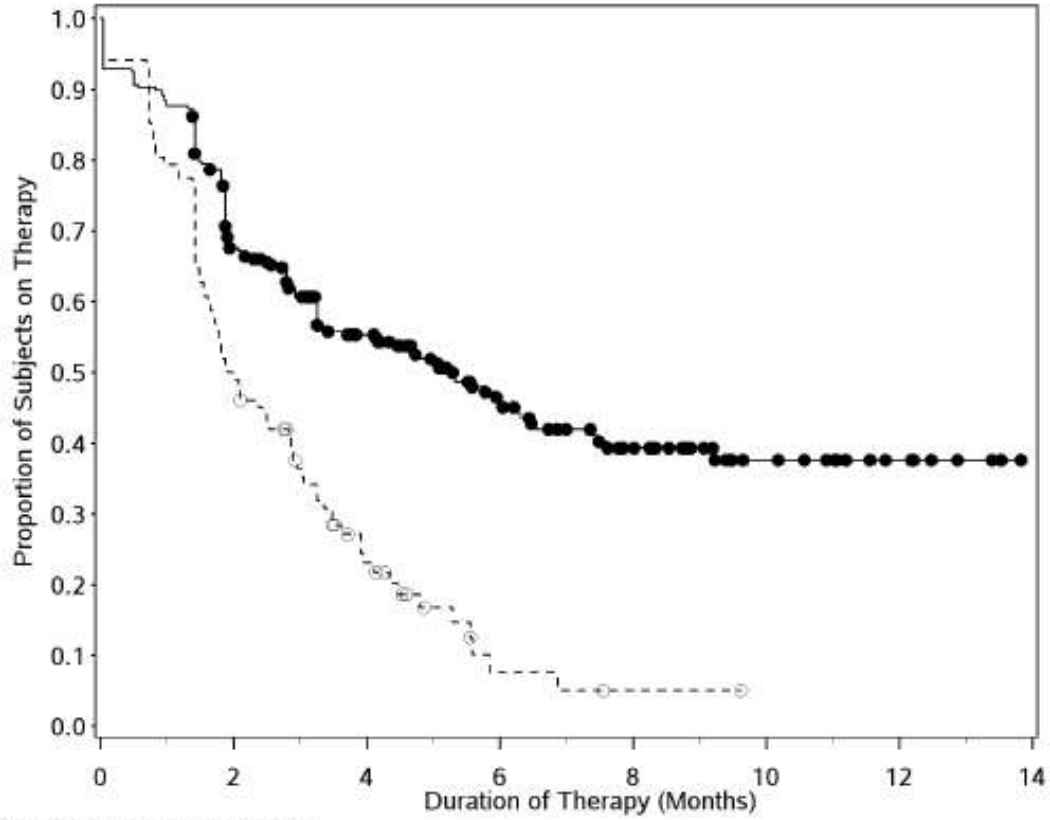
Key: AEs, adverse events; DTIC, dacarbazine; n, number.
Source: CheckMate 067CSR[111]; Larkin et al., 2015[84]

Treatment exposure: CheckMate 037

In CheckMate 037, 268 patients received at least 1 infusion of nivolumab, and 102 patients received at least 1 infusion of ICC.[105, 112] The majority of patients (84.0%) in the nivolumab group received ≥90% of the intended dose. However, the same level of relative dose intensity was achieved in proportionately fewer patients treated with ICC: 71% of patients treated with DTIC, 33.3% of patients treated with carboplatin and 54.4% of patients treated with paclitaxel.

The median number of nivolumab doses was 8, and the median duration of nivolumab therapy was 5.3 months. The median number of DTIC and carboplatin plus paclitaxel doses was 3 and 5, respectively, and the median duration of ICC therapy was 2.0 months. The KM curve for time-on-treatment is presented in Figure 47.

Figure 47: Kaplan–Meier curve for time-on-treatment in CheckMate 037, safety analysis set



Notes: solid line represents nivolumab group; dashed line represents investigators choice group.
Source: CheckMate 037 CSR[105]

Safety profile: CheckMate 037

The majority of patients in both treatment groups experienced at least one AE of any grade, although a slightly higher proportion of patients experienced an AE of Grade 3 or 4 in the ICC group.

The incidence of TRAEs of any grade was also slightly higher in the ICC group compared to the nivolumab group, while TRAEs of Grade 3 or 4 were reported much less frequently in the nivolumab group compared to the ICC control group.

In addition, the safety profile of nivolumab in pre-defined subgroups (age, gender, race, and region) of the CheckMate 037 trial was consistent with the safety profile of nivolumab in all treated patients.

Importantly, no deaths were reported by the investigators as being due to study drug toxicity.

Summary safety data are presented in Table 50.

Table 50: Summary of safety data from CheckMate 037, safety analysis set

	Nivolumab (n=268)		ICC (n=102)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All AEs, n (%)	255 (95.1)	92 (34.3)	95 (93.1)	44 (43.1)
TRAEs, n (%)	181 (67.5)	24 (9.0)	81 (79.4)	32 (31.4)
All SAEs, n (%)	118 (44.0)	78 (29.1)	22 (21.6)	16 (15.7)
TRSAEs, n (%)	17 (6.3)	12 (4.5)	10 (9.8)	9 (8.8)
DC due to AEs, n (%)	25 (9.3)	19 (7.1)	12 (11.8)	5 (4.9)
DC due to TRAEs, n (%)	6 (2.2)	6 (2.2)	8 (7.8)	3 (2.9)
Deaths relating to study drug, n (%)	0		0	

Key: AEs, adverse events; DC, discontinuation; ICC, investigator's choice chemotherapy; n, number; SAEs, serious adverse events; TRAEs, treatment-related adverse events; TRSAEs, treatment related serious adverse events.
Source: CheckMate 037 CSR[105]; Weber et al., 2015[112]

The most frequently reported TRAEs in the nivolumab group were fatigue (25.0%) and pruritus (16.0%), whereas the most frequently reported TRAEs in the ICC group were: nausea (37.3%); fatigue (34.3%); alopecia (27.5%); anaemia (22.5%); vomiting (19.6%); neutropenia (18.6%); and decreased appetite (15.7%).[105]

The only TRSAEs reported by more than 1 patient were hyperglycaemia (2 patients) in the nivolumab group and vomiting (2 patients) in the ICC group. No TRSAEs leading to the discontinuation of the study drug were reported in more than 1 patient in either treatment group.

As was the case in CheckMate 066 and 067, Select AEs were mostly low-grade (Grade 1-2). Select AEs of at least Grade 3 that were considered to be related to study treatment were uncommon, and Select TRAEs of Grade 3 or 4 were not reported by more than 3 patients in a single organ category.

In the nivolumab group, the majority of Select AEs were resolved in the gastrointestinal, renal and hypersensitivity/infusion reaction categories, and ≥45% of patients experienced resolution of their hepatic, pulmonary and skin Select AE categories.

Select AEs belonging to the endocrine category had the longest median time to resolution in the nivolumab group (24.1 weeks) and although a majority resolve, some will require ongoing hormone replacement therapy. Select AEs belonging to the skin category had the second longest time to resolution (16.1 weeks).

Median time to resolution for all other Select AE categories ranged from 0.4 to 6.1 weeks, depending on organ category.

The median time to resolution of Select AEs in patients who received immunosuppressive medication did not exceed 3.7 weeks for any category other than in the skin Select AE category, where the median time to resolution in patients who received immunosuppressive medication was 12.6 weeks.

Select AE data are presented in Table 51.

Table 51: Select AE data from CheckMate 037, safety analysis set

	Nivolumab (n=268)		ICC (n=102)	
	All causality	**Drug related**	**All causality**	**Drug related**
Endocrine category				
All AEs, n (%)	32 (11.9)	21 (7.8)	2 (2.0)	1 (1.0)
Grade 3-4 AEs, n (%)	1 (0.4)	0	0	0
Time to onset, median weeks	8.1	8.4	3.1	3.1
Time to resolution, median weeks	24.1	24.1	-	3.3
Gastrointestinal category				
All AEs, n (%)	55 (20.5)	31 (11.6)	17 (16.7)	15 (14.7)
Grade 3-4 AEs, n (%)	4 (1.5)	3 (1.1)	2 (2.0)	2 (2.0)
Time to onset, median weeks	6.3	5.7	4.0	4.0
Time to resolution, median weeks	1.1	1.7	0.7	0.7
Hepatic category				
All AEs, n (%)	28 (10.4)	12 (4.5)	7 (6.9)	6 (5.9)
Grade 3-4 AEs, n (%)	9 (3.4)	2 (0.7)	0	0
Time to onset, median weeks	4.1	7.4	4.1	4.6
Time to resolution, median weeks	6.1	3.3	9.4	9.4
Pulmonary category				
All AEs, n (%)	8 (3.0)	6 (2.2)	0	0
Grade 3-4 AEs, n (%)	0	0	0	0
Time to onset, median weeks	8.7	-	8.2	-
Time to resolution, median weeks	6.0	-	6.0	-
Renal category				
All AEs, n (%)	18 (6.7)	4 (1.5)	4 (3.9)	1 (1.0)
Grade 3-4 AEs, n (%)	4 (1.5)	1 (0.4)	1 (1.0)	0
Time to onset, median weeks	6.1	15.3	5.3	3.1
Time to resolution, median weeks	5.1	2.7	1.8	8.0
Skin category				
All AEs, n (%)	96 (35.8)	78 (29.1)	15 (14.7)	12 (11.8)
Grade 3-4 AEs, n (%)	1 (0.4)	1 (0.4)	0	0
Time to onset, median weeks	4.3	4.5	3.6	3.4
Time to resolution, median weeks	16.1	28.6	5.9	5.9

	Nivolumab (n=268)		ICC (n=102)	
	All causality	**Drug related**	**All causality**	**Drug related**
Hypersensitivity/infusion reactions category				
All AEs, n (%)	8 (3.0)	5 (1.9)	8 (7.8)	8 (7.8)
Grade 3-4 AEs, n (%)	1 (0.4)	1 (0.4)	0	0
Time to onset, median weeks	3.9	0.4	0.1	0.1
Time to resolution, median weeks	0.4	0.1	0.1	0.1
Key: AEs, adverse events; DTIC, dacarbazine; n, number. **Source:** CheckMate 037 CSR[105]; Weber et al., 2015[112]				

Of important note, case histories of all patients who developed nivolumab-related, Select AEs in CheckMate 037 were reviewed and no association between ipilimumab-related and nivolumab-related toxic effects could be found. Only one of the seven patients who developed a nivolumab-related Select AE had a history of ipilimumab-related toxic effects (hypophysitis). This patient developed liver function test abnormalities (Grade 2–3), which resolved after dose delay and AE management by steroids.

4.13 Interpretation of clinical effectiveness and safety evidence

Advanced melanoma is an aggressive disease with increasing prevalence that affects a relatively young population (see Section 3.1). Despite recent therapeutic advancements, durable response and long-term survival remain elusive for the majority of patients. There is a clear unmet medical need for additional treatment options with proven long-term clinical benefit in advanced melanoma. Nivolumab meets this unmet need.

Principle findings from the clinical evidence base

Principle findings from the clinical evidence highlighting the clinical benefits and harms of nivolumab 3mg/kg monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults are summarised below:

Nivolumab offers a long-term survival benefit in advanced melanoma in previously untreated and pre-treated patients

- In previously untreated BRAF mutation-negative patients, a significant benefit with respect to OS was observed in the nivolumab group, compared with the DTIC group (HR for death: 0.42 [99.79% CI 0.25, 0.73]; p<0.001).[82, 106]
    - Overall survival rate at 1 year of 73% in the nivolumab group compared with 42% in the DTIC group.
    - An additional 3.6 to 5.1 months survival observed with nivolumab in restricted mean OS and 75% OS analysis, respectively.
- In previously untreated BRAF mutation-negative patients, nivolumab significantly improved PFS compared with DTIC (5.1 vs 2.2 months; HR for death or disease progression: 0.43; [95% CI 0.34, 0.56]; p<0.001).[82, 106]
- In previously untreated patients of mixed BRAF status, nivolumab significantly improved PFS compared with ipilimumab (6.9 vs 2.9 months; HR for death or disease progression: 0.57; [95% CI 0.43, 0.76]; p<0.001).[111, 127]
- In pre-treated patients discontinuing treatment at 96 weeks, nivolumab 3mg/kg demonstrated a median OS of 20.3 months and a 4-year survival rate of 35% in advanced melanoma patients of a single-arm trial.[81]

- Preliminary survival estimates demonstrate an increased survival benefit over all first-line treatment options similar to the magnitude of effect ipilimumab previously demonstrated over traditional chemotherapy:
    - ITC estimates for nivolumab monotherapy versus ipilimumab monotherapy: HR for death, 0.55 (95% CI: 0.36, 0.84).
    - 45-50% of patients estimated to be alive 2 years after treatment initiation with nivolumab monotherapy, compared with ~30% of patients treated with ipilimumab monotherapy or BRAF inhibitor monotherapy (see Section 5.3).

Nivolumab has demonstrated high, rapid and durable clinical response across lines of therapy and BRAF status in advanced melanoma

- In previously untreated BRAF mutation-negative patients, 40% had an objective response, and of these patients, 86% continue to demonstrate response at the time of analysis (follow-up time up to 16.7 months).[82, 106]
- In previously untreated patients of mixed BRAF status, 44% had an objective response, and of these patients, 78% continued to demonstrate response at the time of analysis (median follow-up of over 12 months).[111, 127]
- In previously treated patients, 32% had an objective response, and of these patients, 87% continue to demonstrate response at 6+ months.[105, 112]
- Patients responding to nivolumab therapy often experienced ≥50% reduction in tumour burden, irrespective of treatment history and BRAF status.[82, 84, 105, 106, 111, 112]
- Median time-to-response of 2 to 3 months irrespective of treatment line.[82, 84, 105, 106, 111, 112, 199]
- Median duration of response of approximately 2 years in the advanced melanoma cohort of a single-arm trial.[199]
- Responses durable irrespective of BRAF status and treatment history, as the median duration of response has not yet been reached in any Phase III trials.[82, 84, 105, 106, 111, 112]
- Responding patients who discontinued treatment for reasons other than progressive disease maintained responses in the long-term (16 to 56+ weeks).[199]

Nivolumab is not associated with a reduction in patient HRQL and may enhance it (whilst conferring survival benefit)

- In previously untreated BRAF mutation-negative patients, improvements from baseline in EQ-5D utilities were greater in the nivolumab arm versus DTIC treatment arm (p=0.045), with improvements noted from Week 7.[108]
- Significant improvements from baseline in EQ-5D VAS scores were also observed at multiple time points (p≤0.03) in previously untreated BRAF mutation-negative patients treated with nivolumab.[108]
- Nivolumab was significantly less likely to lead to deterioration and significantly more likely to lead to improvement in EORTC QLQ-C30 global health and the EQ-5D utility index compared with DTIC (p<0.05).[108]
- Considerable improvement is seen in the EQ-5D utility index (HR = 0.55, p=0.002) which is striking due to the rarity of demonstration of significant improvement of this magnitude with the EQ-5D.

Nivolumab has an established safety profile across lines of therapy and BRAF status in advanced melanoma

- AEs are mild and transient in the majority of patients and generally manageable according to established algorithms outlined in safety management guidelines and the SmPC.[82, 84, 105, 106, 111, 112]
- The most frequently reported TRAEs across trials were the common immuno-oncology AEs of fatigue, pruritus, nausea, diarrhoea and rash.[82, 84, 105, 106, 111, 112]
- Low discontinuations due to TRAEs observed across trials (<8%).[82, 84, 105, 106, 111, 112]
- Reduced rates of Grade 3-4 TRAEs compared with DTIC (11.7% vs 17.6%)[82, 106], ICC (9.0% vs 31.4%)[105, 112] and ipilimumab (16.3% vs 27.3%).[84, 111]
- Reduced rates of TRAEs, TRSAEs, discontinuations due to AEs and common immuno-oncology AEs (particularly gastrointestinal events) compared with ipilimumab.[84, 111]
- Safety profile consistent regardless of treatment history, with no association found between ipilimumab-related and nivolumab-related toxic effects.[105, 112]

Strengths and limitations of the clinical evidence base

Diverse patient populations in the clinical development programme reflective of patients presenting in clinical practice

The CheckMate trial programme provides a diverse evidence base, reflecting the various patient profiles observed in clinical practice. Importantly, despite this diversity, nivolumab demonstrated a consistent efficacy and safety profile across trials. A common criticism of oncology trials in general is that they often only enrol relatively fit patients. The CheckMate trial programme enrolled patients with more advanced disease and multiple comorbidities. In the CheckMate 037 trial, patients with poorer prognosis still demonstrated a significantly improved clinical response when treated with nivolumab therapy.[105, 112] Clinical experts in the field of melanoma confirmed that trial populations of the CheckMate trials are generally in line with equivalent populations presenting in UK clinical practice.[12]

Well-designed RCTs provide comparative evidence to standard of care

CheckMate 066 and CheckMate 037 provide direct RCT evidence of nivolumab compared with palliative chemotherapy in previously untreated, BRAF mutation-negative advanced melanoma patients and previously treated advanced melanoma patients, respectively. At the time of study initiation, this reflected routine clinical practice in NHS England, and palliative chemotherapy is still the relevant comparator for many patients who are ineligible for, or fail to respond to, non-chemotherapy treatment options. CheckMate 067 provides direct RCT evidence of nivolumab compared with ipilimumab in previously untreated advanced melanoma (irrespective of BRAF status), reflecting current clinical practice in NHS England where ipilimumab is often used preferentially in the first-line setting.

All Phase III trials are being conducted in line with GCP guidelines with steps taken to minimise the risk of bias and independent DMCs established to provide oversight of safety and efficacy considerations, study conduct and risk-benefit ratio. The internal validity of the CheckMate 037 trial could be questioned regarding the number of patients who withdrew from the ICC arm prior to treatment initiation. However, good concordance between ITT and per-protocol analyses suggests that this did not markedly impact comparative efficacy estimates of ORR, and sample sizes remain in line with statistical powering calculations.

Study endpoints are clinically relevant

Each of the CheckMate RCTs presented in this submission were designed to capture the endpoints most relevant to advanced melanoma patients and clinicians i.e. clinical response, PFS, ORR, OS and HRQL, and are consistent with other studies of therapeutic agents in advanced melanoma. An important endpoint of interest to both patients and clinicians in current practice is OS as the majority of patients fail to achieve long-term remission with

current treatment options. Furthermore, in light of the unconventional immune responses and potential "pseudo-progression" observed with immuno-oncology therapies when assessed using traditional RECIST criteria (see Sections 2.1 and 4.7), clinical response and PFS endpoints do not necessarily capture the full potential benefit of nivolumab therapy.

Immune-related response criteria have recently been designed to reflect unconventional immune responses[52] but have not been widely applied in clinical trial design to date. In clinical practice, response to immuno-oncology therapy will be largely based on symptomatic assessment, clinical examination and laboratory tests, with CT scans relied on less heavily and consideration given to potential response after an initial increase in tumour burden or in the presence of new lesions in line with the known immuno-oncology mechanism of action.

Overall survival estimates are clinically valid

The primary limitation of the clinical evidence base supporting the use of nivolumab in advanced melanoma is that OS data are currently only available from the CheckMate 066 trial, although median OS (where 50% of patients have died) has not yet been reached in any of the Phase III melanoma CheckMate trials (although this does reflect the potential survival advantage offered by nivolumab).

Long-term extrapolation of CheckMate 066 data suggests that 45-50% of patients treated with nivolumab therapy will still be in remission 2 years after treatment initiation (see Section 5.3). This is supported with Phase I trial data that showed a 47% 2-year survival rate associated with nivolumab treatment and long-term survival of 4+ years in 35% of patients.[199] Extrapolation of CheckMate 066 OS data (that enrolled treatment naïve, BRAF mutation-negative patients only) to all advanced melanoma patients is supported in the literature base and by the clinical community.[12]

Treatment line has not been shown to independently impact treatment effect in advanced melanoma[23, 51, 190, 191], and there is no pharmacological rationale for an alternative effect in the first- and subsequent-line settings; this was previously acknowledged by NICE in their assessment of ipilimumab for advanced melanoma[4] and holds in modern practice as ipilimumab and nivolumab target different pathways within the immune system.

Similarly, immuno-oncology therapies including nivolumab have demonstrated clinical benefit in BRAF mutation-positive and BRAF mutation-negative patients.[51, 83, 191] Furthermore, clinical response is demonstrated across patient types in the CheckMate trial programme, and retrospective modelling of tumour size dynamics and OS have demonstrated an association between clinical response to immuno-oncology therapy and OS in patients with advanced melanoma.[200]

As is the case with any ITC, the analyses required for comparisons of nivolumab with ipilimumab and BRAF inhibitor therapies is an additional limitation of OS data only being available from the CheckMate 066 trial at this time and adds a level of uncertainty to these comparisons. However, the approach taken is designed to minimise this uncertainty by accounting for the nuances in the trial data available for comparison, e.g. non-proportional hazards between BRAF inhibitors and other therapies due to different mechanisms of action, crossover, differences in prognostic characteristics of patients enrolled in the trials and differences in subsequent therapy use. Additionally ITC estimates for PFS for nivolumab versus ipilimumab are in line with observed PFS within the 067 clinical trial providing validation to the methodology used to provide comparison to ipilimumab and the results of this comparison.

Duration of treatment

Although the CheckMate 003 trial data supports the hypothesis that it is clinically valid to stop treatment with nivolumab at 2 years for patients who have had either a complete or partial response to therapy at that time point, it is based on a very small number of patients for whom data is available at the licenced dose. However, this assumption has also been validated extensively with UK and international melanoma clinicians in advisory board settings and 1:1 correspondence.[11] These clinicians have confirmed that a maximum

treatment duration of 2 years would be appropriate in UK clinical practice. BMS are committed to generating additional data to better understand the relationship between treatment discontinuation and response and are currently developing an appropriate trial programme to investigate this.

End of life treatment considerations

Advanced melanoma is associated with a short life expectancy, with median survival estimates of 6-10 months consistently reported in published systematic reviews and meta-analyses, key clinical trials and patient database analyses.

Survival analyses of CheckMate 066 trial data sufficiently indicate that nivolumab therapy offers an extension to life of at least 3 months compared with palliative chemotherapy.

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 nivolumab in accordance with its marketing authorisation and the decision problem. Nivolumab is also indicated for the treatment of locally advanced or metastatic squamous NSCLC in accordance with its EU marketing authorisation. The expected number of relapsed cases of squamous NSCLC in England and Wales for 2015 is 853.

Nivolumab is therefore suitable for consideration as a life-extending treatment at the end of life, as summarised in Table 37. This is in line with alternative technologies for advanced melanoma appraised by NICE in recent years, which were also considered to meet end of life criteria.[4, 73, 74]

Table 52: End of life criteria

Criterion	Data available	Cross reference
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median life expectancy: 6-10 months Source: published systematic reviews and meta-analyses[23, 33, 34]; pivotal clinical trials of novel therapies[54, 62, 82, 154, 201]; large patient database studies in the UK and US[25, 35]	Section 3.1; Section 3.3
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	Restricted mean survival times[a]: Nivolumab: 410 days DTIC: 301 days Between group difference: 109 days (3.6 months) 75% survival times[b]: Nivolumab: 313 days DTIC: 157 days Between group difference: 156 days (5.1 months) Source: CheckMate 066 patient level data	Section 4.7
The treatment is licensed or otherwise indicated for small patient populations	Advanced melanoma population for 2016: 1,304 Source: ONS population estimates for 2013[85] and melanoma incidence estimates for 2012[29] extrapolated using increased incidence rate of 3.5% previously used in melanoma submissions[4, 73-75] Advanced or metastatic, relapsed squamous NSCLC population for 2015: 853 Source: Advanced or metastatic NSCLC estimates for 2013[89] and proportion of patients with squamous NSLC[90] combined with estimates of proportion of patients receiving treatment[91] and of those, patients who relapse [92]	Section 3.3; Section 6

Key: NHS, National Health Service.
Notes: [a], mean survival time calculated from within trial analysis; [b], when a quarter of the patients have died.

4.14 Ongoing studies

Additional evidence from all trials presented in this submission to support the use of nivolumab monotherapy for the treatment of advanced melanoma is likely to become available in the next 12 months, as summarised in Table 53.

Table 53: Data likely to be available in the next 12 months to further support the use of nivolumab monotherapy for the treatment of advanced melanoma

Study	Additional evidence	Expected date of availability
CheckMate 066	Overall survival; extended follow-up	November 2015 for 18 month OS Q4 2016 for 2 year OS
CheckMate 067	Overall survival Progression-free survival; extended follow-up HRQL	Q4 2016
CheckMate 037	Overall survival Progression-free survival; extended follow-up HRQL	November 2015
	Overall survival; extended follow-up	June 2016
Key: HRQL, health-related quality of life; Q4, quarter 4.		

In addition to these trials, two ongoing RCTs (CheckMate 067 and CheckMate 069) are investigating the clinical efficacy of nivolumab in combination with ipilimumab in advanced melanoma, and are expected to report interim data within the next 12 months. A further Phase II study (CheckMate 064) investigating the clinical efficacy of nivolumab administered sequentially with ipilimumab is also estimated to report preliminary data within the next 12 months. However, these data lie outside of the decision problem of interest to this submission.

5 Cost effectiveness

Summary

- A de novo economic decision model was developed with a structure that captures the unique characteristics of immunotherapy, including nivolumab, 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 nivolumab and the comparators through the use of an indirect treatment comparison analysis
    - 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, treatment with nivolumab 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 DTIC and 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 nivolumab is cost-effective versus all comparators both with and without the inclusion of a PAS for the comparator technologies
- At the threshold of £50,000, the probabilities of nivolumab being most cost - effective are 95% and 99% 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, a systematic review was conducted to identify cost-effectiveness studies for the treatment of advanced melanoma with nivolumab. The detailed search strategy is presented in Appendix 9.

To ensure that the literature was comprehensively reviewed, a wide range of databases were searched on 25 November 2014: 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 54 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 54.

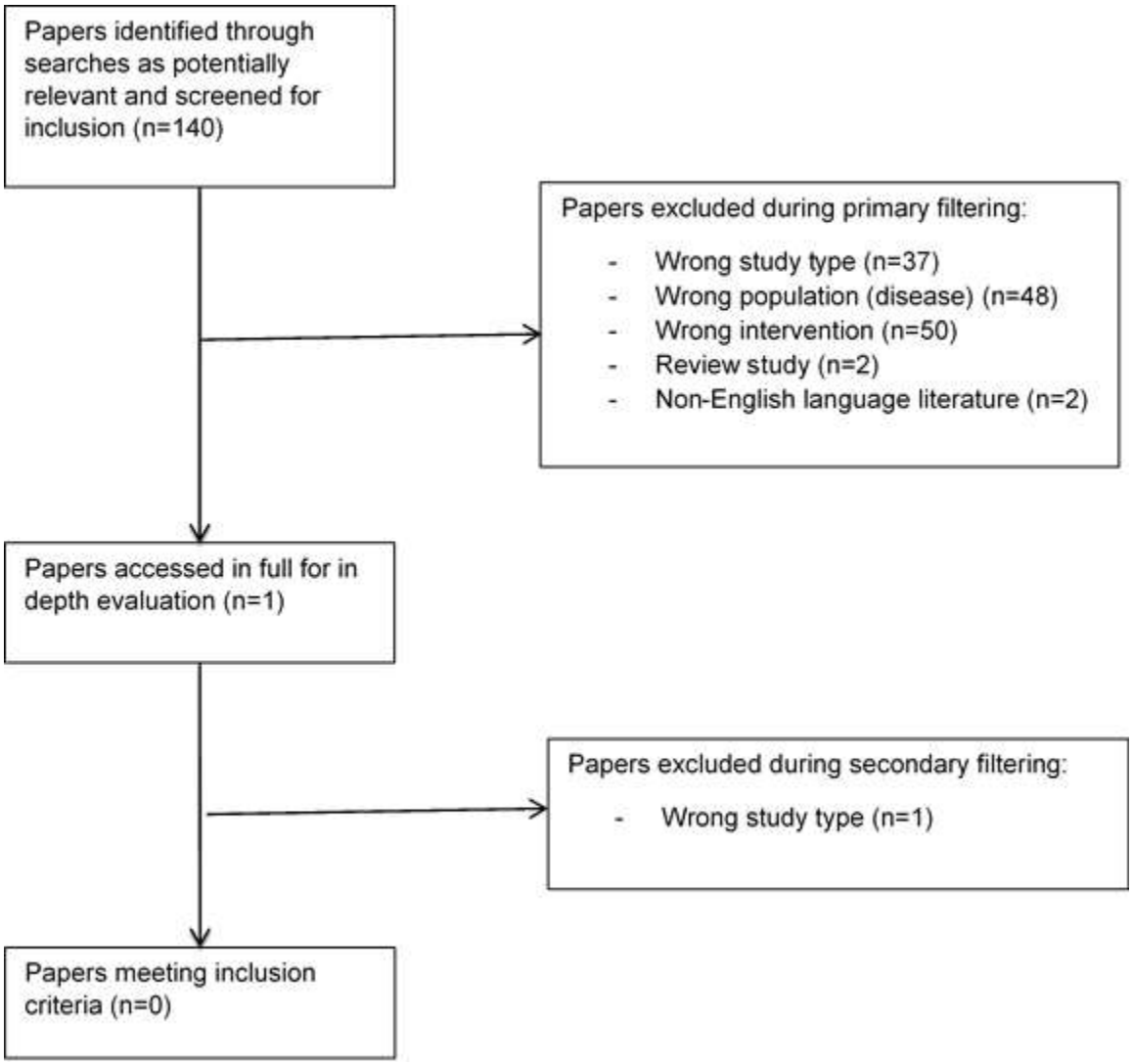
Table 54: Eligibility criteria for economic evaluation publications and rationale for each criterion

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

Of 140 initially identified studies, 139 were excluded during primary filtering (references available upon request), as illustrated in Figure 48. One study remained for secondary filtering; however, 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, and a de novo cost-effectiveness model was developed.

Figure 48: Identification of economic evaluations relevant to the decision problem



5.2 De novo analysis

5.2.1 Patient population

The licensed indication for nivolumab as a monotherapy in the EU is "for the treatment of adult patients with advanced (unresectable or metastatic) melanoma."[10] The indication for nivolumab has no restriction on 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, if possible; where patients are not fit enough to receive ipilimumab, they receive traditional chemotherapies like DTIC, which were standard of care prior to the availability of ipilimumab and BRAF inhibitors.

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 or DTIC.

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.[4, 23] and is further substantiated by the similarity of outcomes between CheckMate 066 and CheckMate 037 (Section 4).

The patient groups are defined in line with the scope and decision problem for this appraisal.

5.2.2 Model structure

A de novo semi-Markov survival model was developed, where health-states were defined by four different measures relevant to the evaluation of the clinical effectiveness and cost effectiveness of nivolumab compared to its comparators (see Figure 49 for a simplified model structure):

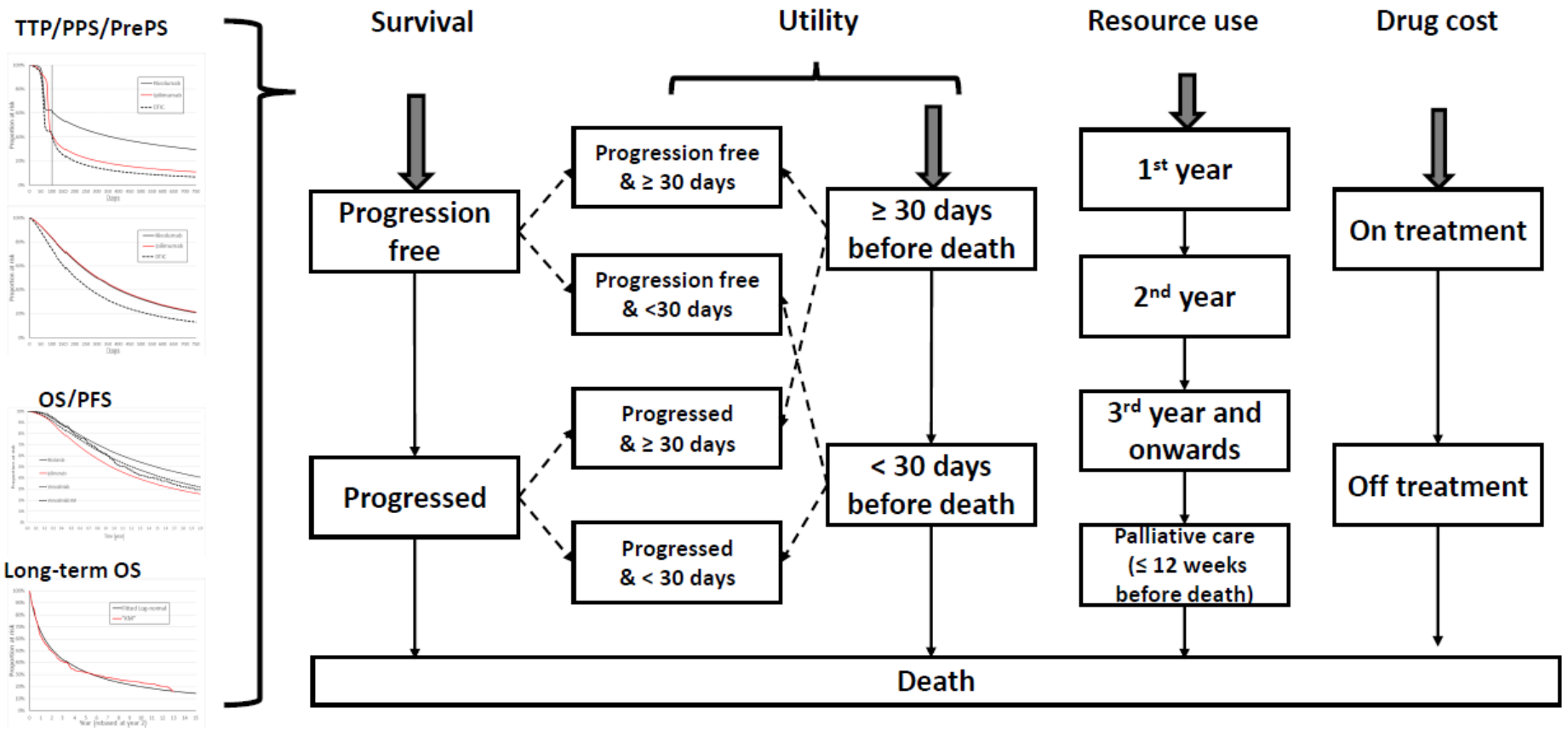
- Progression status for modelling survival and utility (3 states): progression-free, progressed and dead.
- Time to death for modelling utility (2 states): ≥30 days before death, and <30 days before death.

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 (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 49: 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 nivolumab, ipilimumab and DTIC, 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.[202-204] It was also deemed appropriate for the decision problem by UK health economics and clinical experts during validation meetings.[12]

For nivolumab, ipilimumab and DTIC, parametric curves for TTP, PPS and PrePS were fitted based on a covariate-adjusted indirect comparison for the three treatments using patient level data from trials CheckMate 066 (nivolumab and DTIC) and MDX010-20 (ipilimumab and GP100, which is assumed to have the same efficacy as DTIC). Please see Section 4.10 for more details on the rationale, assumptions, methods and results of the indirect comparison.

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 AUC 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[73]), 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 possible, as discussed in the recent ipilimumab NICE appraisal (TA319[4]), 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[62, 63, 139].

The survival methods outlined above are applied within the first 2 years of the model for DTIC and BRAF inhibitors and within the first 3 years for nivolumab and ipilimumab in the base case. The 2- and 3-year cut-off was chosen because: a) the maximum follow-up period for the CheckMate 066 trial is around 18 months, and therefore, long-term extrapolation of OS is subject to greater uncertainty; b) a maximum treatment period of 2 years was assumed for nivolumab based on the evidence from the Phase I CheckMate 003 trial and consultation with UK melanoma clinicians (see Section 5.2.3 for detailed discussion), meaning alternative survival efficacy inputs can be used from Year 2 or Year 3 onwards (Section 5.2.3); c) recent published long-term pooled ipilimumab study showed a plateau in the OS beginning around Year 3[51] and this is assumed for immunotherapies 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[205] (from Year 2 onwards for DTIC and BRAF inhibitors in the base case), long-term ipilimumab OS data[51] (from Year 3 onwards for nivolumab and ipilimumab in the base case), and general UK population mortality as background mortality.

For TTP, the KM data were used for the first 100 days due to the trial protocol effect where the first tumour assessments were performed at week 9 and week 12 in CheckMate 066 and MDX010-20 respectively (Section 4.10). 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 and PPS. Therefore, similar to TTP, the KM data were used for PrePS in the base case (Section 4.10).

Structure for modelling utility

The use of RECIST criteria to assess progression and response in the nivolumab trials can make interpreting the clinical evidence challenging. Unlike conventional anti-cancer therapies, where response to treatment can be observed as a reduction in tumour size, immunotherapies such as nivolumab can result in varying patterns of response. In some cases, T-cell activity around the tumour cells can have the effect of making the tumour appear bigger, due to the proliferation of activated T-cells infiltrating the tumour. This well recognised phenomenon is commonly described as 'unconventional immune related responses' and can result in 'pseudo-progression' where patients who ultimately achieve a positive clinical outcome of increased OS may have tumours that appear to have enlarged when assessed in the early stages of treatment. RECIST criteria classes these patients as having progressed, when in fact they are responding to treatment, which makes PFS a less than ideal proxy for modelling survival, utilities and resource use for immunotherapies.

Utility analysis based on EQ-5D data collection in the CheckMate 066 trial was used in the model base case (see Section 5.4 for detailed utility analysis). Due to the issues of using RECIST criteria as a surrogate outcome for quality of life, however, a more complex analysis framework may be better suited to capture the impact of quality of life, as was the case in TA319[4].

Consequently, in the final utility model the key factors used for the base case model include progression status and whether time to death is less than 30 days. To incorporate the utility analysis into the model, separate health states were used representing the proportion of patients who were alive and who were less than 30 days from death.

It is important to note that the Markov model is able to estimate the proportion of people who die in each cycle, and therefore, it is straightforward to back-calculate, for any given cycle, the proportion of patients who are less than 4 weeks (close to the 29 days cut-off in the utility model) to death (i.e. a life expectancy less than 4 weeks). In the model, 4 composite health states are therefore used: 1) progression-free and less than 30 days to death; 2) progression-free and 30 days or more to death; 3) progressed and less than 30 days to death; and 4) progressed and 30 days or more to death, with each state having different utility values.

Progression status based utilities are widely used for cancer patients and time to death based utilities have been used in the recent NICE appraisal for ipilimumab (TA319[4]) where data from both the MDX010-20 and CA184-024 trials were shown to demonstrate only a tenuous link between progression status and utility with a greater link shown between time to death and utility – the most accurate model, which has since been published, uses a combination of both progression status and time to death based modelling.[40]

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[4]) mainly used resource use inputs from the Oxford Outcomes study[206], 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[12], 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.[12] Therefore, after consulting with clinical experts[12], 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).

Structure for modelling drug cost

The marketing authorisation (MA) for nivolumab recommends that 'treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient'.[10] Two health states were therefore defined within the model – on treatment and off treatment – to better calculate the nivolumab drug cost, 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 066 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 the nivolumab 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.

For the comparators, patients in the ipilimumab treatment arm had a maximum on treatment period of 16 doses (4 doses for the induction period and up to 12 doses for potential re-induction based on the MDX010-20 trial). The on treatment period for patients in the DTIC and BRAF inhibitor treatment arms is defined based on the progression free and progressed health states.

Modelling subsequent anti-cancer therapies

With the exception of ipilimumab, subsequent anti-cancer therapies were not explicitly modelled. The proportion of patients receiving ipilimumab as subsequent therapy (excluding the ipilimumab arm) is one of the key covariates in the fitted TTP parametric curves from the indirect treatment comparison, and therefore has impact on both PFS and OS. Consequently, the cost of subsequent ipilimumab use is also modelled (Section 5.5.5). There is no attempt to control for the effects of other subsequent anti-cancer therapies on the other efficacy inputs (both short-term trial-based estimates and long-term survival) as the other subsequent therapies received within the CheckMate 066 trial were chemotherapies that have never been demonstrated to impact overall survival; and the costs for other subsequent therapies are also not considered for any of the treatment arms.

Table 55 summarises the key features of the de novo analysis.

Table 55: 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[207]
Were health effects measured in QALYs; if not, what was used?	Yes	
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 56 summarises the dosing regimen and continuation rules for nivolumab and comparators.

Table 56: Dosing regimen and continuation rules applied in the model for nivolumab and comparators

Treatment	Dosing regimen	Justification	Continuation rules as per SmPC	Continuation rules implemented in the model	Justification implementation in the model
Nivolumab	3mg/kg, every 2 weeks by IV	SmPC[10]	The MA 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 066 trial	In line with MA and the use of CheckMate 066 trial data
				Maximum 2 years	Clinical opinion and likely clinical practice supported by CheckMate 003
Ipilimumab	3mg/kg, every 3 weeks by IV	SmPC[71]	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 and the possibility of reinduction for up to 16 doses (see Table 57 for details)	Used in NICE TA319 based on trial MDX010-20. Whilst reinduction is not UK clinical practice and not recommended in the SmPC, including the cost of this is consistent with the efficacy inputs used for ipilimumab in the model
Dabrafenib	150mg twice daily, oral	SmPC[70]	SmPC states that treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.	Until progression	Assumption based on clinical practice and consistency across these comparators
Vemurafenib	960mg twice daily, oral	SmPC[72]	SmPC states that treatment should continue until disease progression or the development of unacceptable toxicity.	Until progression	
DTIC	1000mg/m^2, every 3 weeks by IV	Dosing regimen used in CheckMate 066 and 037	SmPC states that, in advanced melanoma, the duration of treatment depends on the efficacy and tolerability in the individual patient.	Until progression	

Key: IV, intravenous infusion; MA, market authorisation; SmPC, summary of product characteristics.

Nivolumab

The MA recommends that nivolumab treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.[10] As stated in Section 4, treatment duration in CheckMate 066 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 5.3).

As discussed in Section 4, 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 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 003 trial and UK clinical expert opinion indicate no loss of response upon discontinuation of therapy, it is assumed that when patients discontinue nivolumab their treatment effect is maintained. To test the sensitivity of the model to this assumption, a range of scenario analyses were conducted assuming that, after 2 years, 0%, 25%, 50%, 75% and 100% of patients experience the same survival rate as estimated for the DTIC arm (i.e. melanoma registry OS).

Comparator treatments

Table 57 shows the detailed dosing for ipilimumab used in the model. The proportion of patients receiving doses 1 to 4 (induction 1) is based on the CA184-024 trial and reinduction (induction 2 to 4) is based on the MDX010-20 trial; these are the same inputs that were used in the recent ipilimumab NICE appraisal (TA319[4]). Although ipilimumab is used for a maximum of 4 doses in the UK, reinduction (induction 2 to 4, or a maximum of 16 doses) was considered in the model base case as this is consistent with the efficacy data for ipilimumab used in the model, which is also based on the MDX010-20 trial. Scenario analysis was performed investigating the impact of costing a maximum of 4 doses of ipilimumab; information is not available to adjust the efficacy in line with UK clinical practice.

Table 57: Ipilimumab detailed dosing

Induction number	% of patients receiving induction	% of patients receiving dose				Mean doses received	Sample size
		Dose 1	Dose 2	Dose 3	Dose 4		
Induction 1	100.00%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	247
Induction 2	7.44%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	511
Induction 3	1.37%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	511
Induction 4	0.20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	511
		Mean number of doses received:				[redacted]	

For dabrafenib, vemurafenib and DTIC, 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 58 summarises the key sources of clinical evidence that were used to populate the model.

An indirect treatment comparison using the CheckMate 066 and MDX010-20 trials was used for the base case model. The use of the CA184-024 trial to estimate the efficacy of ipilimumab within the indirect treatment comparison was tested in a scenario analysis.

The NICE DSU model selection algorithm was used to select the most appropriate structure for all fitted parametric curves.[208]

Table 58: Sources of key clinical evidence used to populate the model

Clinical evidence	Brief description	Use in the model
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 were used in the indirect comparison to fit TTP, PPS and PrePS parametric curves • Patient level data in the nivolumab arm were used to fit TOT parametric curves for nivolumab • EQ-5D data were used for trial-based utility analysis • Used for modelling AEs for nivolumab and DTIC • 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
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[75], TA319[4])	• Patient level data were used in the indirect comparison to fit TTP, PPS and PrePS parametric curves • EQ-5D data were used for scenario analysis
CA184-024	Pivotal Phase III trial in previously untreated advanced melanoma patients that investigates the efficacy of ipilimumab 10mg/kg + DTIC (n=250) compared with DTIC (n=252) Trial considered as supportive in the FAD for ipilimumab NICE appraisal at first line (TA319[4])	• Patient level data were used in the indirect comparison to fit TTP, PPS and PrePS parametric curves for scenario analysis
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)	• Relative risks of AEs for the ipilimumab treatment arm • Validation of outcomes for PFS for nivolumab vs ipilimumab
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,

Clinical evidence	Brief description	Use in the model
		PrePS and TOT parametric curves for nivolumab 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[73] 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[205]	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 2 onwards for BRAF inhibitors and DTIC
Pooled long-term OS of ipilimumab[51]	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 nivolumab and ipilimumab
General population mortality	Latest England general population mortality by single year of age	• Used to supplement long-term registry OS from ACJJ 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: ACJJ, 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 Overall survival – BRAF mutation-negative

As stated previously, for BRAF mutation-negative patients, the modelled OS for nivolumab and the comparators ipilimumab and DTIC is calculated within the model using covariate-adjusted parametric curves fitted for TTP, PPS and PrePS using patient characteristics based on CheckMate 066 for the first 2 years for DTIC and the first 3 years for nivolumab and ipilimumab, and registry OS and long-term pooled ipilimumab OS from Year 2 and 3 onwards. General population mortality is also used to set the minimum mortality rate for each model cycle.

Patient characteristics

Table 59 shows the patient characteristics used in the base case model for BRAF mutation-negative analysis based on the total patient population in CheckMate 066 (n=418)[82] and details how they are used in the model.

Table 59: Patient characteristics in the base case model

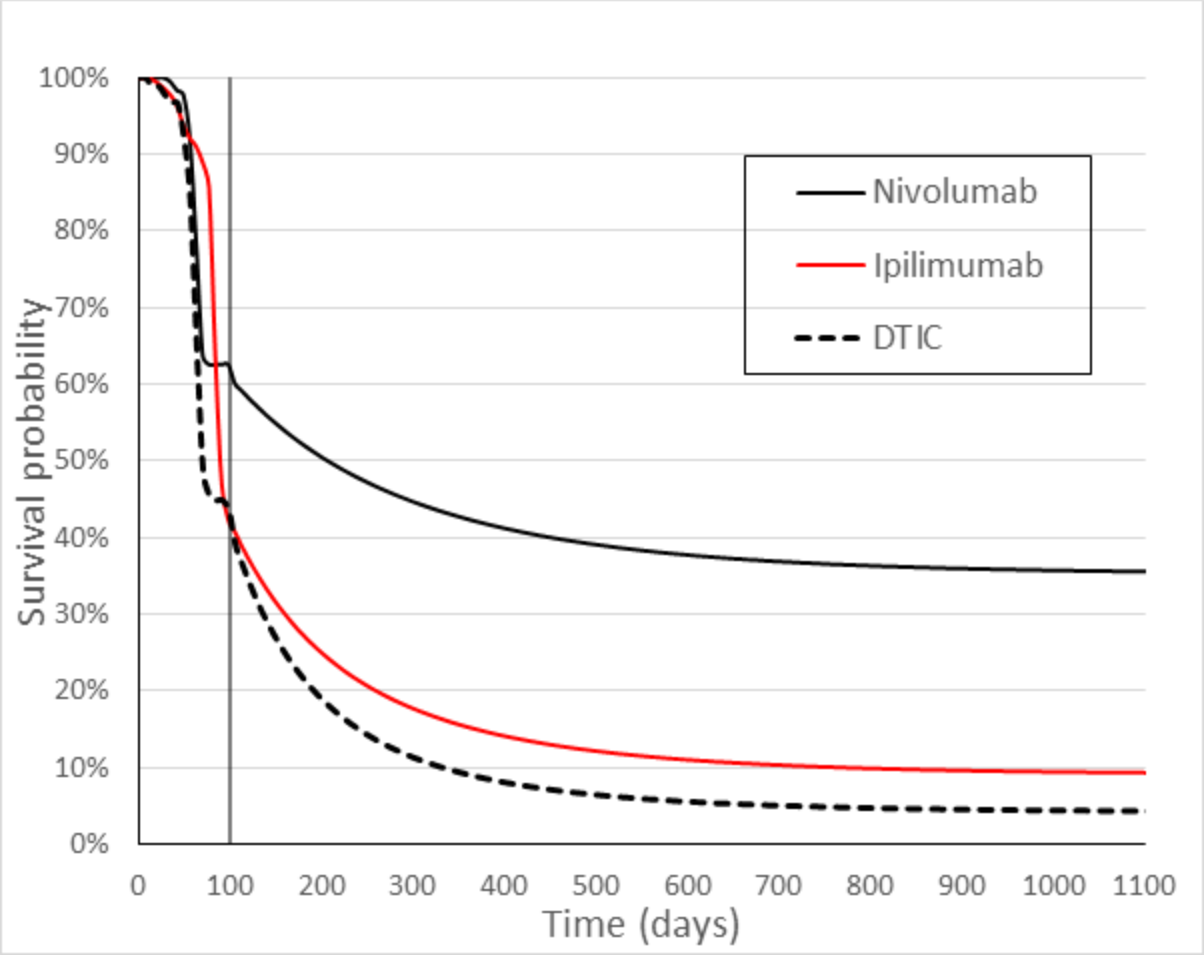
	BRAF mutation-negative[82]	**Use in the model**
Mean age	63	Starting age in the model
% male	58.9%	TTP, PPS, PrePS, TOT
% under 65	47.8%	TTP, PPS, PrePS, TOT
Mean weight (kg)	78.7	Drug dosing
Mean body surface (m^2)	1.9	Drug dosing
% stage M1c	61.0%	TTP, PPS, PrePS, TOT
ECOG status = 0	64.5%	TTP, PPS, PrePS, TOT
% elevated LDH (>ULN)	36.6%	TTP, PPS, PrePS, TOT
% with brain metastases	3.6%	TTP, PPS, PrePS, TOT
% subsequent ipilimumab treatment	29.7%	PPS

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.
Notes: [a], Assumed the same as BRAF mutation-negative patients in the absence of data.

Time to progression

As discussed in Section 4.10, time to progression is modelled using KM data for the first 100 days, and fitted parametric curves based on the indirect treatment comparison post 100 days. Among the six parametric curves fitted, the Gompertz curve is chosen for the base case based on the NICE DSU guidance[208] (see Section 4.10 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 50 shows the final modelled time to progression for BRAF mutation-negative patients combining the KM data for the first 100 days and parametric curves post 100 days. Patient characteristics shown in Table 59 are applied to the Gompertz covariate-adjusted TTP and to the observed KM TTP data in the first 100 days to account for bias resulting from different patient characterises among trials and treatment arms.

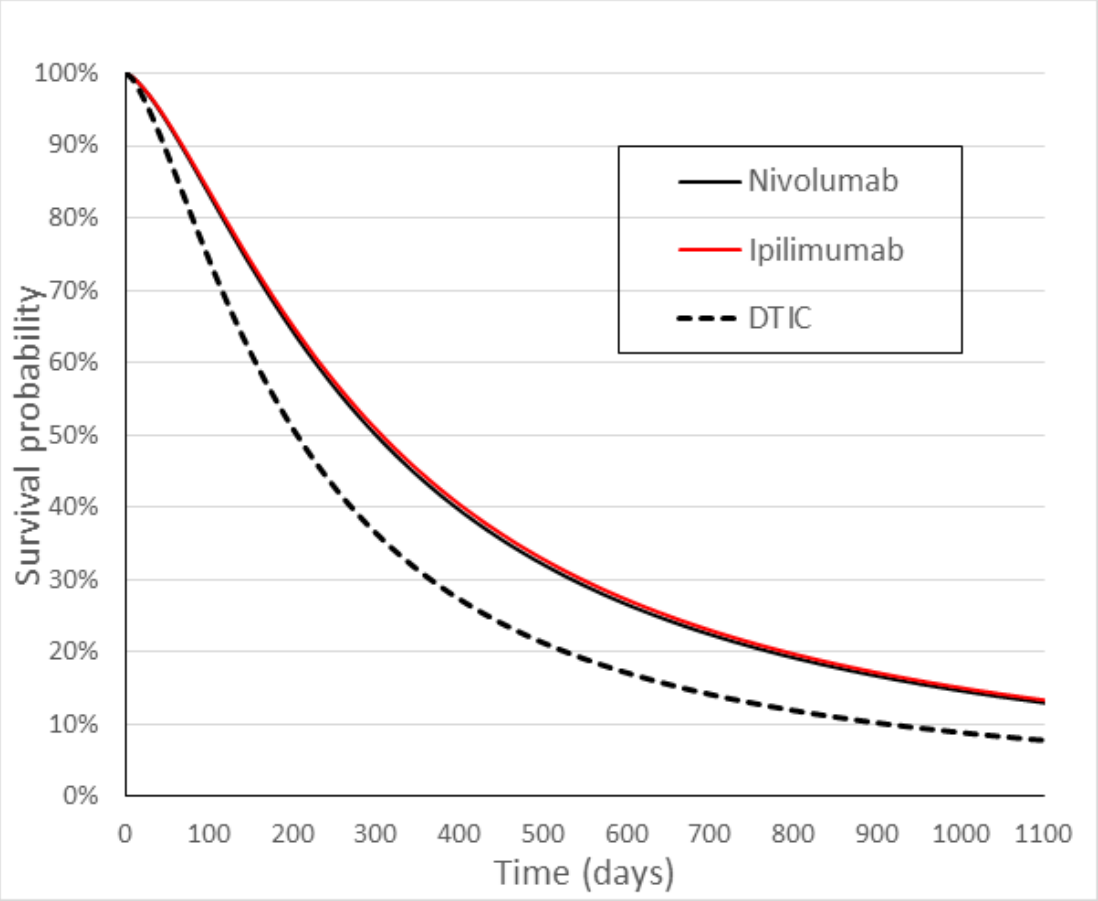
Figure 50: Time to progression in the base case model for BRAF mutation-negative analysis over 2 years



Post-progression survival

Among the six parametric curves fitted, log-logistic curve is chosen for the base case based on the NICE DSU guidance[208] (see Section 4.10 for detailed discussion). Other types of curves were tested as scenario analyses. Figure 51 shows the final modelled post-progression survival for BRAF mutation-negative patients after applying the patient characteristics shown in Table 59. Figure 51 shows that PPS for nivolumab and ipilimumab is higher than for DTIC. A plausible clinical explanation is the experience of "pseudo progression" among nivolumab and ipilimumab patients in CheckMate 066 and MDX010-20 trials where progression was assessed by RECIST. Figure 51 shows that PPS is similar between nivolumab and ipilimumab, and a combined PPS for nivolumab and ipilimumab is tested as a scenario analysis. The similarity of combined PPS for nivolumab and ipilimumab supports the assumption of similar long-term efficacy between the two immunotherapies used within the model.

Figure 51: Post-progression survival in the base case model for BRAF mutation-negative analysis



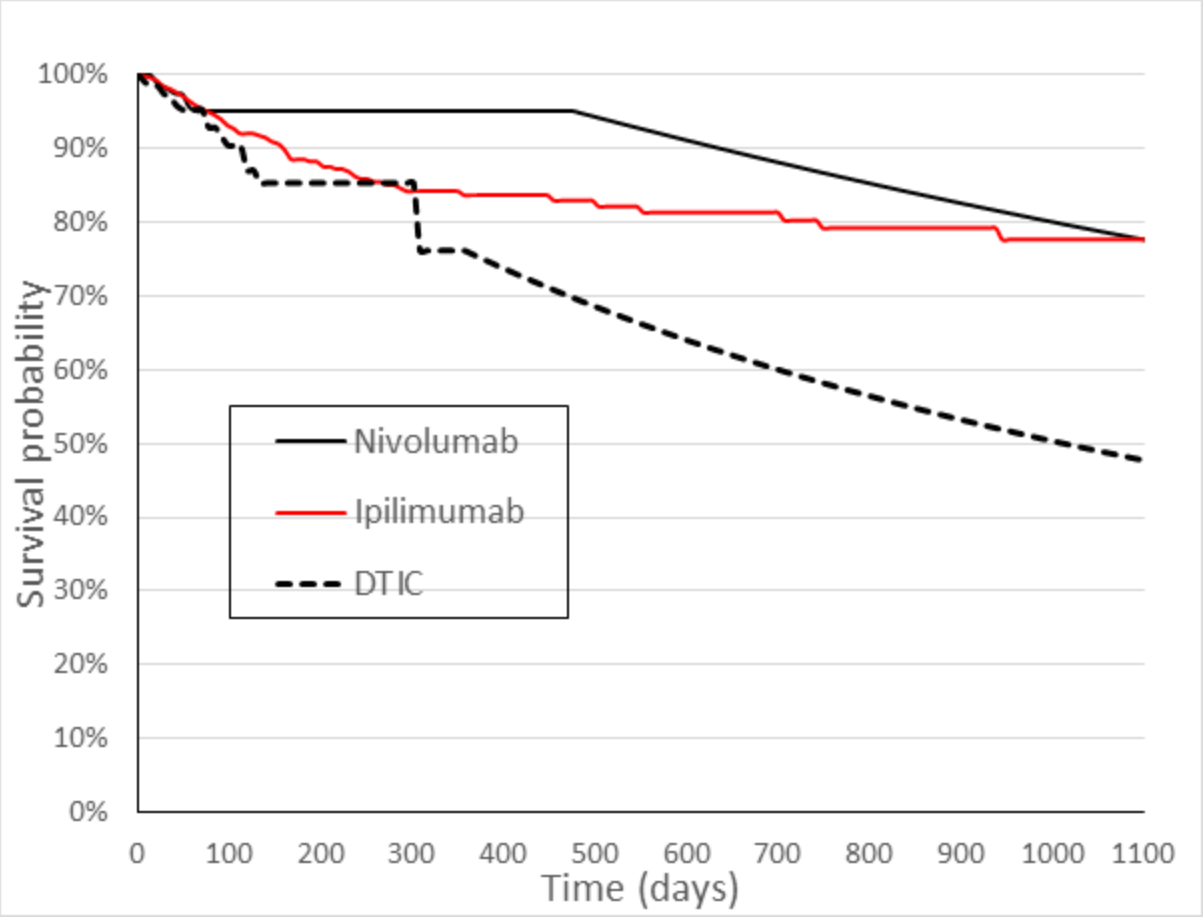
Pre-progression survival

Six parametric curves were fitted for PrePS; however, none of the standard parametric curves provided an acceptable visual fit to observed data (Section 4.10). Therefore, similar to the method for TTP pre-100 days, PrePS is modelled using available KM data in the base case (Section 4.10). The longest follow-up for observed PrePS data for nivolumab and DTIC in the CA209-006 trial is within 2 years; therefore, mortality rates based on the best fitted PrePS parametric curve (log-normal based on AIC/BIC) were used for the PrePS for nivolumab and DTIC after the last observed KM data and before switching to long-term OS (pooled ipilimumab long-term OS for nivolumab at Year 3 and melanoma registry OS for DTIC at Year 2).

Figure 52 shows the final modelled pre-progression survival for BRAF mutation-negative patients after applying the patient characteristics shown in Table 59. The figure shows that PrePS for nivolumab is higher than ipilimumab in the first 2 years and the PrePS for both nivolumab and ipilimumab is higher than DTIC. This is likely due to a high number of progression-related deaths in the DTIC arm of the trial prior to the first assessment of progression (i.e., genuine post progression death events in the DTIC arm wrongly classified as pre-progression death events due to the timing of first tumour assessment).

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.

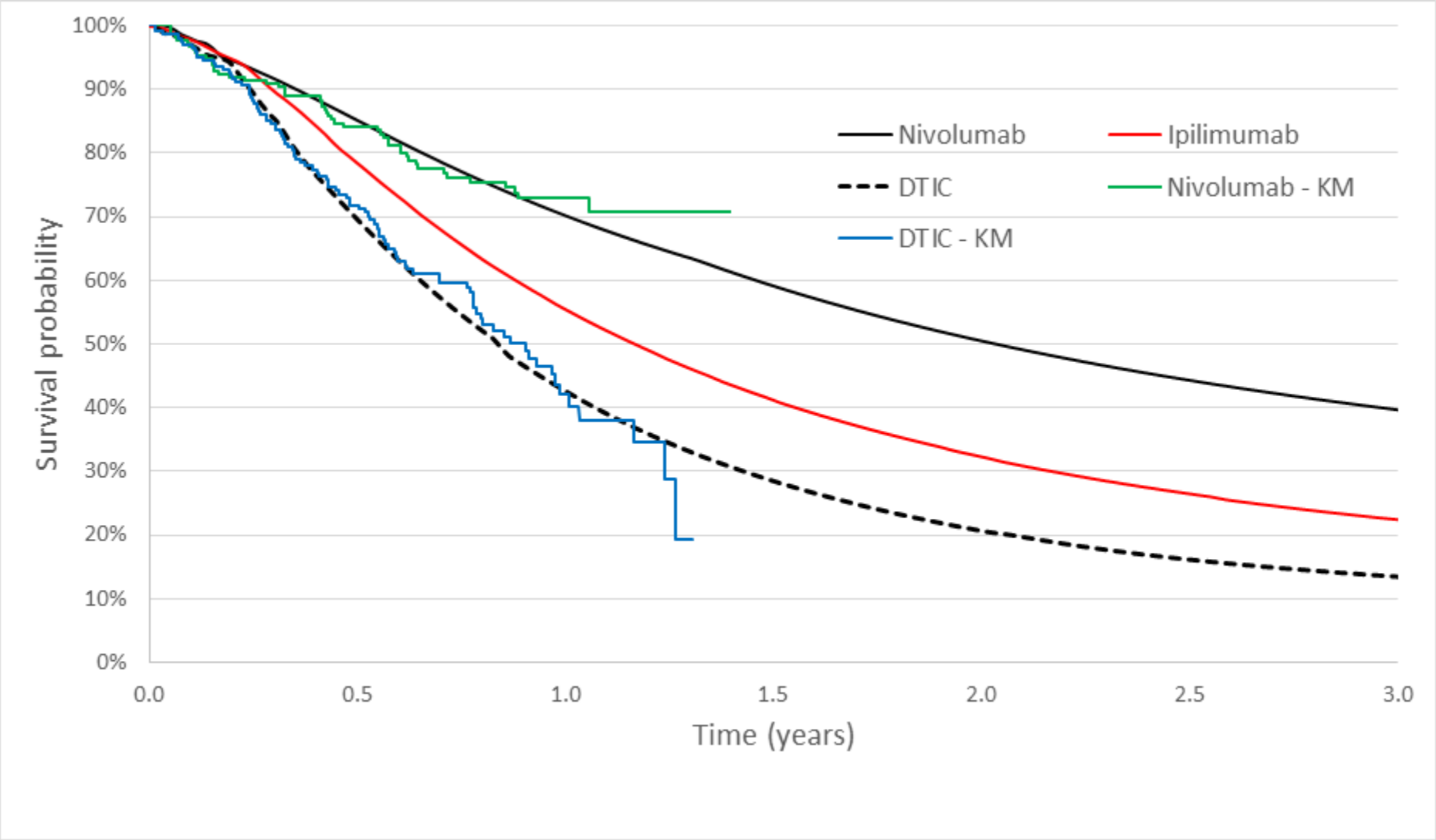
Figure 52: Pre-progression survival in the base case model for BRAF mutation-negative analysis



Overall survival for the first 3 years

The modelled OS for BRAF mutation-negative patients for the first 3 years is presented in Figure 53, which combines the TTP, PPS, and PrePS shown in Figure 50, Figure 51 and Figure 52, respectively. The OS KM curves for nivolumab and DTIC from CheckMate 066 are also presented in the figure for comparison and validation. The OS KM curve for ipilimumab from MDX010-20 is not presented in Figure 53 because patient characteristics in the MDX010-20 trial are different from the base case patient characteristics used in the base case model (Table 59). The modelled OS for ipilimumab as shown in Figure 53 represents the estimated OS for patients who have the characteristics shown in Table 59 being treated with ipilimumab. The OS KM for ipilimumab in MDX010-20 and the modelled OS for ipilimumab using patient characteristics from the ipilimumab arm of MDX010-20 are shown in Appendix 12 and demonstrate a good fit between the model prediction and the KM data for ipilimumab. The modelled OS fits reasonably well with the KM data for nivolumab and DTIC. For nivolumab, modelled OS appears to underestimate KM survival towards the end of the curve. For DTIC, modelled OS appears to overestimate KM towards the end. Consequently, the gaps seen from the KM curves are wider than the gaps estimated based on the modelled OS towards the end of the KM curves of nivolumab and DTIC, which is conservative regarding the effectiveness of nivolumab over DTIC.

Figure 53: 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, three sources of evidence were used to model long-term survival for BRAF mutation-negative patients:

Melanoma registry OS by the AJCC[205] for the DTIC arm from Year 2 onwards.

This is because no trial data exist for DTIC after 18 months (the longest follow-up for the CheckMate 066 trial), which is deemed the best available long-term OS for chemotherapy. The use of melanoma registry OS from Year 2 onwards for all or a proportion of patients in the nivolumab arm who discontinue treatment at Year 2 was tested as scenario analyses.

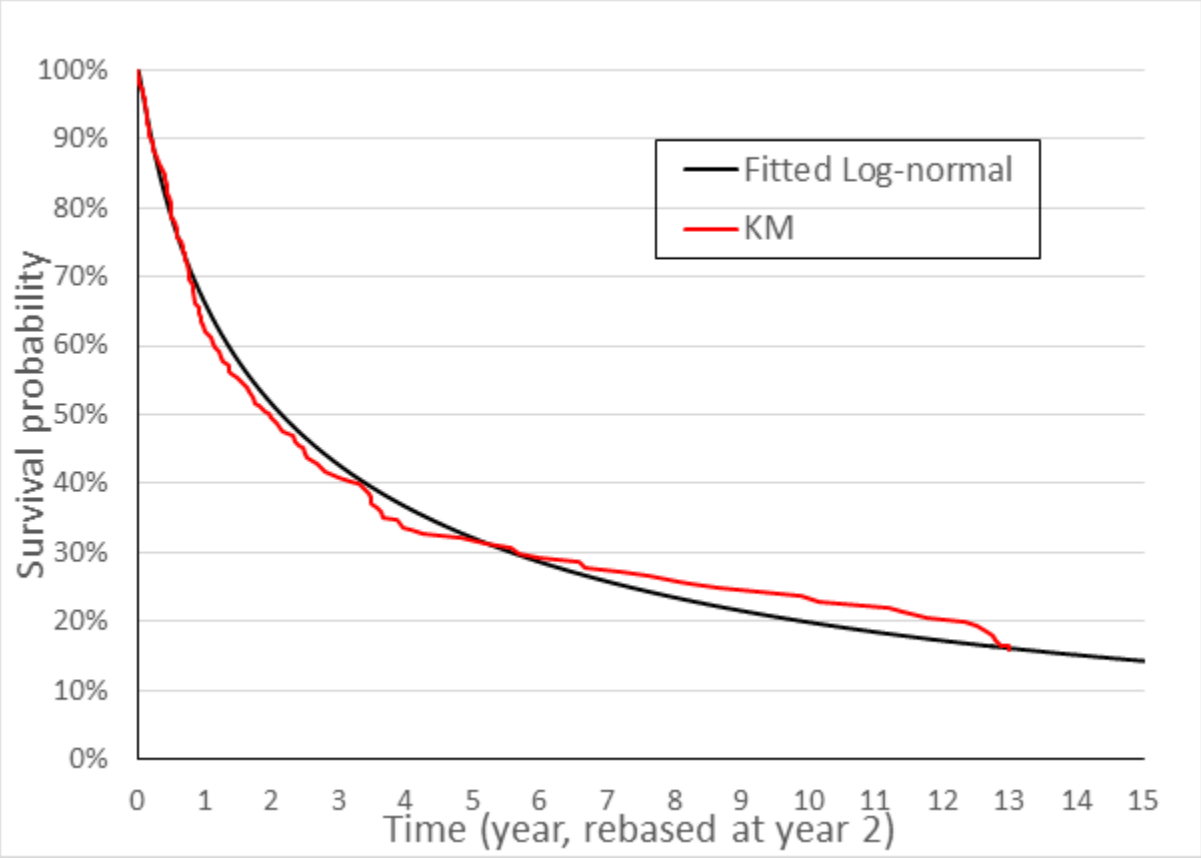
Pooled ipilimumab long-term OS[51] for nivolumab and ipilimumab from Year 3 onwards.

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 nivolumab due to similarity of mechanism of action (both are immunotherapies); this was considered a reasonable and potentially conservative assumption based on clinical opinion.[12]

The AJCC registry survival data for Stage IV reported by Balch et al[205]

This 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 2 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 54). Other curve fits are tested in scenario analyses. Please refer to Appendix 8 for curve fit parameters and goodness of fit statistics.

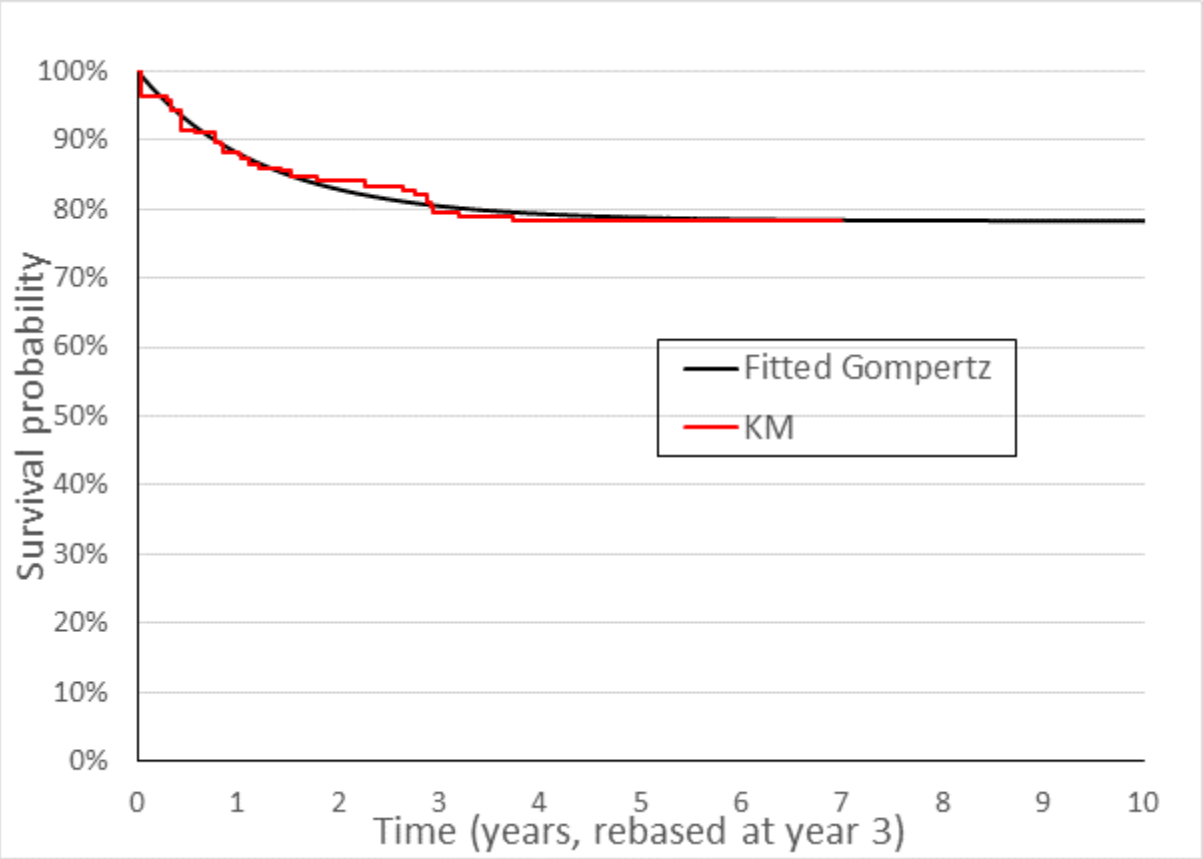
Figure 54: KM and fitted base case OS (rebased at 2 years) using registry data



The pooled ipilimumab long-term survival data reported by Schadendorf et al[51] 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 55). Other

curve fits are tested in scenario analyses. Please refer to Appendix 8 for curve fit parameters and goodness of fit statistics.

Figure 55: KM and fitted base case OS (rebased at 3 years) using long-term pooled ipilimumab data

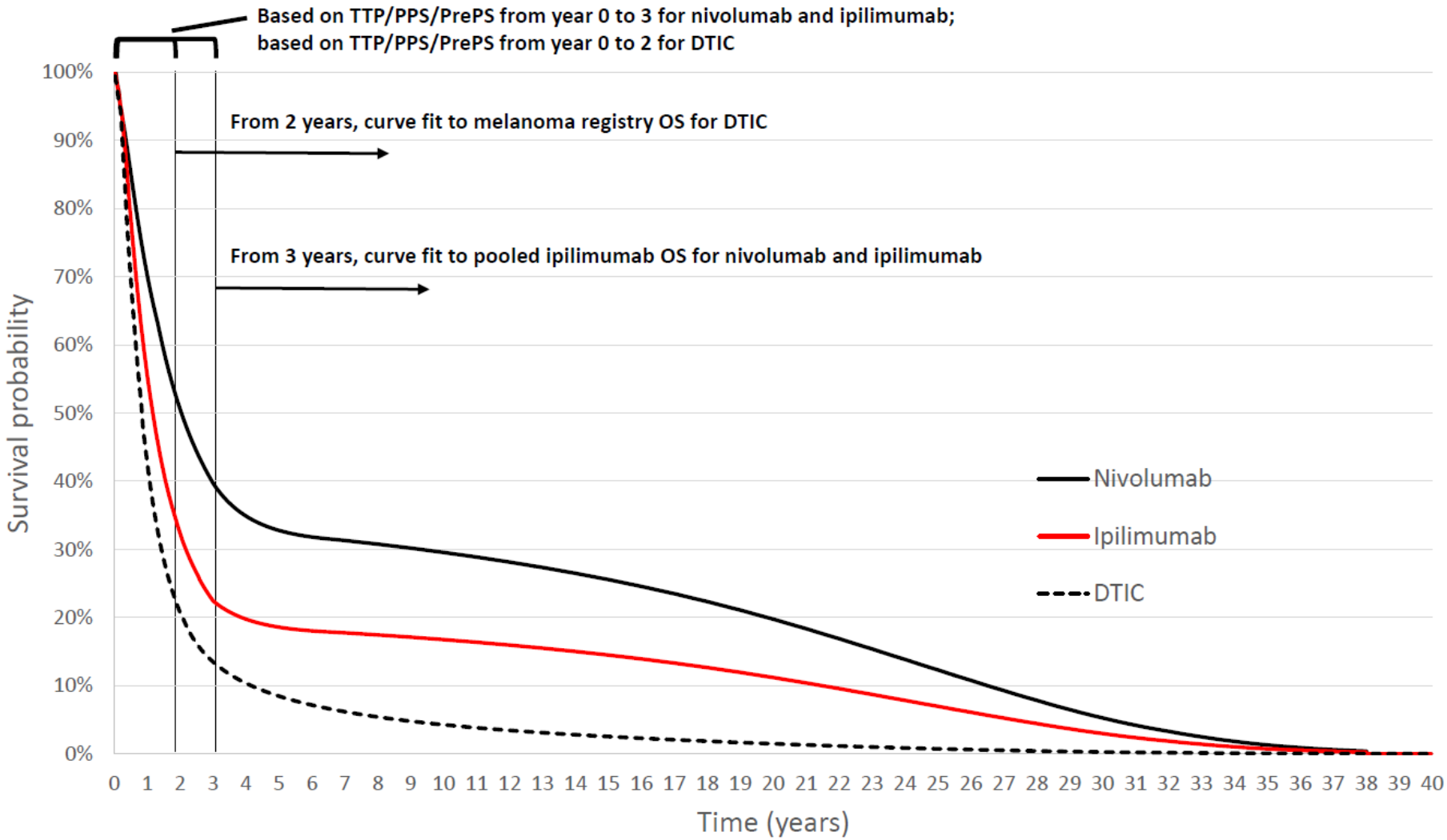


As the AJCC registry data records only melanoma-specific mortality rates, additional age-specific background survival rates were applied. These were taken from Life Tables for England (2011-2013)[209], as a weighted average of male and female mortality risks using the gender distribution of participants of the CheckMate 066 trial. The general population mortality was also used to set the minimum threshold mortality rates for modelled patients in all treatment arms.

Final overall survival

The final modelled OS for BRAF mutation-negative patients, combining short-term trial-based estimates, long-term OS from registry or pooled ipilimumab estimates, and general population mortality, over 40 years, is presented in Figure 56.

Figure 56: Final overall survival in the base case model for BRAF mutation-negative analysis over life time (40 years)



5.3.3 Overall survival – BRAF mutation-positive

Nivolumab and ipilimumab for the first 3 years

The comparators for the BRAF mutation-positive analysis include dabrafenib, vemurafenib and ipilimumab. For nivolumab and ipilimumab, the same method used for the BRAF mutation-negative analysis was used for estimating 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 OS and PFS used for the dabrafenib and vemurafenib arms (see Table 60).

Table 60: Patient characteristics in the base case model

	BRAF mutation-positive[62]	**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)	78.7[a]	Drug dosing
Mean body surface (m^2)	1.9 [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
% subsequent ipilimumab treatment	22.0%	PPS

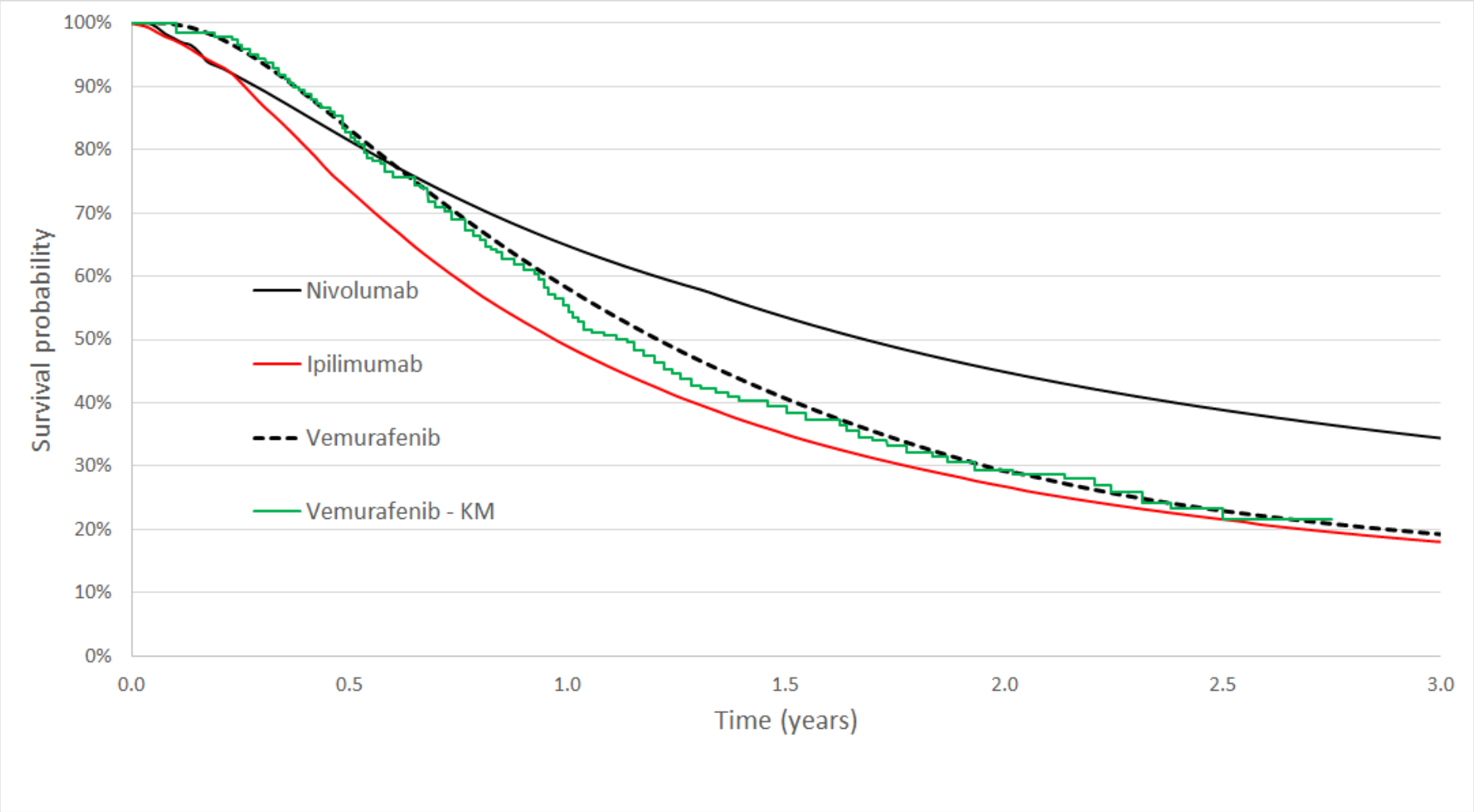
Key: ECOG, Eastern Cooperative Oncology Group; kg, kilogram; LDH, lactate dehydrogenase; m, metre; PPS, post-progression survival; PrePS, pre-progression survival; TOT, time on treatment; TTP, time to progression; ULN, upper limit of the normal range.
Notes: [a], Assumed the same as BRAF mutation-negative patients in the absence of data.

The modelled OS for BRAF mutation-positive patients for the first 3 years for nivolumab and ipilimumab is presented in Figure 57, which combines TTP, PPS, and PrePS using patient characteristics from the vemurafenib arm in the BRIM-3 trial.

Dabrafenib and vemurafenib short-term overall survival

Based upon the NICE recommendation for dabrafenib[73] in the base case, it was assumed that dabrafenib and vemurafenib have the same efficacy for OS and PFS (Section 5.2). 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 OS reported for the BRIM-3 trial by McArthur et al[139] was selected to represent the OS for both dabrafenib and vemurafenib in the base case. Reported KM data were digitised 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 57). Figure 57 also shows the KM data for vemurafenib for comparison and validation. The fitted OS fits well with the KM data. The KM data for nivolumab based on the CheckMate 066 trial (as shown in Figure 53) are not presented because the predicted OS for nivolumab and ipilimumab as shown in Figure 57 was based on BRAF mutation-positive patient characteristics. Other parametric curve fits are tested in scenario analysis. Please refer to Appendix 8 for curve fit parameters and goodness of fit statistics.

Figure 57: Overall survival in the base case model for BRAF mutation-positive analysis for the first 3 years



Long-term overall survival

For nivolumab 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 55), and general population mortality used as background mortality.

For dabrafenib and vemurafenib, the same method used for BRAF mutation-negative patients for DTIC was used, i.e. melanoma registry survival used from Year 2 onwards (Figure 54) and general population mortality used as background mortality. This assumption is supported by the most recent data cuts for vemurafenib[139] (BRIM-3 trial data cut-off on 1 February 2012) and dabrafenib[122] (BREAK-3 trial data cut-on in January 2014) (Section 4). Whilst BRAF inhibitors have demonstrated short-term survival benefits, the long-term survival benefit for BRAF inhibitors appears to be similar to DTIC 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 58.

5.3.4 Progression-free survival – BRAF mutation-negative

Final modelled PFS for nivolumab, ipilimumab and DTIC for the BRAF mutation-negative analysis and the KM data for nivolumab and DTIC in CheckMate 066 trial are presented in Figure 59. The final modelled PFS combines TTP (as shown in Figure 50), PrePS (as shown in Figure 52) and long-term survival estimates (as OS is set as the upper threshold for PFS in the model). The fitted PFS fits well with the KM data.

5.3.5 Progression-free survival – BRAF mutation-positive

The final modelled PFS for nivolumab and its comparators for BRAF mutation-positive patients is presented in Figure 60. For nivolumab and ipilimumab, the final PFS combines TTP and PrePS based on BRIM-3 trial patient characteristics.

For dabrafenib and vemurafenib, similar to the method for OS, 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 60). Figure 60 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 8 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 60 also uses the long-term survival estimates as OS is set as the upper threshold for PFS.

Figure 58: Final overall survival in the base case model for BRAF mutation-positive analysis over life time (40 years)

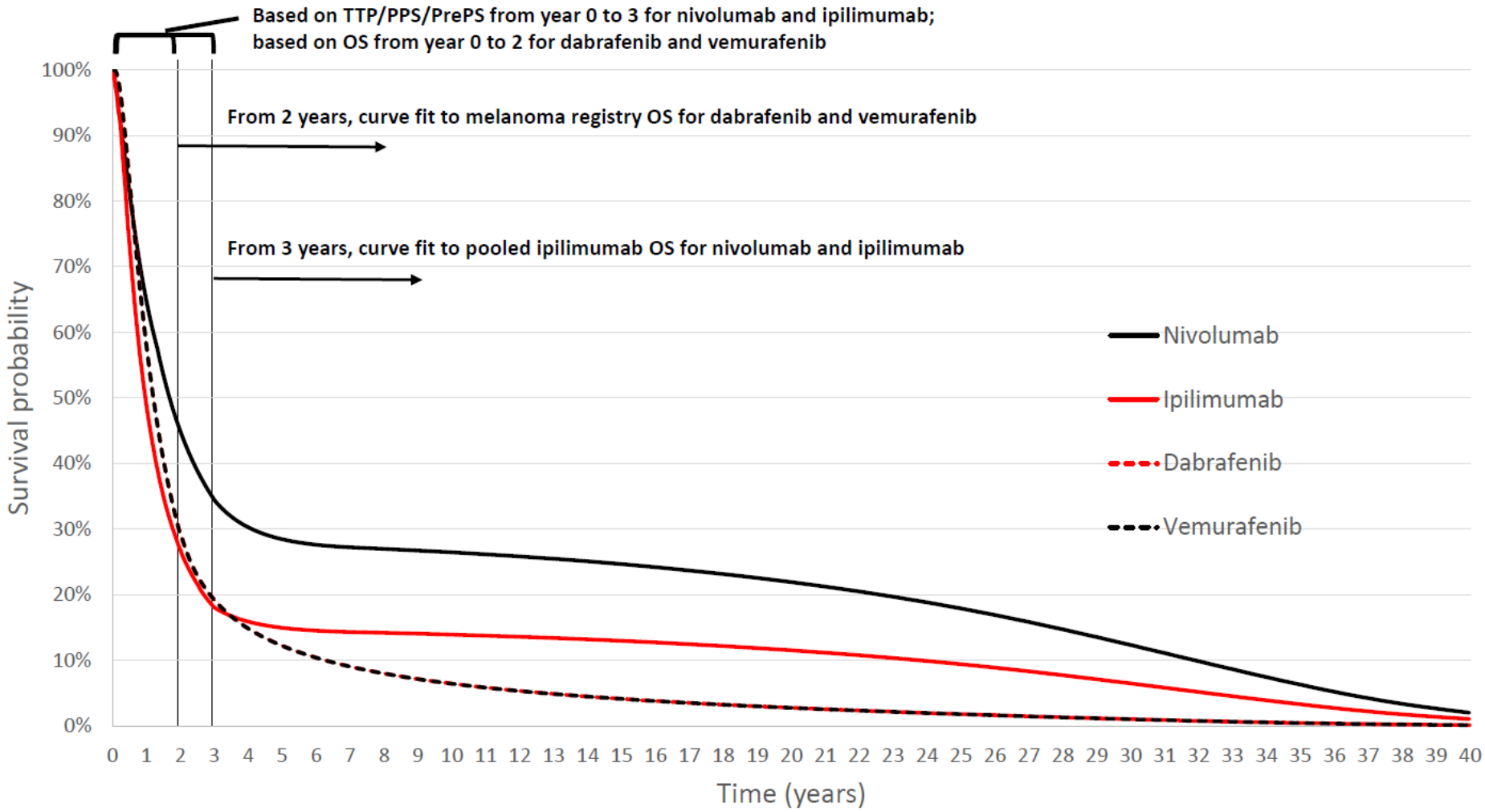


Figure 59: Final PFS in the base case model for BRAF mutation-negative analysis

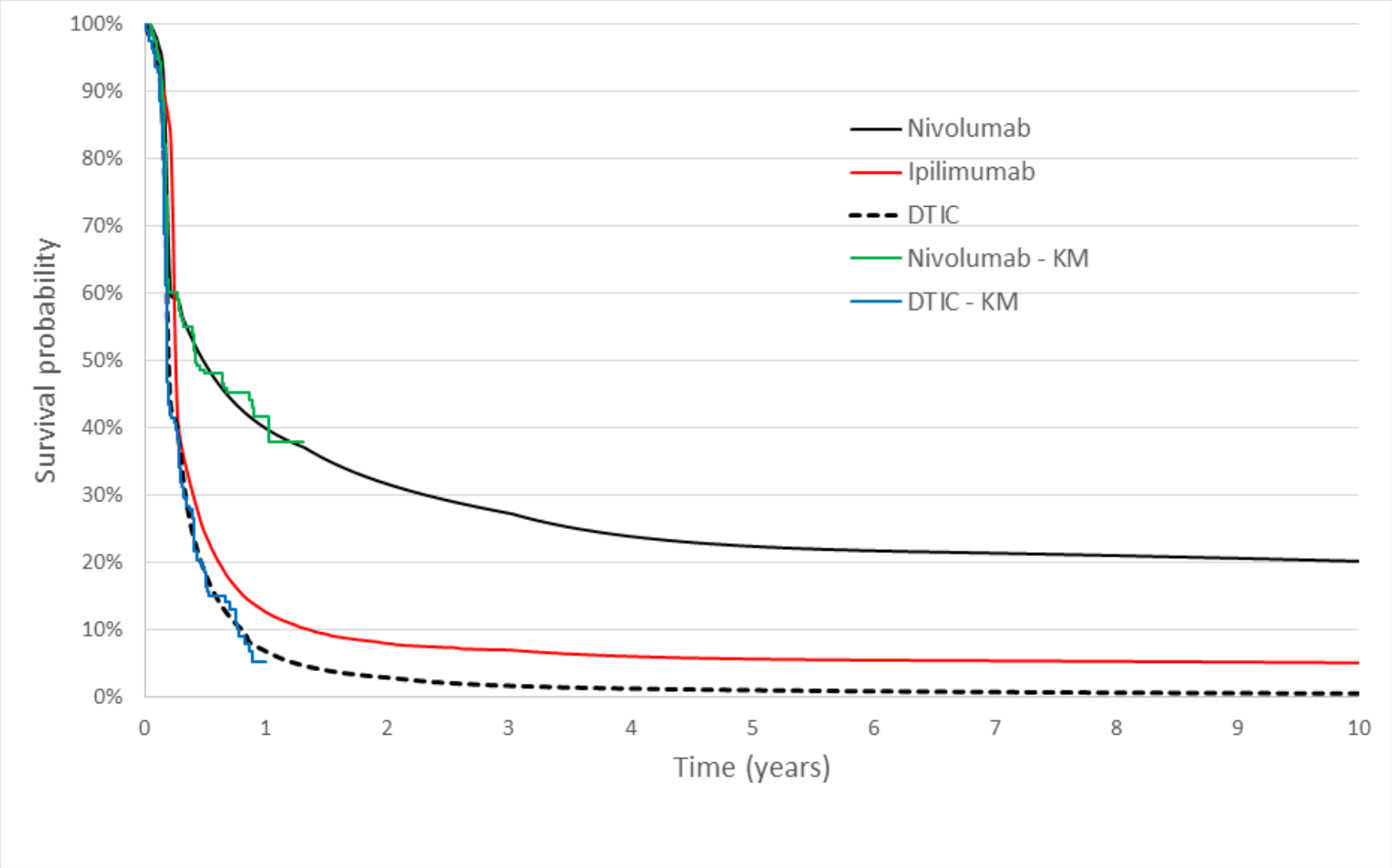
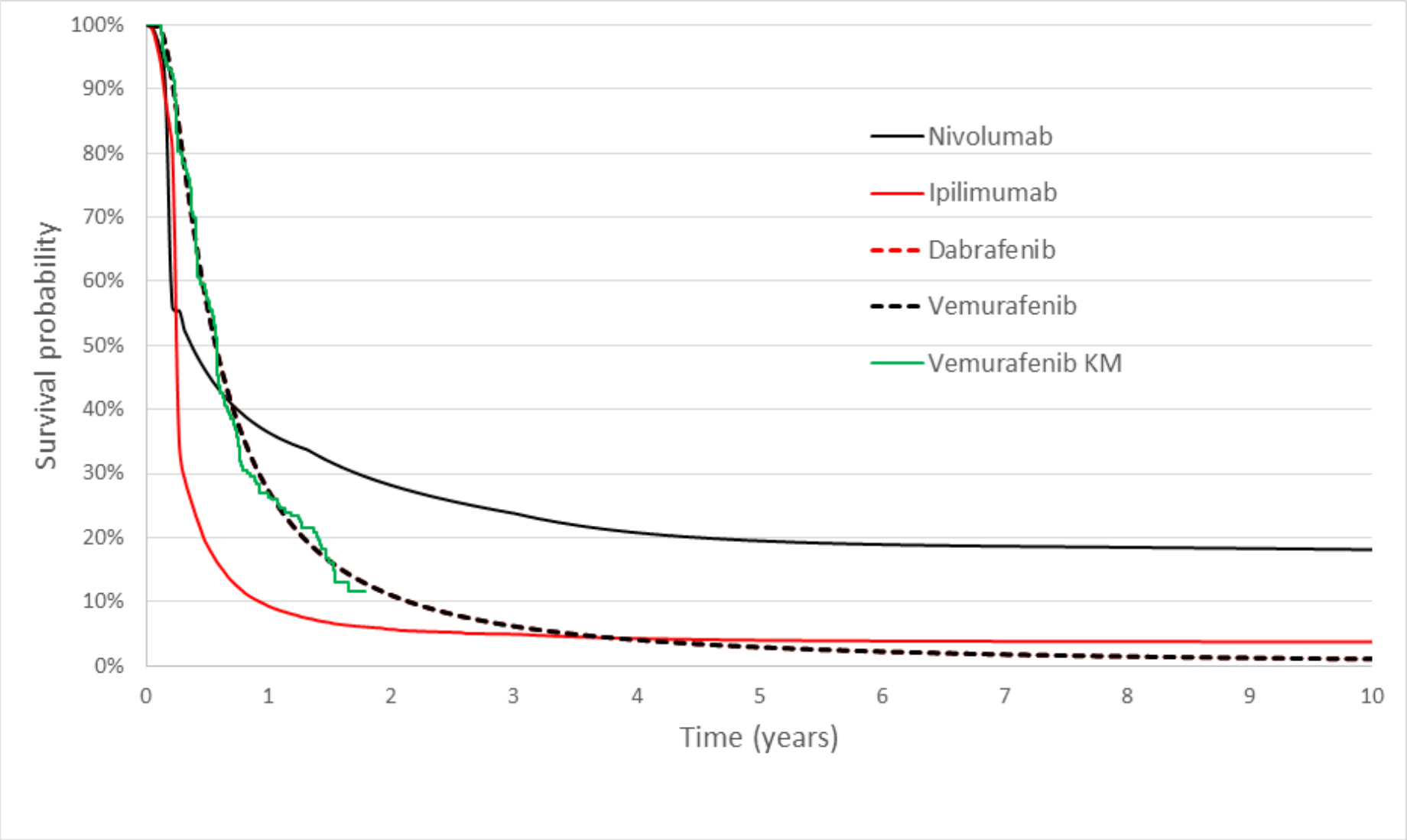


Figure 60: Final PFS in the base case model for BRAF mutation-positive analysis

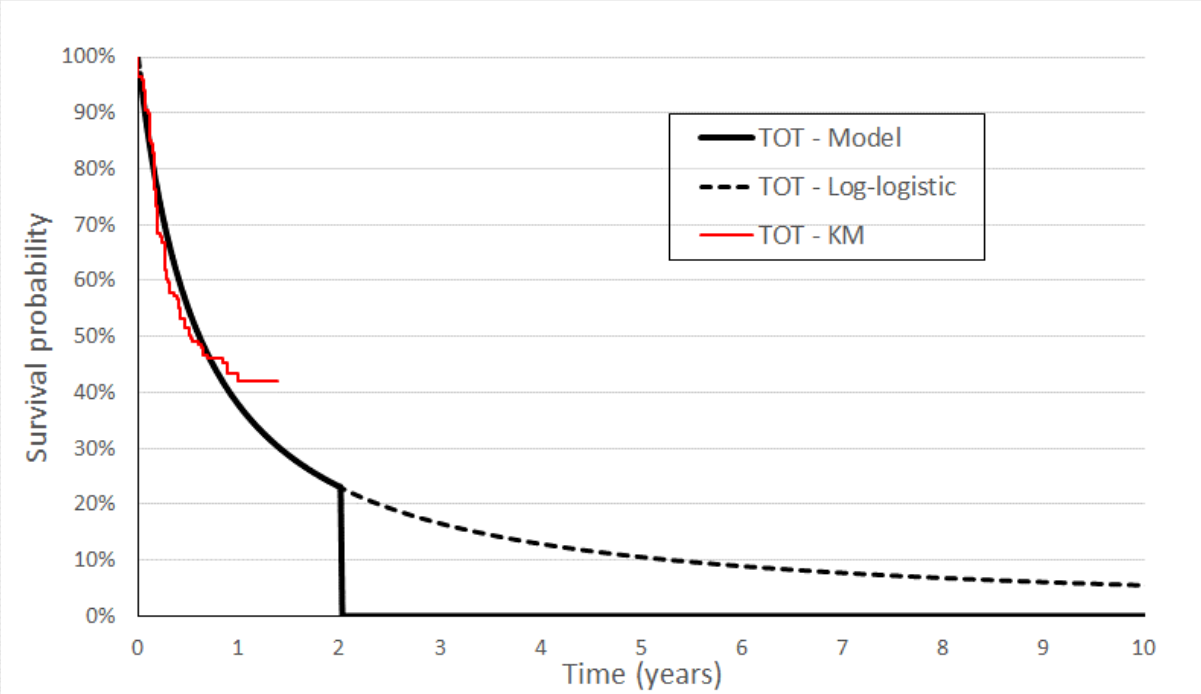


5.3.6 *Time on treatment (nivolumab) – BRAF mutation-negative*

TOT patient level data for nivolumab from CheckMate 066 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 second lowest AIC/BIC scores and has plausible prediction at the tail (Figure 61). The Gompertz curve has the lowest AIC/BIC, but was not used in the base case because the tail of the predicted curve becomes almost horizontal from Year 2 onwards, with 37.6% and 36.7% estimated to be on treatment at Year 2 and Year 40, respectively. This may not be clinically plausible as it predicts almost no decrease for patients taking nivolumab from Year 2 onwards. The tail predicted by Gompertz also contradicts the feedback from the UK clinicians that patients may discontinue treatment from Year 2 or even Year 1 onwards. Figure 61 also shows the KM data for comparison and validation. Other parametric curve fits were tested in the scenario analysis. Please refer to Appendix 8 for curve fit parameters and goodness of fit statistics.

The final modelled nivolumab TOT for BRAF mutation-negative patients shown in Figure 61 have also used the OS as upper thresholds and a maximum treatment duration of 2 years (Section 5.2 for detailed discussion).

Figure 61: Final TOT in the base case model for BRAF mutation-negative analysis



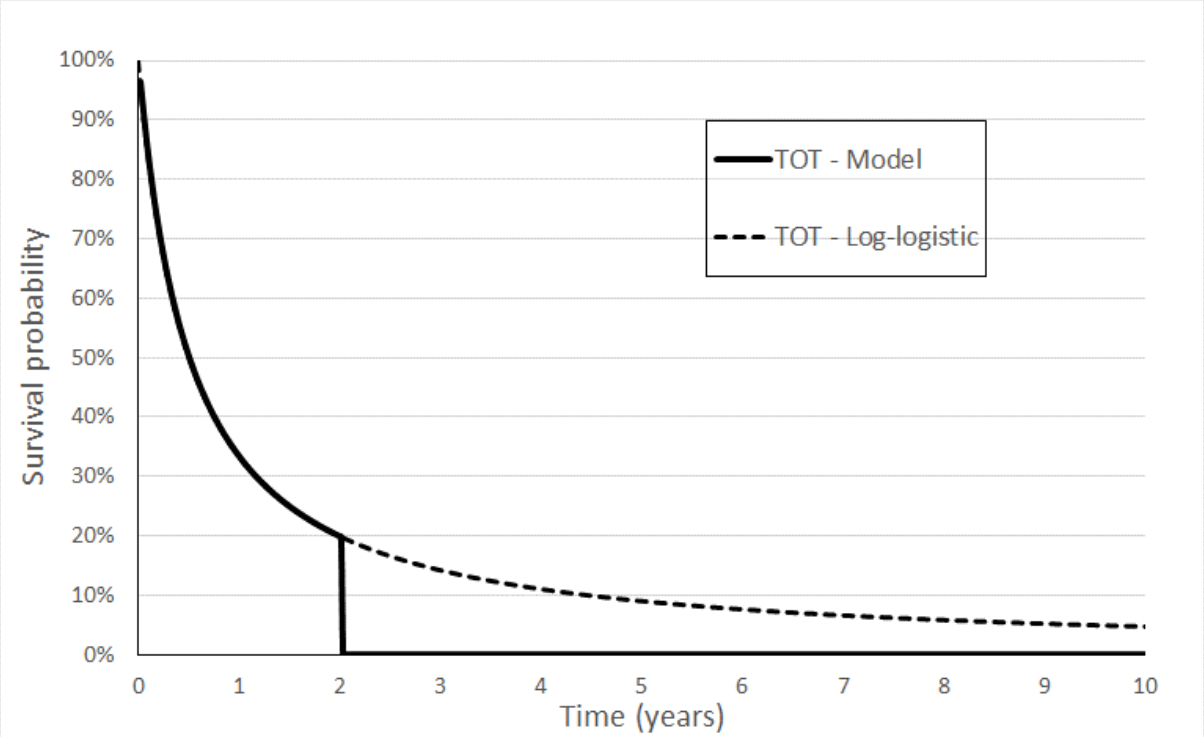
Time (year)	0	0.5	1	1.5
No. at risk				
TOT - KM	199	93	26	0

No parametric curves were fitted for the DTIC arm in the CheckMate 066 trial for simplicity and due to the relatively short-term duration of therapy and low cost of the drug. The time on treatment for comparators are determined based on the information shown in Table 56.

5.3.7 *Time on treatment (nivolumab) – BRAF mutation-positive*

The final modelled nivolumab TOT for BRAF mutation-positive patients is shown in Figure 62. The only difference compared to BRAF mutation-negative patients is that patient characteristics are based on the vemurafenib arm of BRIM-3.

Figure 62: Final TOT in the base case model for BRAF mutation-positive analysis



5.3.8 Safety

Nivolumab and DTIC

Clinical opinion suggested that all drug-related AEs of Grade 3 or higher for nivolumab are clinically important, and their impact on patient utility and resource use needs should be captured by the model.[12] Clinical opinion from a recent NICE appraisal on ipilimumab (TA319[4]) also suggested that any grade of endocrine disorder and Grade 2 or high diarrhoea are clinically relevant and need to be captured. Patient-level AE data from CheckMate 066 were used to calculate the proportion of patients in the nivolumab and DTIC 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 61). The inclusion of all Grade 3+ adverse events captures 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 adverse event).

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 61 for the nivolumab and DTIC arms. The proportions of patient requiring outpatient visits presented in Table 61 are based on the following assumptions from the Oxford Outcome study[206] used in the recent ipilimumab NICE appraisal (TA319): 25% and 0% of patients having endocrine disorders require outpatient visits for patients treated with immunotherapy and chemotherapy, respectively; 19.2% and 27.0% for diarrhoea; and 17.2% and 15.0% for other AEs.

Table 61: Summary of adverse event analysis using patient level data from the CheckMate 066 trial

	Nivolumab	DTIC
Patient numbers for AE analysis	206	205
Endocrine disorder (any grade)		
% of patient	8.7%	1.0%
Total hospitalisation days	48	0
% of patients requiring outpatient visits	2.2%	0.0%
Diarrhoea (Grade 2+)		
% of patient	4.4%	3.4%
Total hospitalisation days	5	0
% of patients requiring outpatient visits	0.8%	0.7%
Other AEs (Grade 3+)		
% of patient	9.7%	17.6%
Total hospitalisation days	91	80
% of patients requiring outpatient visits	**1.7%**	**2.6%**

Ipilimumab, dabrafenib and vemurafenib

Patient-level AE data were not available for ipilimumab 3mg/kg, dabrafenib or vemurafenib in the CheckMate 066 trial. To maintain comparability and consistency, CheckMate 067, BREAK-3 and BRIM-3 trials were used to derive the proportions of patients expected to experience an endocrine disorder (any grade), diarrhoea (Grade 2+) and other AEs (Grade 3+) for the ipilimumab, dabrafenib and vemurafenib arms versus the nivolumab and DTIC, respectively. The ratios of these treatment arms to the nivolumab or DTIC arms were then applied to the results in Table 61 to derive comparable estimates for the ipilimumab, dabrafenib and vemurafenib arms (Table 62). This indirect approach may not be ideal for estimating AEs for BRAF inhibitors due to different mechanisms of action of immunotherapy (nivolumab 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 066 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 adverse events associated with immunotherapies.

Table 62: Summary of adverse event analysis for ipilimumab, dabrafenib and vemurafenib

	% based on CheckMate 067		Final modelled % for ipilimumab
	Ipilimumab	Nivolumab	
Endocrine disorder (any grade)	10.6%	14.1%	6.6%[a]
Diarrhoea (Grade 2+)	17.7%	6.1%	12.7%
Other AEs (Grade 3+)	23.8%	15.7%	14.7%

	% based on BREAK-3		Final modelled % for dabrafenib
	Dabrafenib	DTIC	
Endocrine disorder (any grade)	0.0%	0.0%	0.0%
Diarrhoea (Grade 2+)	0.0%	0.0%	0.0%
Other AEs (Grade 3+)	53.0%	44.0%	21.2%
	% based on BRIM-3		**Final modelled % for vemurafenib**
	Vemurafenib	DTIC	
Endocrine disorder (any grade)	0.0%	0.0%	0.0%
Diarrhoea (Grade 2+)	5.5%	1.5%	8.9%
Other AEs (Grade 3+)	8.0%	11.0%	12.8%
Notes: [a]: as an example, 6.6% = (10.6%/14.1%)*8.7%, where 8.7% is taken from Table 61.			

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

In the CheckMate 066 trial, HRQL is assessed using the EQ-5D, which is consistent with the NICE reference case. On-study assessments of EQ-5D were scheduled on days 1, 15, 22, and 29 (9 weeks from randomisation), continuing every 6 weeks thereafter for the first 12 months, and then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. During the follow-up phase (when the decision to discontinue a patient from study therapy is made, i.e. no further treatment with study therapy) EQ-5D assessments continued to be taken every 3 months for the next 12 months, and then every 6 months thereafter. A total of 1,540 visits involving 362 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

Two 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.[4] An update to this systematic review was conducted using the same methods and process as the first review (apart from the span of the search period) in November 2014 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; the week commencing 20 May 2013 for the first systematic review and on 25 November 2014 for the update. 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 63 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 63.

Table 63: Eligibility criteria for utility and HRQL studies

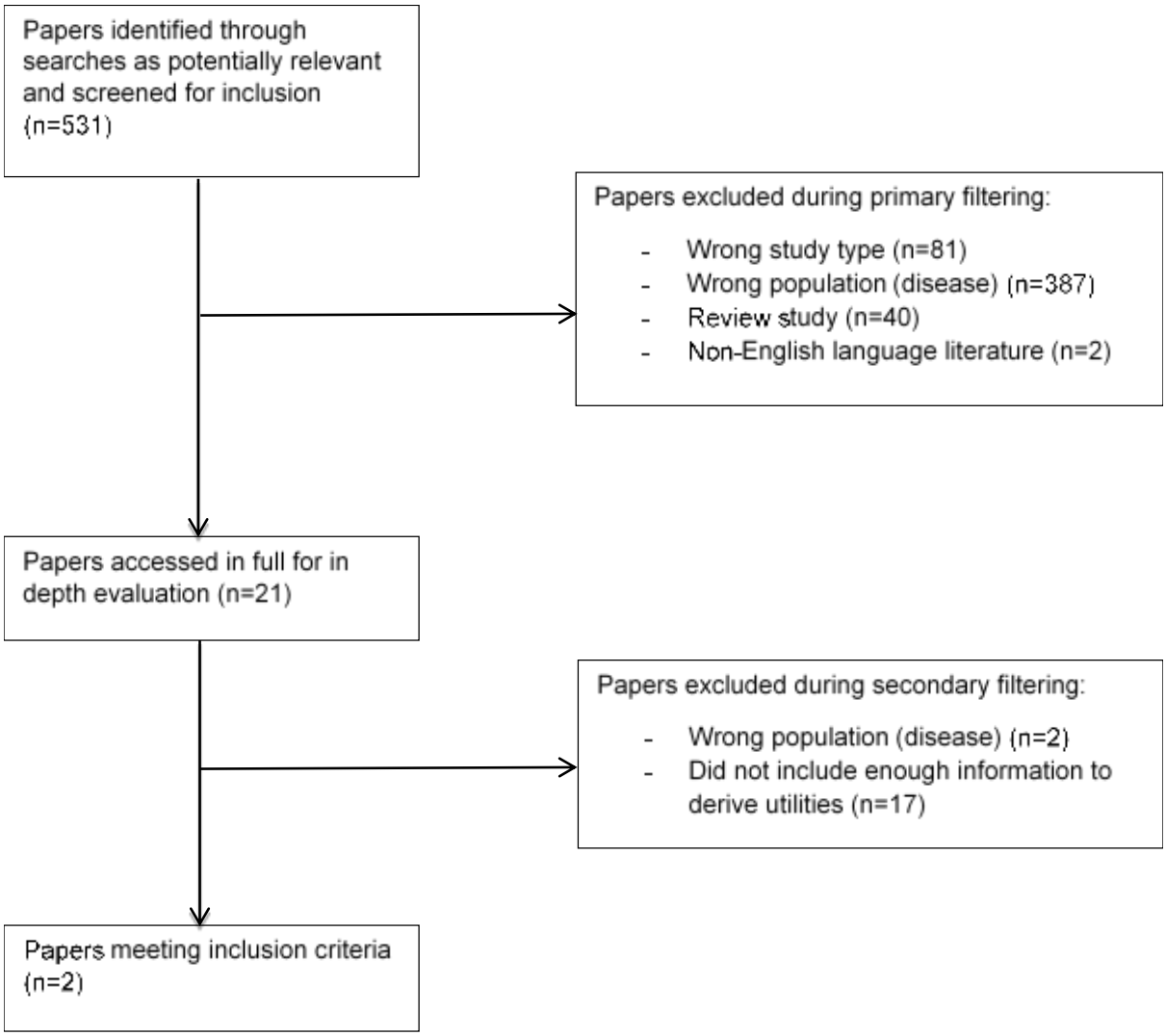
Inclusion criteria		
Category	**Inclusion criteria**	**Rationale**
Study type	Studies reporting utilities or HRQL data	The aim of the review was to identify relevant utility data
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant population
Interventions	No restriction 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 systematic review update performed in November 2014, as illustrated in Figure 63, a large proportion of the initially identified papers failed to meet the eligibility criteria (Table 63). The main reason for exclusion was on the basis of population (387 out of 531 papers). Other papers were excluded on the basis of study type or were not written in English.

During secondary filtering, most papers were excluded because they did not report utilities or had HQRL outcomes that could not be mapped to utility values. Other papers were further excluded on the basis of population. This left two studies that met all the inclusion criteria following both primary and secondary filtering.

Figure 63: Identification of utility and HRQL studies relevant to the decision problem



Overview of relevant studies

Both studies identified in the systematic review update are primary utility studies.[40, 210] They used the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and applied a validated mapping algorithm for deriving utilities.

Thirteen studies are included from the first systematic review that reported relevant HRQL data. Seven of the studies directly measure quality of life. Beusterien et al. (2009)[211] and Hogg et al. (2010)[55] measure utilities and utility decrement for eight toxicity states in members of the general public. Dixon et al. (2006) [212] and King et al. (2011)[213] measure utilities in the melanoma population. Askew et al. (2011) [214] validate a technique for mapping FACT-Melanoma to EQ-5D utilities, and both studies by Batty et al. (2011, 2012)[215, 216] compare several mapping techniques. The six remaining studies are cost-effectiveness studies using utilities from published articles.

Table 64 summarises the characteristics of these included utility and HRQL studies. Appendix 13 presents the detailed results, as well as information on the methods used, of the studies identified in the second and first review, respectively.

Table 64: Characteristics of the utility and HRQL studies

Systematic review	Reference	Location (patients)	Population	Study type	Utilities included
Systematic review update (November 2014)	Porter et al. 2014[210]	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[217]	Pre-progression, post-progression and time to death
	Hatswell et al. 2014[40]	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[217]	Pre-progression, post-progression and time to death
First systematic review (May 2013)	Askew et al. 2011[214]	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[218]	USA	Pre-treated advanced melanoma	Secondary: cost-effectiveness paper primarily using utilities by Beusterien et al., 2009[211]	Complete/partial response, stable disease, progressive disease, death, inpatient treatment, outpatient treatment
	Batty et al. 2011[215]	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[216]	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

Systematic review	Reference	Location (patients)	Population	Study type	Utilities included
	Beusterien et al. 2009[211]	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[219]	USA	Previously treated, metastatic melanoma	Secondary: cost-effectiveness paper primarily using utilities by Kilbridge et al., 2001[220]	NED, NED with HDI treatment, salvage LR, salvage DR, LR, DR
	Dixon et al. 2006[212]	UK	Malignant melanoma	Primary: cost-effectiveness study also measuring HRQL	Follow-up after interferon-alpha treatment. Years 1-5.
	Hirst et al. 2012[221]	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[220, 222-224]	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[55]	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[213]	USA	Melanoma	Primary: HRQL outcomes study	Stages I, II, III and IV disease. New diagnoses and established diagnoses
	Lee et al. 2012[225]	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[226]	USA	Melanoma	Secondary: Cost-effectiveness paper primarily using utilities by Chen et al., 2004[224]	Stages I/II and Stages III/IV

Systematic review	Reference	Location (patients)	Population	Study type	Utilities included
	Mooney et al. 1997[227]	USA	Melanoma	Secondary: Cost-effectiveness paper using utilities published by Hillner et al., 1992 and Wong et al., 1995[228, 229]	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; HDI, High dose interferon-α; HRQL, Health-related quality of life; LR, local recurrence; NED, no evidence of disease.					

5.4.3 Adverse reactions

AEs considered in the model include endocrine disorder (any grade), diarrhoea (Grade 2+) and other AEs (Grade 3+). The impacts of these AEs on HRQL are captured in the model by applying a utility decrement for patients who experience these AEs. The utility decrement represents an estimated one-off average utility loss due to the AE. The utility decrements were taken from Beusterien et al. (2009)[211], and these were applied to the percentage of patients estimated to experience each category of the modelled AEs (Table 61 and Table 62) to estimate the overall utility decrement for each treatment arm (last row in Table 65).

For simplicity, these treatment arm specific utility decrements are applied at the start of the model, and then periodically to patients who are still on treatment, where the cycle to apply the decrement is determined by the mean follow-up of the CheckMate 066 trial, which is 35 weeks.[82]

Table 65: Utility decrements for modelled AEs

	Utility decrement	**Modelled % of patients having AE (see Table 61 and Table 62)**				
		Nivolumab	**Ipilimumab**	**DTIC**	**Dabrafenib**	**Vemurafenib**
Endocrine disorder (any grade)	-0.11	8.7%	6.6%	1.0%	0.0%	0.0%
Diarrhoea (Grade 2+)	-0.06	4.4%	12.7%	3.4%	0.0%	8.9%
Other AEs (Grade 3+)	-0.12	9.7%	14.7%	17.6%	21.2%	12.8%
Overall utility decrements for each treatment		**-0.0239**	**-0.0325**	**-0.0236**	**-0.0279**	**-0.0218**

5.4.4 Health-related quality-of-life data used in cost-effectiveness analysis

Table 66 presents the final chosen statistical model fitted using EQ-5D data collected in CheckMate 066 trial and includes variables for progression status (i.e. post progression) and time to death (i.e. <30 days from death). The longitudinal models were conducted to predict utility. Detailed methods and procedure used for fitting the statistical model are presented in Appendix 14.

The utilities derived from the statistical model were used for all treatment arms. As expected, both being post progression and being <30 days from death are associated with decreased utility values (estimated mean coefficients are -0.0741 and -0.0223, respectively). The result for the treatment arm (estimated mean coefficient is -0.0689) is not used in the model, because including this would double count the disutilities already modelled for AEs for different treatment arms. Table 67 summarises the utilities used in the base case model including the utilities for different health states defined by progression status and time to death, and utility decrements for AEs for different treatment arms. Utilities used in the recent ipilimumab NICE appraisal[4] were tested in a scenario analysis.

Table 66: Statistical model results using EQ-5D data from CheckMate 066

	Coefficient	**95% confidence interval**	**p-value**
Intercept	0.3676	(0.2999, 0.4354)	<.0001
Post-progression	-0.0741	(-0.099, -0.0491)	<.0001

<30 days to death	-0.0223	(-0.0483, 0.0037)	0.0923
Baseline EQ-5D	0.6030	(0.5242, 0.6817)	<.0001
Treatment: DTIC	-0.0689	(-0.1090, -0.0289)	0.0008
Sample size = 288; Baseline EQ-5D = 0.72; significance cut-off p=0.10			

Table 67: 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 and time to death				
Pre-progression + days left >= 30 days	0.8018	Sampling using variance-covariance matrices assuming multivariate-normal distribution	Section 5.4	Based on statistical models fitted using EQ-5D data collected in CheckMate 066 trial
Pre-progression + days left <30 days	0.7795			
Post-progression + days left >= 30 days	0.7277			
Post-progression + days left <30 days	0.7054			
Utility decrements for adverse events				
Nivolumab	-0.0239	Sampling using beta distribution, assuming standard error to be 20% of mean	Section 5.4	Utility decrements based on published literature and % of patients experiencing different types of AE based on trial data
Ipilimumab	-0.0325			
DTIC	-0.0236			
Dabrafenib	-0.0279			
Vemurafenib	-0.0218			

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, two 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.[4] An update to this systematic review was conducted using the same methods and process as the first review (apart from the span of the search period) in November 2014. A precise search strategy was used that included terms for costs, resource use and melanoma; see Appendix 11 for details.

To ensure that the literature was comprehensively reviewed, a wide range of databases were searched in the week commencing 20 May 2013 for the first systematic review and on 25 November 2014 for the systematic review update. 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 68 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 68.

Table 68: Eligibility criteria for cost and resource use studies and rationale for each criterion

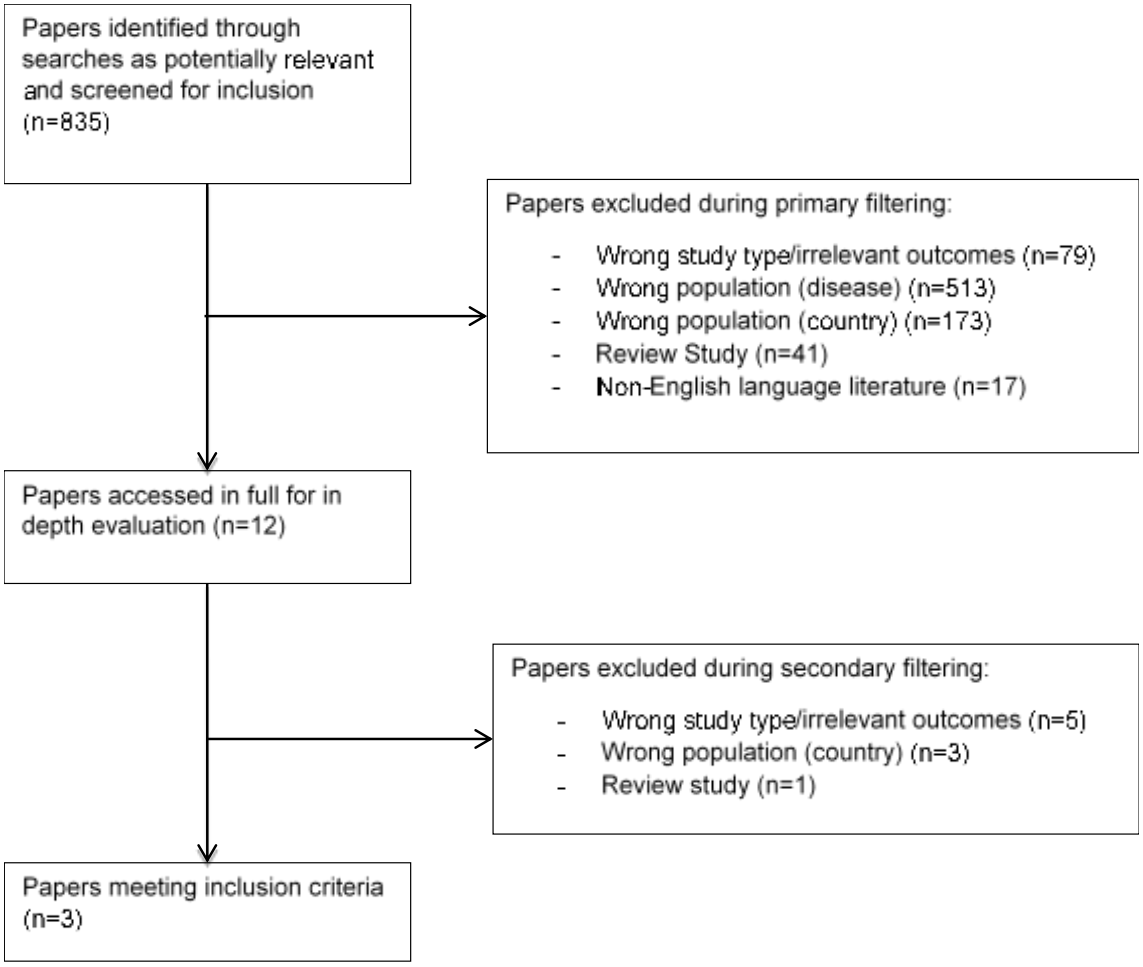
Inclusion criteria		
Category	Inclusion criteria	Rationale
Study type	Studies reporting costs and resource use	The aim of the review was to identify relevant costs and use of resources
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population
Interventions	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 systematic review update performed in November 2014, as illustrated in Figure 64, the majority of papers originally identified failed to meet the eligibility criteria. Of 835 identified papers, 513 were excluded based on the population. Other papers were excluded based on the type of study or a review study, in the wrong country, or not written in English.

During secondary filtering, papers were excluded on the basis of type of study, country, or was a review study. Following both primary and secondary screening, three papers met all the eligibility criteria.

Figure 64: Identification of cost and resource use studies relevant to the decision problem in the second systematic review



Overview of relevant studies

The three studies identified in the systematic review update reported only drug cost: one cost-analysis study[230] and two structured abstracts[231, 232]. Five studies identified in the first systematic review are economic impact and cost-effectiveness analyses[212, 225, 233] or cost and resource utilisation studies[49, 234]. These 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 69 presents the key characteristics of the studies included in the first systematic review and the update. Appendix 15 provides the full results, as well as information on methods used, for both systematic reviews (updated and initial).

None of the available studies report on the costs or resource use associated with disease management for newly available immunotherapies or BRAF inhibitors.

Table 69: 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[230]	UK	Metastatic melanoma	Cost analysis	Costs for drugs
	NIHR et al. 2013[231]	UK	Malignant melanoma	Summary safety, efficacy or effectiveness of new drugs	Costs for drugs

Systematic review	Reference	Country	Population	Study type	Resource use and costs included
	NIHR et al. 2013[232]	UK	Advanced melanoma	Summary safety, efficacy or effectiveness of new drugs	Costs for drugs
First systematic review (May 2013)	Dixon et al. 2006[212]	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[233]	UK, Italy and France	Advanced melanoma	Economic impact	Hospitalisation and outpatient costs, use of hospital and hospice
	Lee et al. 2012[225]	UK	Previously treated metastatic melanoma	Cost-effectiveness analysis	Costs for drugs, treatment, palliative and terminal care
	Lorigan et al. 2010[234]	UK	Advanced melanoma	Healthcare resource utilisation study	Hospitalisation rates and duration of hospitalisation
	Morris et al. 2009[49]	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 and all comparators (Table 70). In a scenario analysis, known and assumed patient access scheme (PAS) discounts are used (Table 70).

Table 70: 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 April 2015
		40ml	200	£15,000.00	[redacted]	MIMS April 2015
DTIC	100mg		100	£3.48	n/a	EMIT December 2014 (Pack of 10 = £34.75)
	200mg		200	£4.82	n/a	EMIT December 2014 (Pack of 10 = £48.21)
	500mg		500	£20.05	n/a	EMIT December 2014
	1000mg		1000	£30.42	n/a	EMIT December 2014
Dabrafenib	50mg	28 tablets	1400	£933.33	[redacted]	MIMS April 2015
	75mg	28 tablets	2100	£1,400.00	[redacted]	MIMS April 2015
Vemurafenib	240mg	56 tablets	13440	£1,750.00	[redacted]	MIMS April 2015
[redacted]						

The dosing regimen for each treatment is presented in Table 56. For DTIC, a mean body surface area of 1.90 m^2 was used based on a mean weight of 78.7kg (UK patients in CheckMate 066, CheckMate 037, MDX010-20 and CA184-024) and a mean height of 1.70cm (CA184-024). For nivolumab 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 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[4]). Table 71 shows the total dose required and the drug costs for each administration for the base case and with PAS.

Table 71: Dose required and drug costs for each administration

Drug	Dosing regimen	Dose per administration	Drug cost per administration (without PAS)	Drug cost per administration (with PAS)
Nivolumab	3mg/kg, every 2 weeks by IV	236mg	£2,809.47 per IV	n/a
Ipilimumab	3 mg/kg	236mg	£19,574.00 per IV	[redacted]
DTIC	1000mg/m2, every 3 weeks by IV	1902mg	£48.21 per IV	n/a
Dabrafenib	300mg, daily oral	300mg	£200.00 per day	[redacted]
Vemurafenib	1920mg, daily oral	1920mg	£250.00 per day	[redacted]

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.[4] The administration cost assumptions for ipilimumab, DTIC and vemurafenib are the same as those within the previous ipilimumab NICE submission.[4] The summary of administration costs used within the model is shown in Table 72.

Table 72: Unit costs for each type of administration

Resource use element	Unit cost	Source
Complex parenteral chemotherapy - 1st attendance	£297.46	NHS Reference costs 2013/2014 SB13Z
Subsequent elements of a chemotherapy cycle	£320.35	NHS Reference costs 2013/2014 SB15Z
Exclusively oral chemotherapy	£156.68	NHS Reference costs 2013/2014 SB11Z
Laboratory tests – complete metabolic panel (CMP)	£1.18	NHS Reference costs 2013/2014 DAPS04

5.5.3 Health-state unit costs and resource use

As discussed in Section 5.2, resource use is modelled 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.

Table 73 presents the detailed resource use estimates for the one-off treatment initiation and end of life costs. The unit costs and resource use for each item are sourced from an Oxford Outcomes report[235] and NHS reference costs and updated according to UK clinical opinion to match current treatment practice based upon questionnaires distributed at an advisory board including four leading UK clinicians.[12] These sources were also used in the recent ipilimumab NICE appraisal.[4]

Table 74 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. The length of palliative care is assumed to be 12 weeks based on clinical opinion[12], which is also consistent with the recent ipilimumab NICE appraisal.[4]

Table 75 summarises the resource use for the defined health states used in the economic model.

Table 73: 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	£140.17	81.0%	3.6			NHS Reference costs 2013/2014 Total OPATT 370
Radiation oncologist outpatient visit	£125.76	6.0%	2.3			NHS Reference costs 2013/2014 Total OPATT 800
General practitioner visit	£38.00	4.0%	2.0			PSSRU 2014: pg195 without qual. with indirect costs
Palliative care physician outpatient visit	£95.31	1.3%	1.0			NHS Reference costs 2013/2014 Weight Ave of total for SD04A and SD05A
Psychologist outpatient visit	£138.00	0.5%	1.0			PSSRU 2014: pg183 per hour of client contact. 1 hour visit assumed
Plastic surgeon outpatient visit	£93.14	2.0%	1.5			NHS Reference costs 2013/2014 Total OPATT 160
Inpatient (resource use and unit cost measured by days)						
Oncology/general ward – inpatient	£280.74	6.0%	2.8			NHS Ref costs 2013/2014 Ave of excess bed days for elective and non-elective inpatients for all HRGs. Weighted by activity.
Terminal care						
Hospice stay	£6,280.99			23.1%	1.0	Improving Choice at End of Life, Addicott and Dewar, the Kings Fund, 2008. PSSRU 2014
Laboratory tests						
Complete blood count (CBC)	£3.00	100.0%	1.2			NHS Reference costs 2013/2014 Total DAPS05
Complete metabolic panel (CMP)	£1.18	100.0%	1.2			NHS Reference costs 2013/2014 Total DAPS04
Lactate dehydrogenase (LDH)	£1.18	100.0%	1.2			NHS Reference costs 2013/2014 Total DAPS04
Radiological examinations						
CT scan (any)	£96.49	100.0%	1.0			NHS Reference costs 2013/2014 Ave of total for RA08A/RA09A/RA10Z

Resource use item	Unit cost	Treatment initiation – one off		End of life care – one off		Sources
		% Patients	Resource use number	% Patients	Resource use number	
MRI of brain	£149.04	14.5%	1.0			NHS Reference costs 2013/2014 Ave of total for RA01A/RA02A/RA03Z
PET scan	£149.04	5.0%	1.0			NHS Reference costs 2013/2014 Ave of total for RA01A/RA02A/RA03Z
Bone scintigraphy	£183.00	16.8%	1.0			NHS Reference costs 2013/2014 Total RA35Z
Echography	£55.14	4.5%	1.0			NHS Reference costs 2013/2014 Ave of total for RA23Z/RA24Z/RA25Z/RA26Z/RA27Z
Chest x-ray	£97.62	17.5%	1.0			NHS Reference costs 2013/2014 Total RA16Z

Table 74: 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	£140.17	79.3%	1.9	39.6%	1.9	23.8%	1.9	62.3%	0.9	NHS Reference costs 2013/2014 Total OPATT 370
Radiation oncologist outpatient visit	£125.76	6.0%	1.0	3.0%	1.0	1.8%	1.0	7.0%	1.5	NHS Reference costs 2013/2014 Total OPATT 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	£95.31							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	£93.14	2.0%	1.5	1.0%	1.5	0.6%	1.5			NHS Reference costs 2013/2014 Total OPATT 160
Nurse visit	£36.52	12.5%	1.0	6.3%	1.0	3.8%	1.0			NHS Reference costs 2013/2014 N02AF
Inpatient (resource use and unit cost measured by days)										
Oncology/general ward – inpatient	£280.74	5.0%	1.3	2.5%	1.3	1.5%	1.3	13.0%	3.6	NHS Ref costs 2013/2014 Ave of excess bed days for elective and non-elective inpatients for all HRGs. Weighted by activity.
Palliative care unit – inpatient	£184.41							24.5%	4.0	NHS Reference costs 2013/2014 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	£85.11							61.0%	1.4	NHS Reference costs 2013/2014 CHS: 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 (CBC)	£3.00	100.0%	1.3	50.0%	1.3	30.0%	1.3			NHS Reference costs 2013/2014 Total DAPS05
Complete metabolic panel (CMP)	£1.18	95.0%	1.3	47.5%	1.3	28.5%	1.3			NHS Reference costs 2013/2014 Total DAPS04
Lactate dehydrogenase (LDH)	£1.18	95.0%	1.3	47.5%	1.3	28.5%	1.3			NHS Reference costs 2013/2014 Total DAPS04
Radiological examinations										
CT scan (any)	£96.49	100.0%	1.0	50.0%	1.0	30.0%	1.0	3.8%	1.0	NHS Reference costs 2013/2014 Ave of total for RA08A/RA09A/RA10Z
MRI of brain	£149.04	18.0%	0.3	9.0%	0.3	5.4%	0.3	1.3%	1.0	NHS Reference costs 2013/2014 Ave of total for RA01A/RA02A/RA03Z
PET scan	£149.04	0.0%	0.4	0.0%	0.4	0.0%	0.4			NHS Reference costs 2013/2014 Ave of total for RA01A/RA02A/RA03Z
Bone scintigraphy	£183.00	1.0%	0.3	0.5%	0.3	0.3%	0.3			NHS Reference costs 2013/2014 Total RA35Z
Echography	£55.14	9.0%	0.3	4.5%	0.3	2.7%	0.3			NHS Reference costs 2013/2014 Ave of total for RA23Z/RA24Z/RA25Z/RA26Z/RA27Z
Chest x-ray	£97.62	27.5%	1.1	13.8%	1.1	8.3%	1.1	1.3%	1.0	NHS Reference costs 2013/2014 Total RA16Z
Pain control										
Morphine – Oral	£10.78							51.0%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014
Morphine – IV	£116.95							22.0%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014
Morphine – Transdermal patch	£39.95							15.0%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014
NSAIDs (Ibuprofen)	£0.74							47.5%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014
Other – Paracetamol	£4.56							36.0%	1.0	Oxford outcomes Melanoma Resource Use report. PSSRU 2014

Table 75: List of health states and associated costs in the economic model

Defined health states	Value
Treatment initiation – one off	£663.18
Year 1 (per week)	£89.74
Year 2 (per week)	£44.87
Year 3 and beyond (per week)	£26.92
Palliative care period – 12 weeks before death (per week)	£214.27
End of life care – one off	£1,450.91

5.5.4 Adverse reaction unit costs and resource use

As discussed in Section 5.4, resource use for treating AEs is based on patient-level CheckMate 066 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 76.

Table 76: Unit costs used for AEs

Items	Value	Reference
Hospital stay for endocrine disorders (day)	£246.24	NHS ref cost 2013/14; Other endocrine disorders with CC Score 4+ (KA08A)
Hospital stay for other AEs (day)	£275.05	NHS ref cost 2013/14; Non elective inpatients – excess bed days (NEL_XS, average across all areas)
Unit cost for outpatient visit (endocrine disorder)	£409.50	Oxford Outcomes[235]
Unit cost for outpatient visit (diarrhoea) for immunotherapy	£570.87	
Unit cost for outpatient visit (diarrhoea) for chemotherapy	£141.58	
Unit cost for outpatient visit (other AEs) for immunotherapy	£345.66	
Unit cost for outpatient visit (other AEs) for chemotherapy	£312.91	

The unit costs are applied to the number of hospital days and outpatient visits for each treatment arm (Table 61 and Table 62), 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 77).

In the same manner as the application of utility decrement for AEs, 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 066 trial.

Table 77: Summary of per patient AE costs in the economic model

	Nivolumab	Ipilimumab	DTIC	Dabrafenib	Vemurafenib
Hospitalisation costs – endocrine disorder (any grade)	£57.38	£43.13	£0.00	£0.00	£0.00
Hospitalisation costs – diarrhoea (Grade 2+)	£6.68	£19.37	£0.00	£0.00	£0.00
Hospitalisation costs – other AEs (Grade 3+)	£121.50	£184.19	£107.34	£129.29	£78.06
Hospitalisation costs – subtotal	***£185.56***	***£246.69***	***£107.34***	***£129.29***	***£78.06***
Outpatient costs – endocrine disorder (any grade)	£9.12	£6.85	£0.00	£0.00	£0.00
Outpatient costs – diarrhoea (Grade 2+)	£4.79	£13.89	£0.93	£0.93	£3.42
Outpatient costs – other AEs (Grade 3+)	£5.76	£8.74	£8.24	£9.92	£5.99
Outpatient costs – subtotal	***£19.67***	***£29.49***	***£9.17***	***£10.86***	***£9.41***
Total cost	**£205.22**	**£276.18**	**£116.51**	**£140.15**	**£87.47**

5.5.5 Miscellaneous unit costs and resource use

One of the patient characteristics used for adjusting fitted TTP curves is the proportion of patients that have been treated with ipilimumab as a subsequent line of therapy (29.7% and 22.0% for BRAF mutation-negative and BRAF mutation-positive patients, respectively, see Table 59). As the subsequent use of ipilimumab affects survival, the corresponding costs should also be captured by the model. Table 78 shows the calculation of the one-off cost for subsequent use of ipilimumab. The one-off cost is applied to a proportion of patients (29.7% or 22.0% in the base case depending on BRAF mutation status) who discontinue treatments (except in the ipilimumab arm). The mean ipilimumab dose used for previously treated patients is based on the NICE TA268.[75]

Table 78: One-off cost for subsequent use of ipilimumab (based on list price of ipilimumab)

Resource use element	Value	Sources
Mean ipilimumab dose	[redacted]	NICE TA268[75]
Drug cost	[redacted]	See Table 71
Administrative cost	£986	See Table 72
Adverse event cost	£276	See Table 77
Total	[redacted]	

5.6 Summary of base case de novo analysis inputs and assumptions

Summary of base case de novo analysis inputs

Table 79 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 79: 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 59	Fixed	See Table 59 in Section 5.3
BRAF mutation-positive	See Table 59	Fixed	
Parametric survival curves based on indirect comparison			
TTP nivolumab, ipilimumab and DTIC	See Figure 50	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Section 5.3.2
PPS nivolumab, ipilimumab and DTIC	See Figure 51		
PrePS nivolumab, ipilimumab and DTIC	See Figure 52		
Parametric survival curves for BRAF inhibitors			
OS - vemurafenib	See Figure 57	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Section 5.3.3
PFS - vemurafenib	See Figure 60		See Section 5.3.5
OS HR dabrafenib vs vemurafenib	1	Fixed	See Section 5.3.3 and 5.3.5
PFS HR dabrafenib vs vemurafenib	1	Fixed	
Parametric survival curves for long-term survival			
Registry survival (rebase at Year 2)	See Figure 54	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Section 5.3.2
Pooled ipilimumab survival (rebase at Year 3)	See Figure 55		See Section 5.3.2
Parametric survival curve for TOT			
TOT nivolumab – BRAF mutation-negative	See Figure 61	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Section 5.3.6
TOT – BRAF mutation-positive	See Figure 62		See Section 5.3.7

Variable	Mean base case value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Utilities			
Pre-progression + days left >= 30 days	0.80	Sampling using variance-covariance matrices assuming multivariate-normal distribution	See Table 67 in Section 5.4
Pre-progression + days left <30 days	0.78		
Post-progression + days left >= 30 days	0.73		
Post-progression + days left <30 days	0.71		
Drug dosing and costs			
Patient height (cm)	170	SE=0.48 (Normal)	Section 5.5
Patient weight (kg)	78.7	SE=0.61 (Normal)	
Patient body surface area (m^2)	1.90	Function of height and weight	
Drug cost of nivolumab per IV	£2,809.47	Fixed	See Table 71 in Section 5.5
Drug cost of ipilimumab per IV	[redacted]	Fixed	
Drug cost of DTIC per IV	£48.21	Function of body surface	
Drug cost of dabrafenib per day	£200.00	Fixed	
Drug cost of vemurafenib per day	£250.00	Fixed	
Administration cost of initial chemotherapy	£298.45	SE assumed to be 20% of mean (Normal)	See Table 72 in Section 5.5
Administration cost of subsequent chemotherapy	£320.35		
Administration cost of oral chemotherapy (one off)	£156.68		
Resource use and costs			
Treatment initiation - one off	£663.18	SE assumed to be 20% of mean (Normal)	See Table 75 in Section 5.5
Year 1 (per week)	£89.74		
Year 2 (per week)	£44.87		
Year 3 and beyond (per week)	£26.92		
Palliative care period (per week)	£214.27		
End of life care - one off	£1,450.91		
Length of palliative care period (weeks)	12	Fixed	Section 5.5
Other costs			
Subsequent ipilimumab treatment (one-off)	[redacted]	Within model calculation	See Table 78 in Section 5.5
Adverse events (rates, costs, utility decrements)			
AE costs for nivolumab	£205.22	SE assumed to be 20% of	See Table 77 in

Variable	Mean base case value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE costs for ipilimumab	£276.18	mean (Normal)	Section 5.5
AE costs for DTIC	£116.51		
AE costs for dabrafenib	£140.15		
AE costs for vemurafenib	£87.47		
AE utility decrement for nivolumab	-0.0239	SE assumed to be 20% of mean (Beta)	See Table 67 in Section 5.4
AE utility decrement for ipilimumab	-0.0325		
AE utility decrement for DTIC	-0.0236		
AE utility decrement for dabrafenib	-0.0279		
AE utility decrement for vemurafenib	-0.0218		
Mean safety follow-up period	35	Fixed	See Section 5.4.3
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 of using CheckMate 066 and MDX010-20 trials for deriving comparative efficacy of nivolumab, ipilimumab and DTIC in terms of TTP, PPS and PrePS (see detailed in Section 4.10).
- The assumptions that underpin the comparison of BRAF inhibitors (dabrafenib and vemurafenib) and immunotherapies (see Section 5.2.2).
- The assumptions of extrapolation of OS using melanoma registry data for DTIC and BRAF inhibitors from Year 2 onwards, and pooled ipilimumab long-term OS for nivolumab 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 80 and Table 81 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 80 and Table 81 do not represent the true costs to the NHS, and consequently, the incremental cost and ICERs of nivolumab will be underestimated compared to these drugs. [redacted] Table 70 [redacted] Table 82 [redacted] Table 83. In both the base case and PAS-based base case, no PAS is assumed for nivolumab.

Table 80: 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)
Dacarbazine	[redacted]	1.74	1.23						
Ipilimumab	[redacted]	3.66	2.64	£48,429	1.92	1.41	£34,261	Extended dominated	Excluded due to extended dominance
Nivolumab	[redacted]	5.75	4.31	£72,578	4.01	3.08	£23,583		£23,583

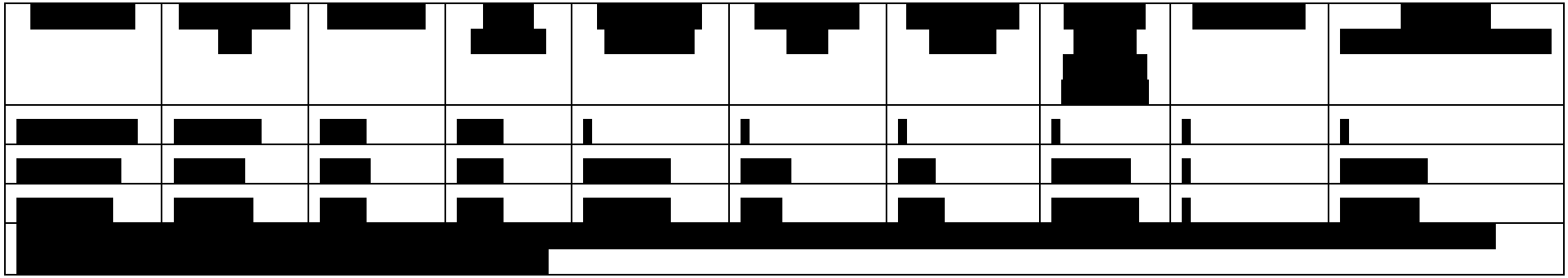
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Incremental costs, LYG and QALYs are presented versus the next non-dominated comparator.

Table 81: 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)
Ipilimumab	[redacted]	3.40	2.44						
Nivolumab	[redacted]	5.70	4.27	£13,374	2.30	1.82	£7,346		£7,346
Dabrafenib	[redacted]	2.37	1.69	£6,228	-3.33	-2.57	-£26,054	Dominated	Excluded due to dominance
Vemurafenib	[redacted]	2.37	1.70	£24,659	-3.33	-2.56	-£51,397	Dominated	Excluded due to dominance

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

[redacted]



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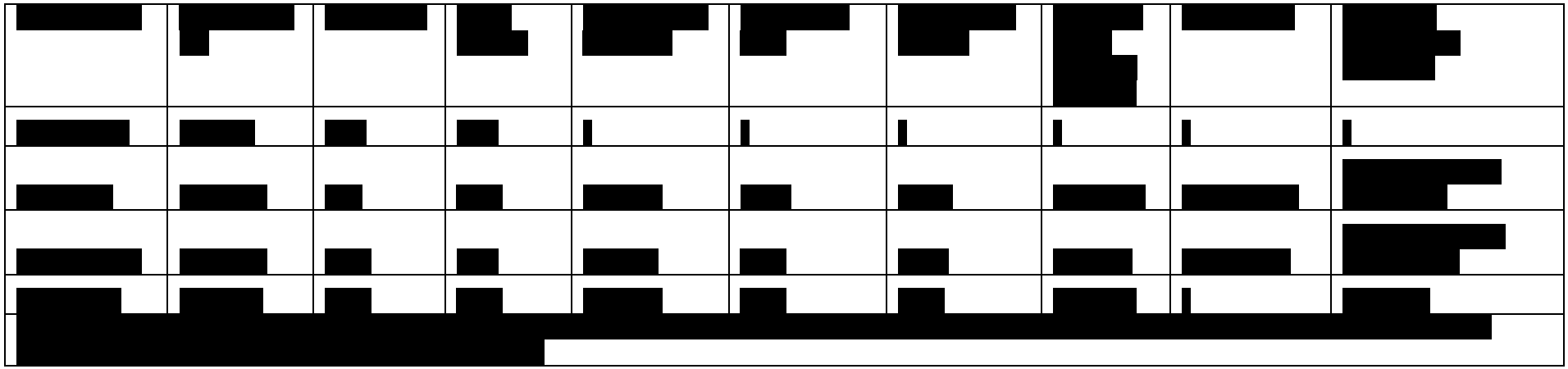


5.7.2 Clinical outcomes from the model

Table 84 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 is slightly higher than what was reported in the pooled ipilimumab anlaysis.[51] This is potentially due to the very small number of patients at risk at Year 10 in the pooled analysis. The modelled long-term survival benefit for nivolumab is also deemed clinically plausible by the UK clinicians based on the survival data from the Phase I CheckMate 003 trial.

Table 84: Summary of model results compared with clinical data

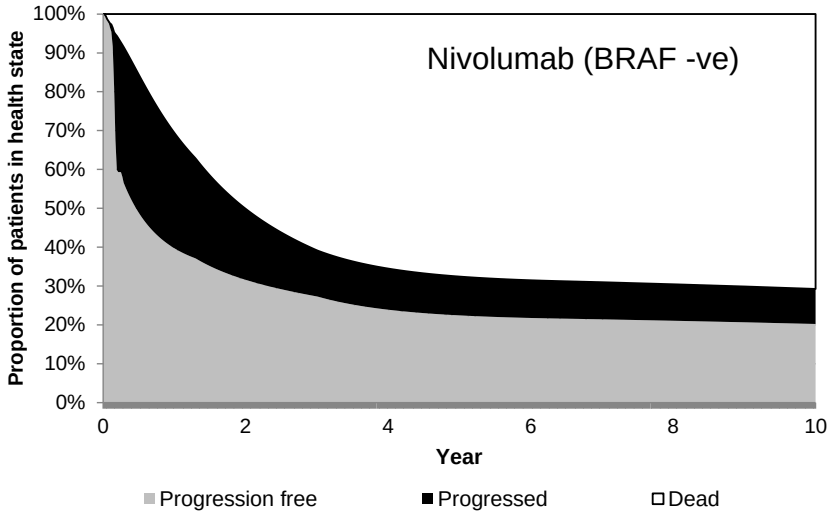
Outcome	Clinical trial result	Model result
BRAF mutation-negative short-term results (trial results based on CheckMate 066)		
OS at Month 6 for nivolumab – BRAF mutation-negative	84.1%	84.8%
OS at Month 6 for DTIC – BRAF mutation-negative	71.8%	69.0%
OS at Year 1 for nivolumab – BRAF mutation-negative	72.9%	70.0%
OS at Year 1 for DTIC – BRAF mutation-negative	42.1%	42.3%
PFS at Month 6 for nivolumab – BRAF mutation-negative	48.0%	50.0%
PFS at Month 6 for DTIC – BRAF mutation-negative	18.5%	18.3%
PFS at Year 1 for nivolumab – BRAF mutation-negative	41.8%	40.5%
PFS at Year 1 for DTIC – BRAF mutation-negative	n/a	6.9%
BRAF mutation-positive short-term results (trial results based on BRIM-3)		
OS at Month 18 for vemurafenib – BRAF mutation-positive	39%	40.5%
PFS at Month 18 for vemurafenib – BRAF mutation-positive	14%	16.2%
Long-term results (clinical results based on pooled ipilimumab analysis)[51]		
OS at Year 3 for ipilimumab	22%	22.4% and 18.0%[a]
OS at Year 10 for ipilimumab	18%	16.8% and 13.9% [a]

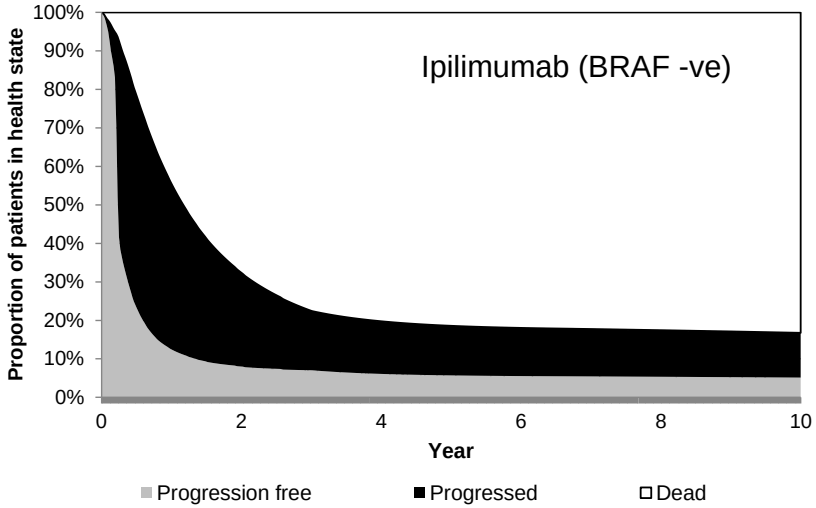
Key: OS, overall survival; PFS, progression free survival.

Notes: [a], model results for BRAF mutation-negative and BRAF mutation-positive patients, respectively.

Figure 65 and Figure 66 present the modelled Markov trace for each treatment arm for BRAF mutation-negative and BRAF mutation-positive patients, respectively.

Figure 65: Markov trace for BRAF mutation-negative analysis





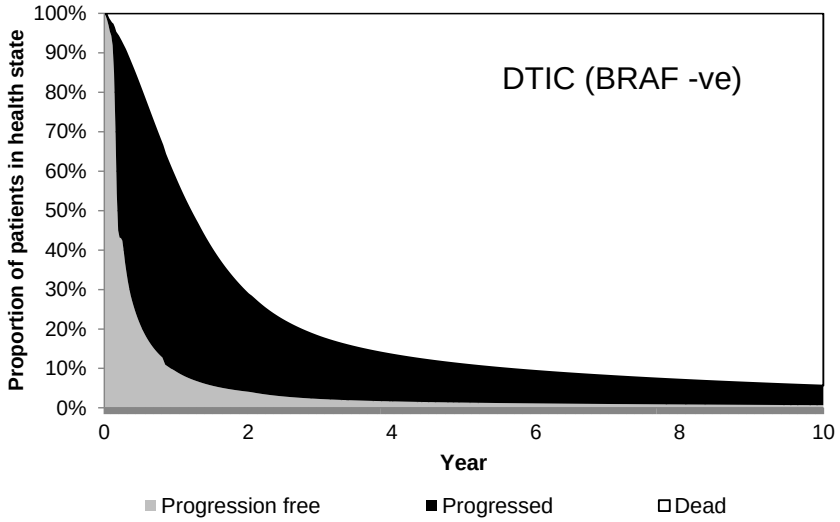
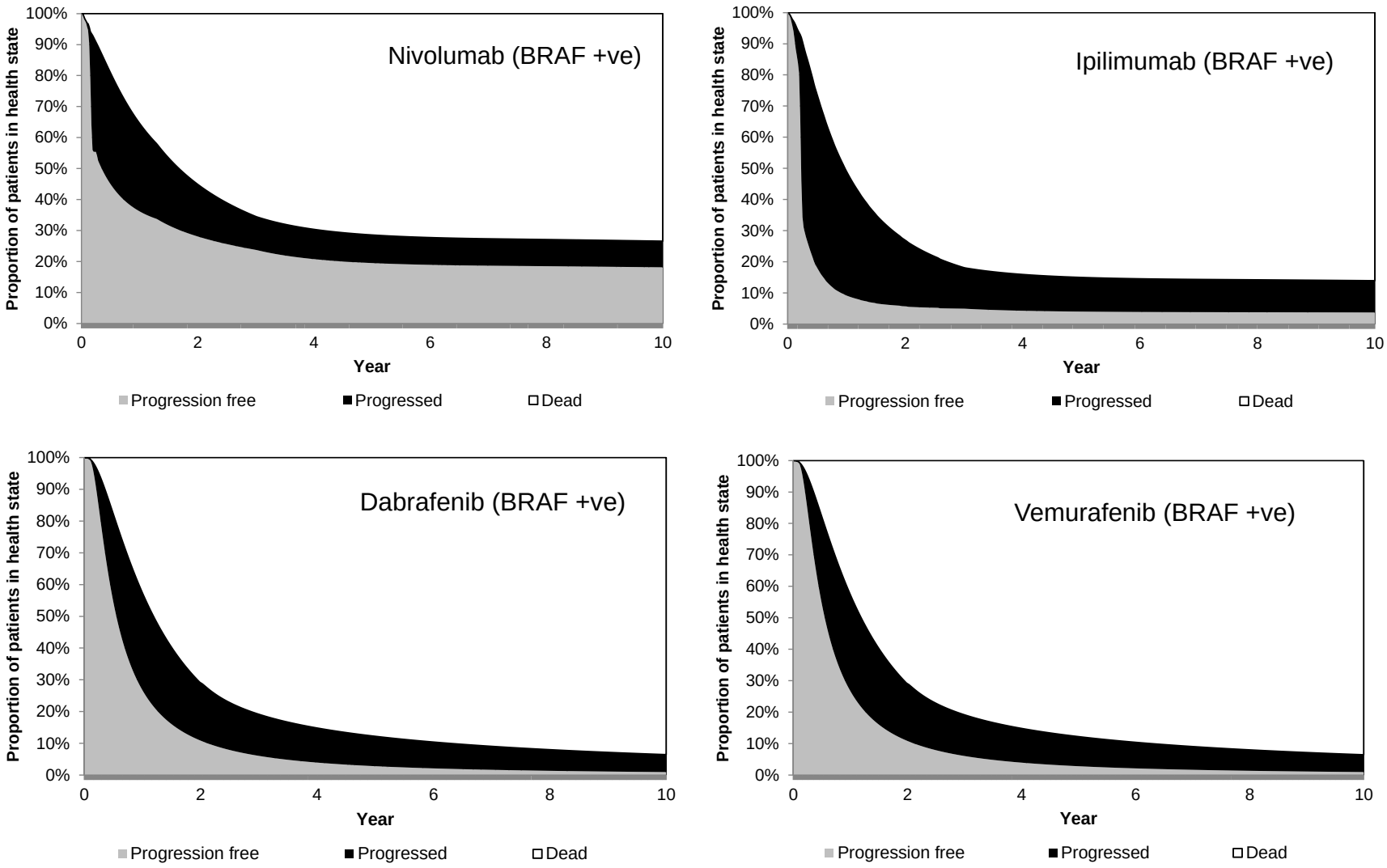


Figure 66: Markov trace for BRAF mutation-positive analysis



5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Table 85 and Table 86 present the disaggregated QALY gains by health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively. Table 87 and Table 88 present the disaggregated LY gains by health state for BRAF mutation-negative and BRAF mutation-positive patients, respectively.

Table 89 and Table 90 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 91 and Table 92 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 nivolumab is more costly than ipilimumab regarding drug cost, drug administration cost, and subsequently ipilimumab cost; and more costly than DTIC BRAF inhibitors regarding drug cost and drug administration cost.

Table 85: Summary of QALY gain by health state – BRAF mutation-negative

Health state	QALY - nivolumab	QALY - ipilimumab	QALY - DTIC	Absolute increment (vs ipilimumab)	Absolute increment (vs DTIC)	% increment (vs ipilimumab)	% increment (vs DTIC)
Progression free & <1 month	0.032	0.018	0.016	0.015	0.017	46%	51%
Progressed & <1 month	0.015	0.033	0.038	-0.017	-0.022	-115%	-148%
Progression free & >1 month	3.029	0.938	0.337	2.091	2.692	69%	89%
Progressed & >1 month	1.273	1.688	0.871	-0.415	0.401	-33%	32%
Disutility due to AE	-0.041	-0.032	-0.031	-0.009	-0.010	21%	24%
Total QALYs	**4.308**	**2.644**	**1.231**	**1.664**	**3.078**	**39%**	**71%**
Key: AE, adverse event; DTIC, dacarbazine; QALY, quality-adjusted life year.							

Table 86: Summary of QALY gain by health state – BRAF mutation-positive

Health state	QALY - nivo	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 & <1 month	0.031	0.016	0.028	0.028	0.015	0.003	0.003	48%	11%	11%
Progressed & <1 month	0.016	0.034	0.026	0.026	-0.018	-0.010	-0.010	-113%	-61%	-61%
Progression free & >1 month	2.938	0.778	0.764	0.764	2.160	2.174	2.174	74%	74%	74%
Progressed & >1 month	1.319	1.649	0.931	0.931	-0.330	0.388	0.388	-25%	29%	29%
Disutility due to AE	-0.039	-0.032	-0.056	-0.044	-0.007	0.017	0.005	17%	-44%	-12%
Total QALYs	**4.265**	**2.445**	**1.693**	**1.705**	**1.821**	**2.573**	**2.561**	**43%**	**60%**	**60%**
Key: dab, dabrafenib; inc, incremental; ipi, ipilimumab; nivo, nivolumab; QALY, quality-adjusted life year; vem, vemurafenib.										

Table 87: Summary of LY gain by health state – BRAF mutation-negative

Health state	LY - nivolumab	LY - ipilimumab	LY - DTIC	Absolute increment (vs ipilimumab)	Absolute increment (vs DTIC)	% increment (vs ipilimumab)	% increment (vs DTIC)
Progression free & <1 month	0.041	0.022	0.020	0.019	0.021	46%	51%
Progressed & <1 month	0.021	0.045	0.052	-0.024	-0.031	-115%	-148%
Progression free & >1 month	3.886	1.204	0.432	2.682	3.454	69%	89%
Progressed & >1 month	1.804	2.393	1.235	-0.589	0.569	-33%	32%
Total QALYs	**5.752**	**3.664**	**1.739**	**2.088**	**4.013**	**36%**	**70%**
Key: DTIC, dacarbazine; LY, life year.							

Table 88: 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 & <1 month	0.039	0.020	0.035	0.035	0.019	0.004	0.004	48%	11%	11%
Progressed & <1 month	0.022	0.047	0.035	0.035	-0.025	-0.014	-0.014	-113%	-61%	-61%
Progression free & >1 month	3.769	0.998	0.980	0.980	2.772	2.789	2.789	74%	74%	74%
Progressed & >1 month	1.870	2.338	1.320	1.320	-0.468	0.550	0.550	-25%	29%	29%
Total QALYs	**5.700**	**3.403**	**2.370**	**2.370**	**2.297**	**3.330**	**3.330**	**40%**	**58%**	**58%**
Key: dab, dabrafenib; inc, incremental; ipi, ipilimumab; LY, life year; nivo, nivolumab; vem, vemurafenib.										

Table 89: Summary of costs by health state – BRAF mutation-negative (base case)

Health state	Cost - nivolumab	Costs - ipilimumab	Costs - DTIC	Absolute increment (vs ipilimumab)	Absolute increment (vs DTIC)	% increment (vs ipilimumab)	% increment (vs DTIC)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent ipi 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.							

Table 90: Summary of costs by health state – BRAF mutation-positive (base case)

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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent ipi 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]

Table 91: Summary of costs by health state – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)

Health state	Cost - nivolumab	Costs - ipilimumab	Costs - DTIC	Absolute increment (vs ipilimumab)	Absolute increment (vs DTIC)	% increment (vs ipilimumab)	% increment (vs DTIC)
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent ipi 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; PAS, patient access scheme.							

Table 92: 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent ipi 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.

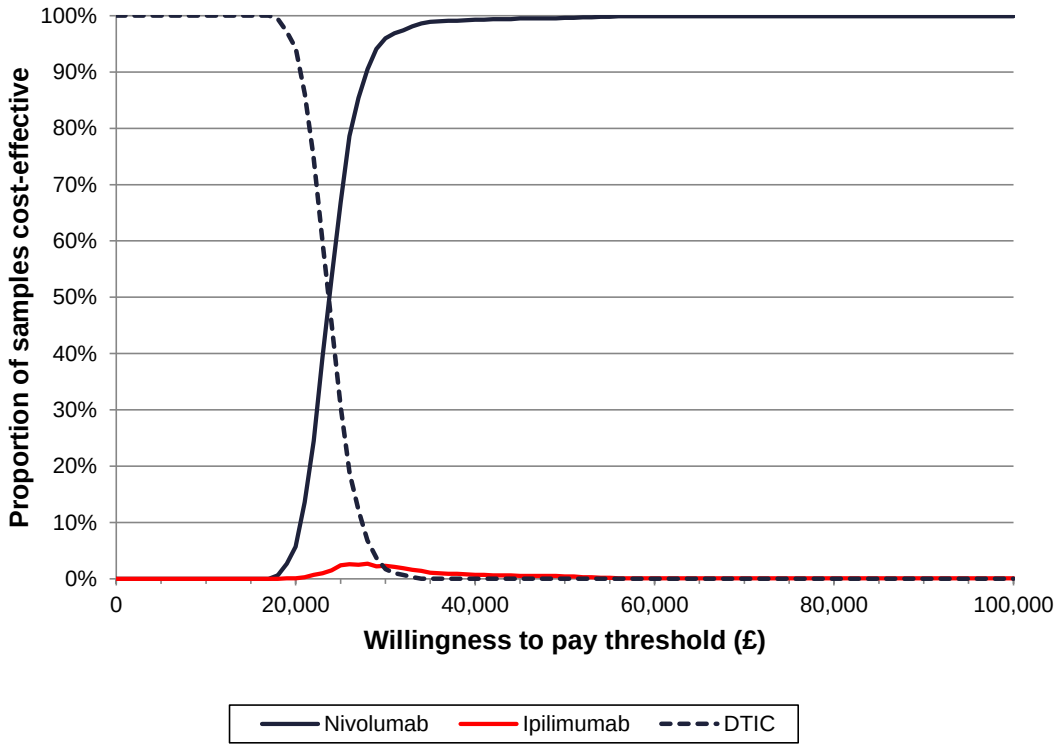
5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Figure 71 and Figure 72 present PSA scatter plots (nivolumab vs its comparators) for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the base case. Figure 73 and Figure 74 present PSA scatter plots (nivolumab 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.

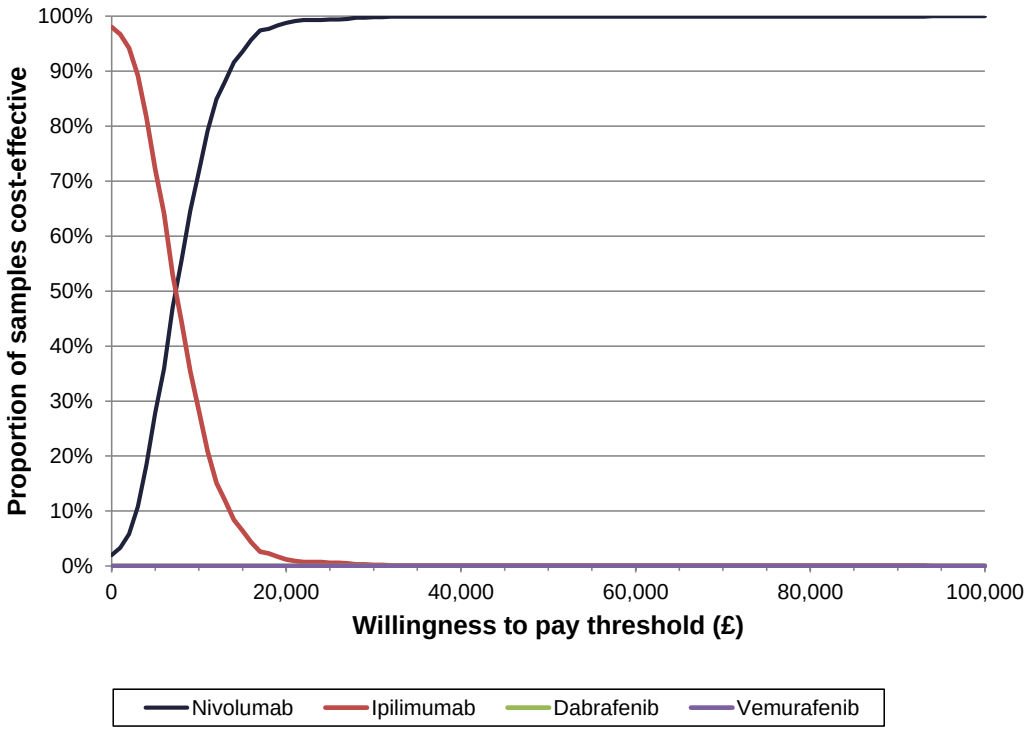
Figure 67 and Figure 68 present the cost-effectiveness acceptability curves (CEACs) for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the base case. The probabilities of nivolumab being most cost effective are 87% and 99% for WTP thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-negative patients. The probabilities of nivolumab 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 69 and Figure 70 present the CEACs for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the PAS-based base case. The probabilities of nivolumab being most cost effective are 63% and 95% for WTP thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-negative patients. The probabilities of nivolumab being most cost effective are 91% and 99% for WTP thresholds of £30,000 and £50,000, respectively, for the BRAF mutation-positive patients.

Figure 67: Cost-effectiveness acceptability curve – BRAF mutation-negative (base case)



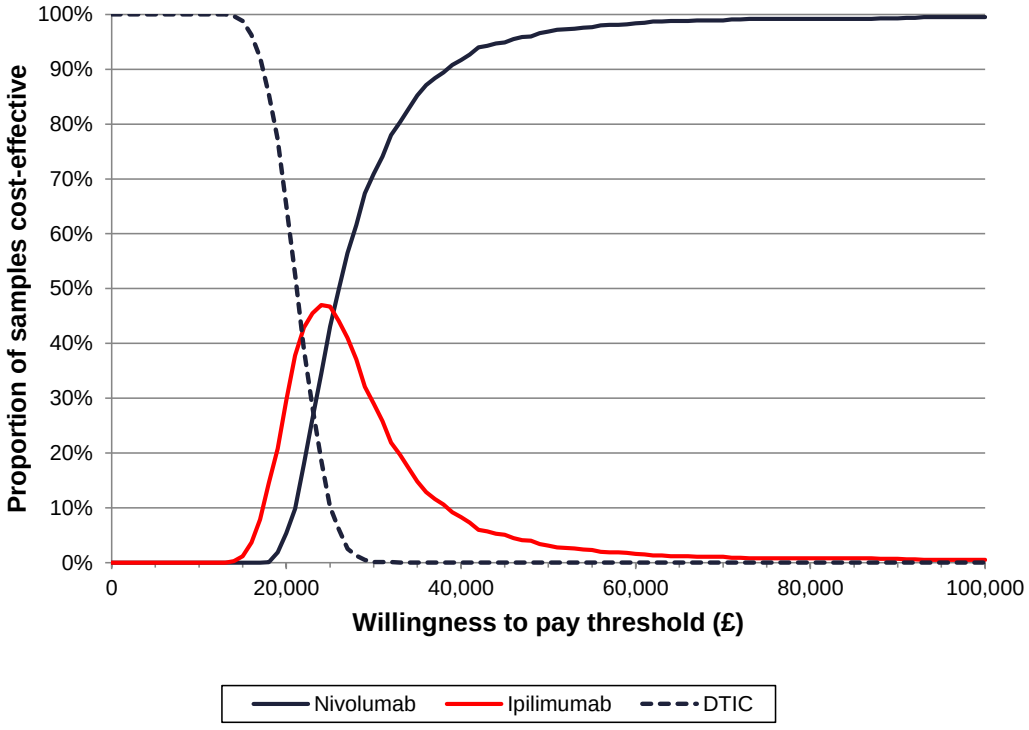
Key: DTIC, dacarbazine; WTP, willingness to pay.

Figure 68: Cost-effectiveness acceptability curve – BRAF mutation-positive (base case)



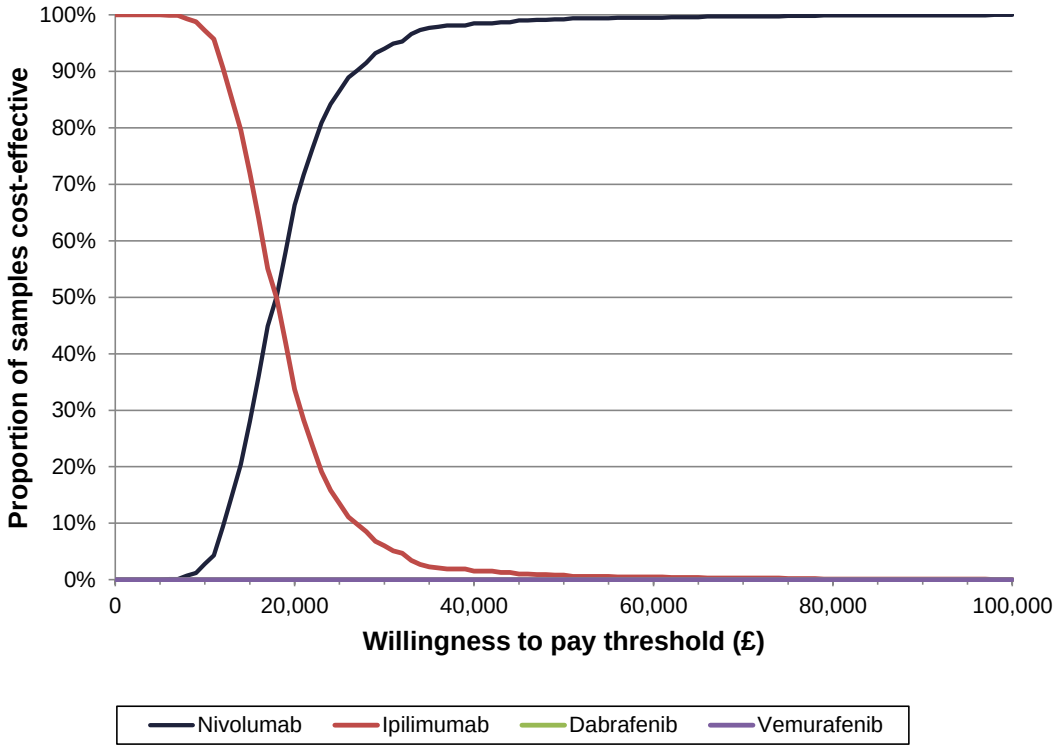
Key: DTIC, dacarbazine; WTP, willingness to pay.

Figure 69: Cost-effectiveness acceptability curve – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)



Key: DTIC, dacarbazine; PAS, patient access scheme; WTP, willingness to pay.

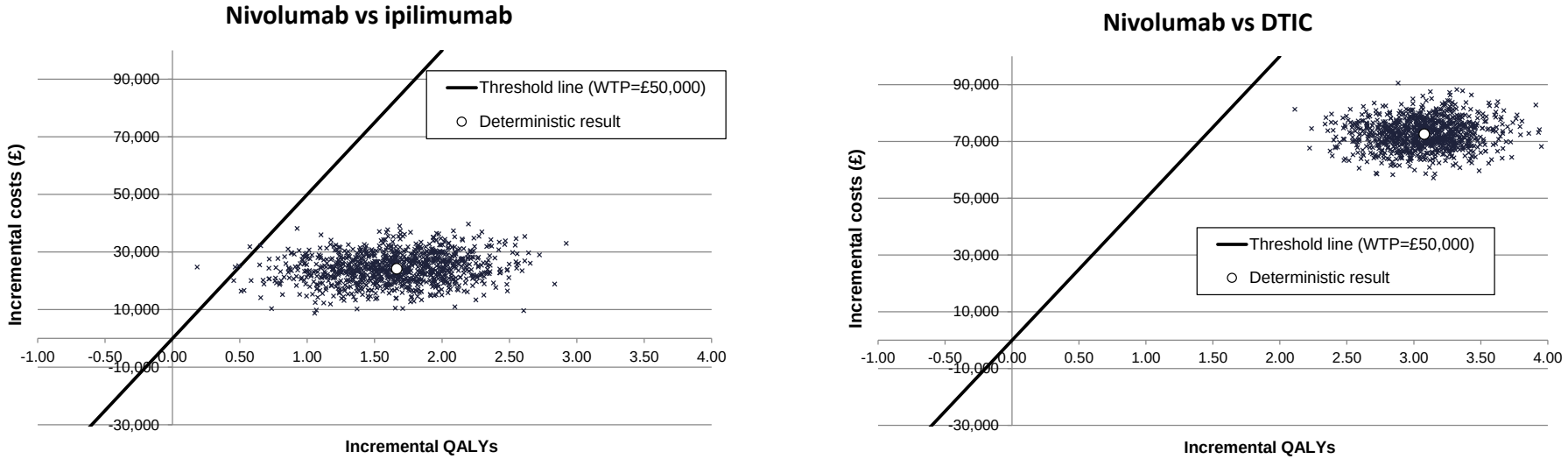
Figure 70: Cost-effectiveness acceptability curve – BRAF mutation-positive assuming PAS drug prices for comparator treatments)



Key: DTIC, dacarbazine; PAS, patient access scheme; WTP, willingness to pay.

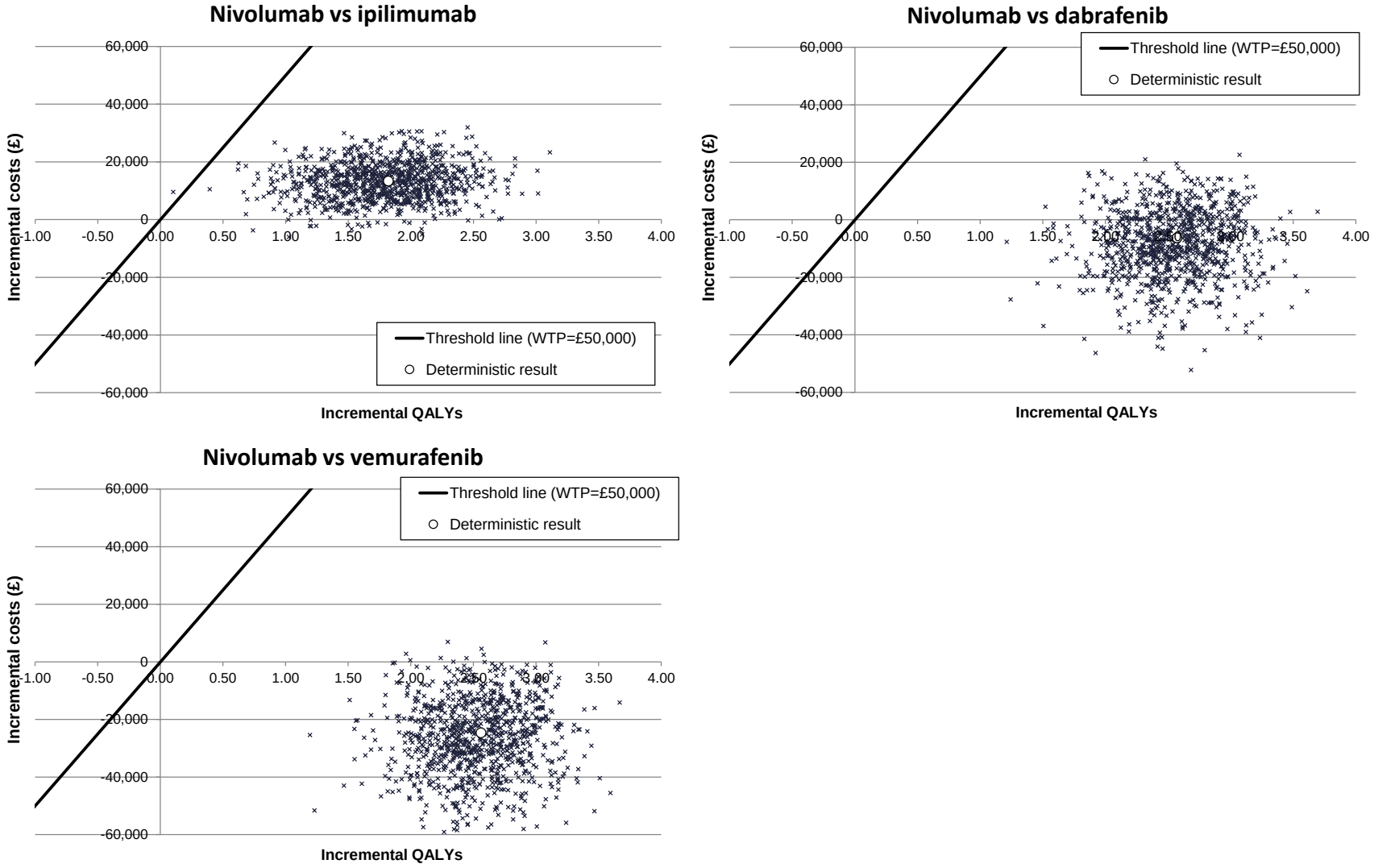
Table 93 and Table 94 present the mean model results based on PSA (1,000 runs) and compare the PSA results with the deterministic results for BRAF mutation-negative and BRAF mutation-positive patients, respectively, for the base case. Table 95 and Table 96 present the same results for the PAS-based base case. The results show that the results of the probabilistic analysis are similar to those of the deterministic analysis.

Figure 71: PSA scatter plots of nivolumab vs its comparators – BRAF mutation-negative (base case)



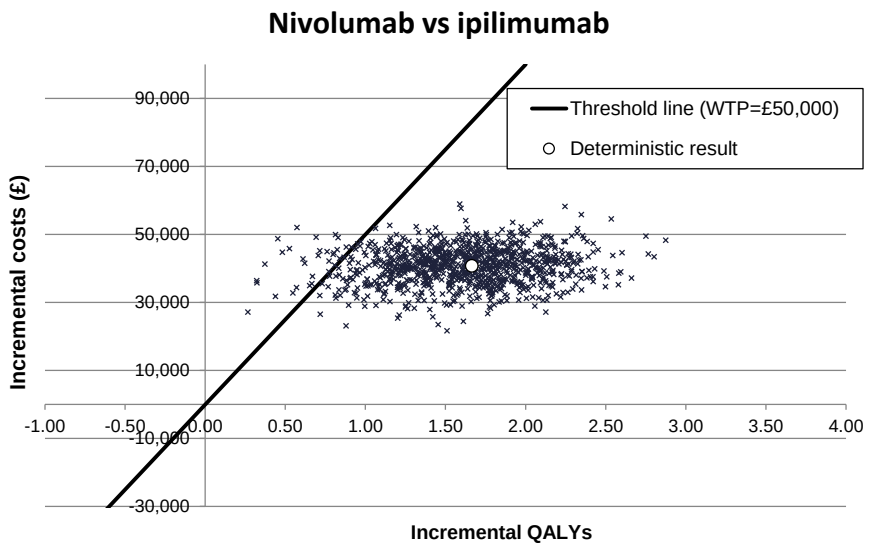
Key: DTIC, dacarbazine; PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

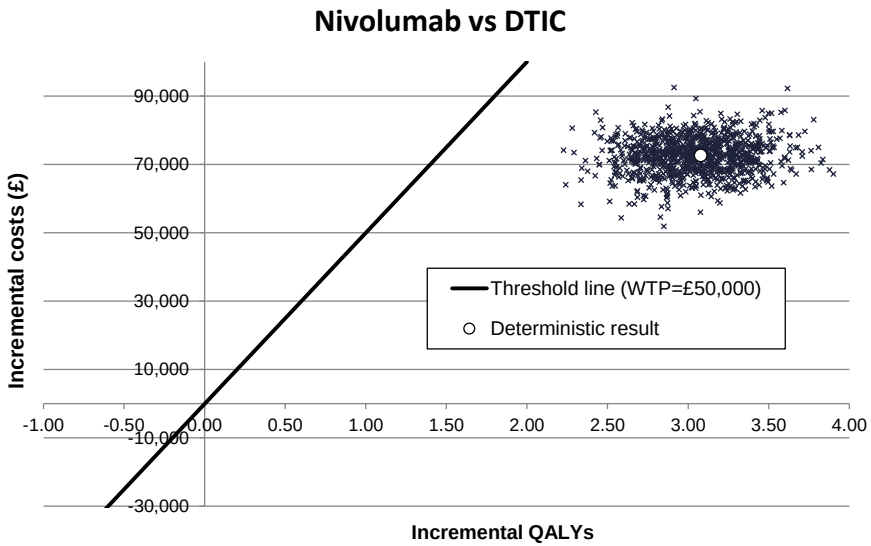
Figure 72: PSA scatter plots of nivolumab vs its comparators – BRAF mutation-positive (base case)



Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

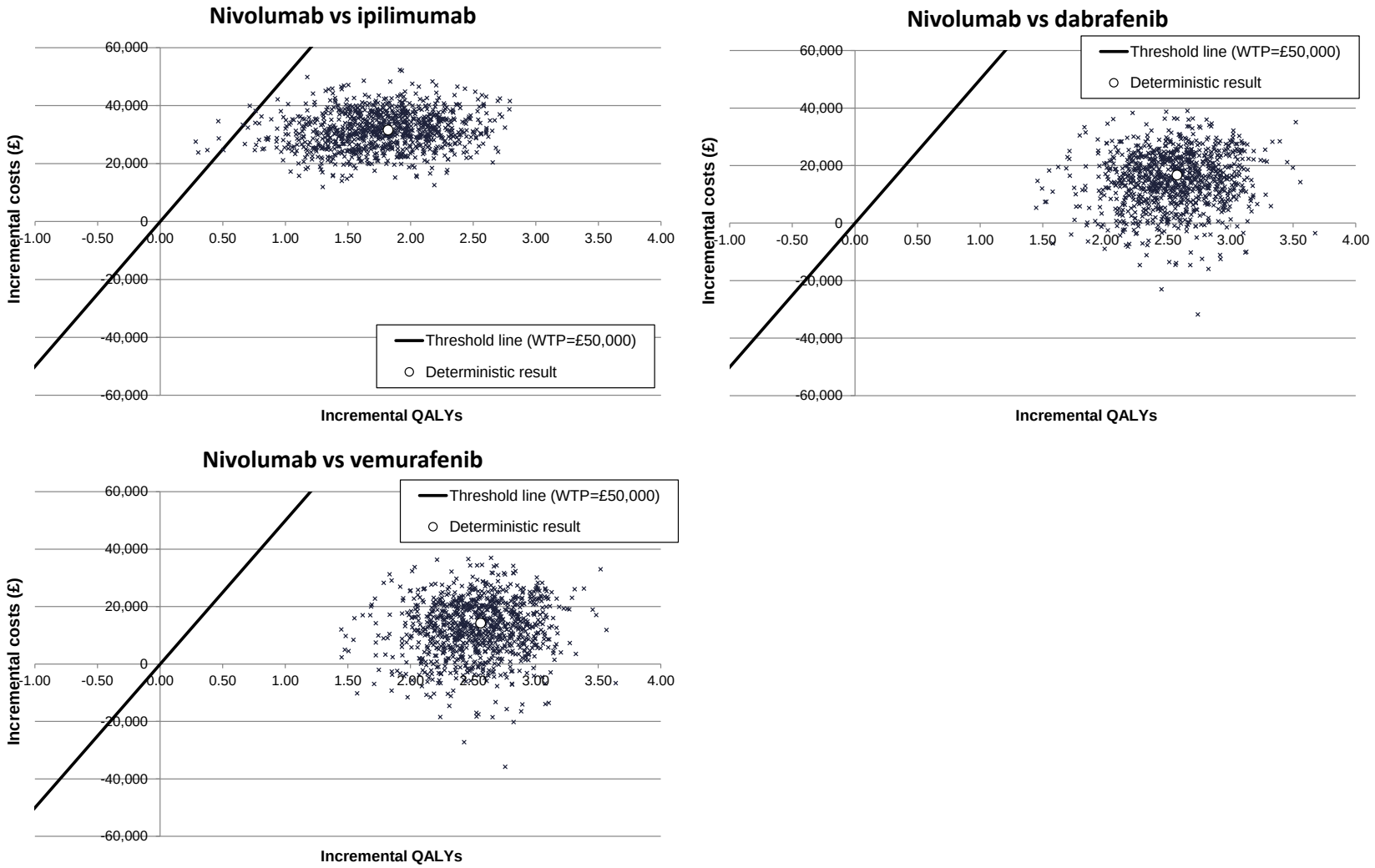
Figure 73: PSA scatter plots of nivolumab vs its comparators – BRAF mutation-negative (assuming PAS drug prices for comparator treatments)





Key: DTIC, dacarbazine; PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 74: PSA scatter plots of nivolumab 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 93: 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
DTIC	[redacted]	[redacted]	1.23	1.23						
Ipilimumab	[redacted]	[redacted]	2.66	2.64	£34,013	£34,261	Extended dominated	Extended dominated	Excluded due to extended dominance	Excluded due to extended dominance
Nivolumab	[redacted]	[redacted]	4.30	4.31	£23,718	£23,583			£23,718	£25,558
Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.										

Table 94: 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]	2.46	2.44						
Nivolumab	[redacted]	[redacted]	4.24	4.27	£7,422	£7,346			£7,422	£7,346
Dabrafenib	[redacted]	[redacted]	1.70	1.69	-£28,335	-£26,054	Dominated	Dominated	Excluded due to dominance	Excluded due to dominance
Vemurafenib	[redacted]	[redacted]	1.71	1.70	-£54,105	-£51,397	Dominated	Dominated	Excluded due to dominance	Excluded due to dominance
Key: DTIC, dacarbazine; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.										

Table 95: 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
DTIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[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 96: 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]		
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Nivolumab	[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

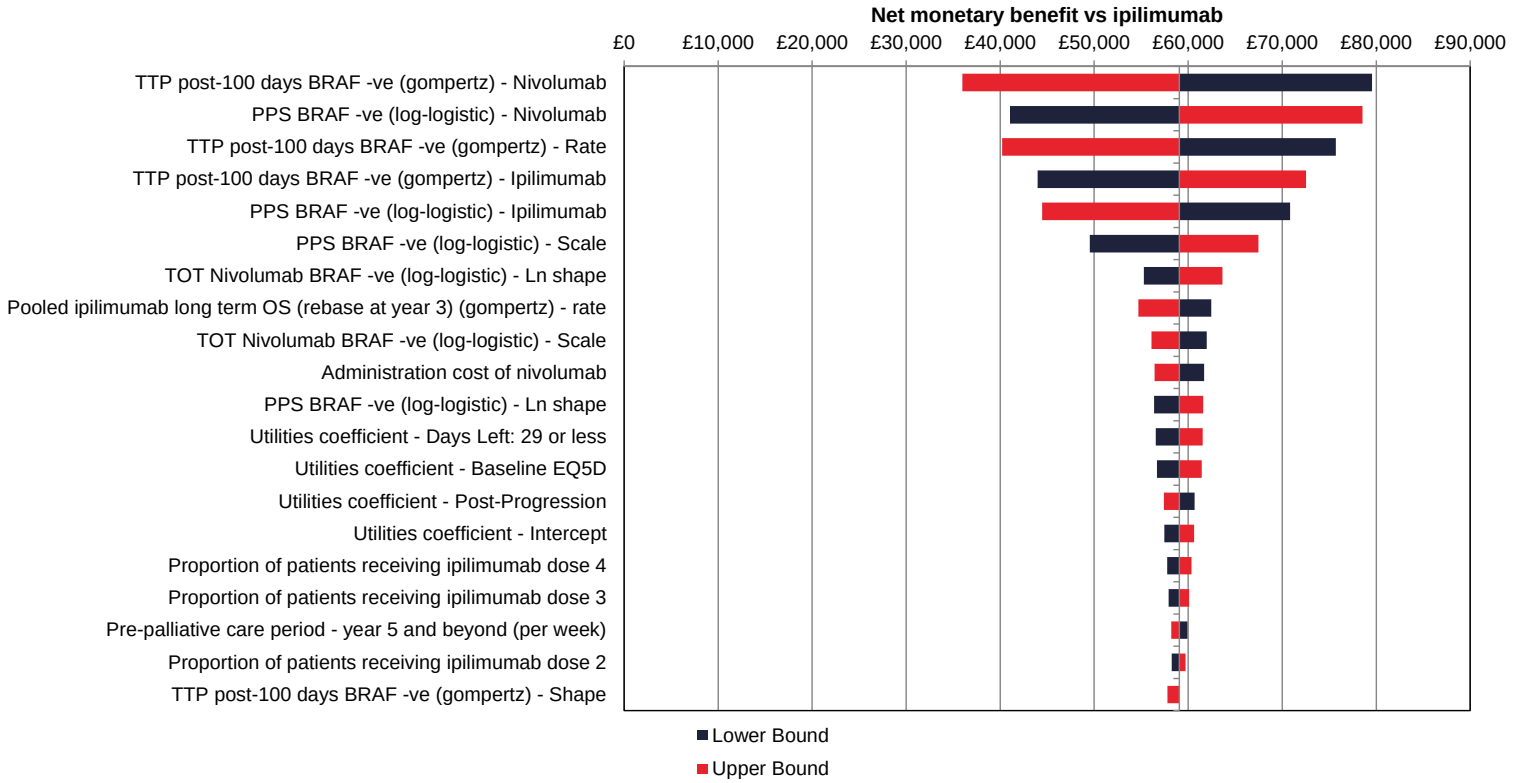
Figure 75 and Figure 76 present tornado diagrams from the deterministic one-way sensitivity analyses (OWSA), illustrating the effect on the net benefit per patient of treatment with nivolumab of varying the 20 most influential parameters between their upper and lower bounds, for BRAF mutation-negative 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 willingness to pay (WTP) threshold for a QALY used in the net benefit calculation is £50,000 based on the assumption that nivolumab qualifies as end-of-life treatment. The same analysis was performed for the PAS-based base case, and the results were similar and shown in Appendix 16.

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 IV.

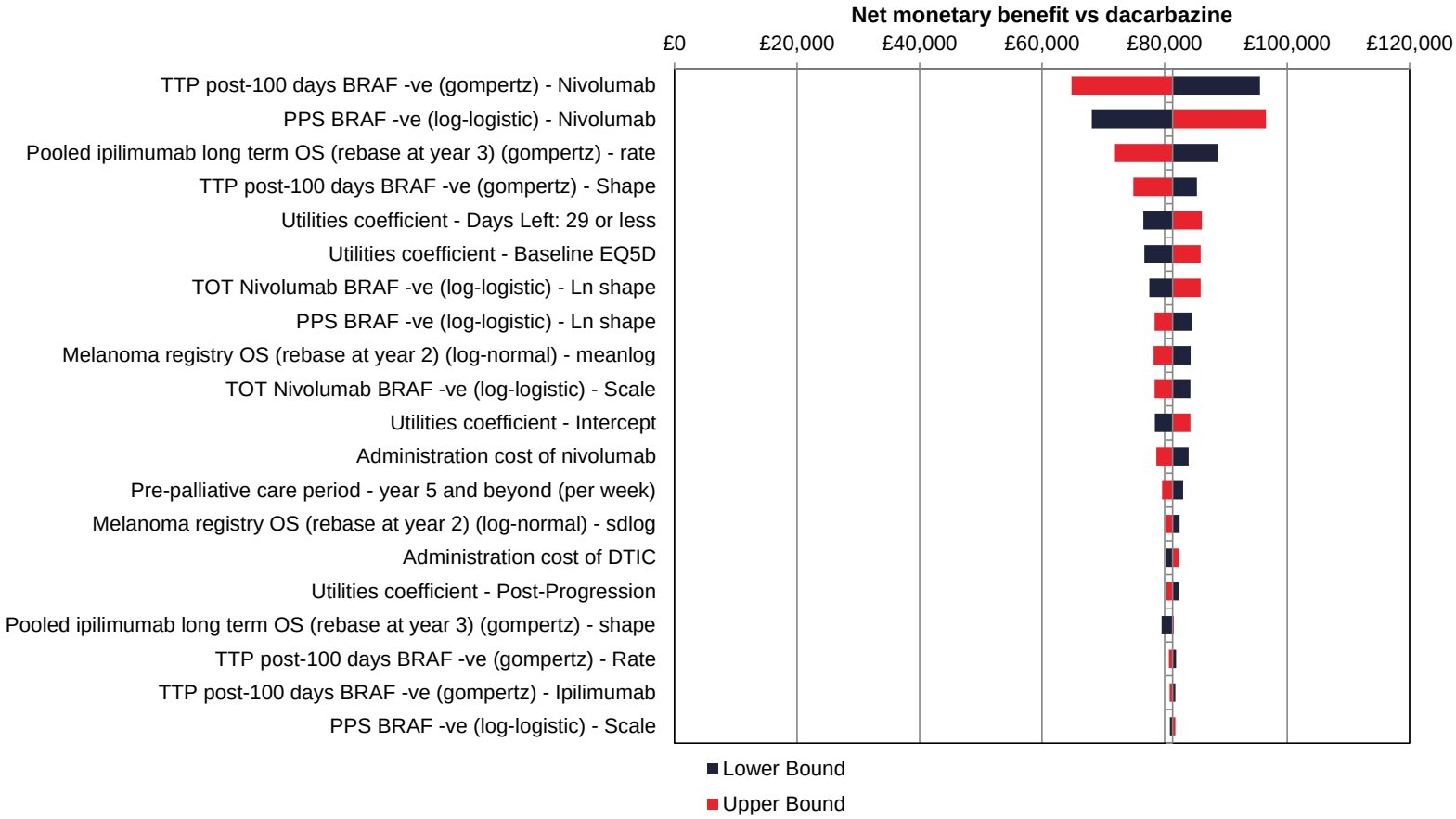
5.8.3 Scenario analysis

Table 97 and Table 98 present the scenario analysis performed for BRAF mutation-negative and BRAF mutation-positive patients, respectively, with the base case and PAS-based base case results shown in different columns.

Figure 75: Tornado diagram containing 20 most influential parameters – BRAF mutation-negative (base case)



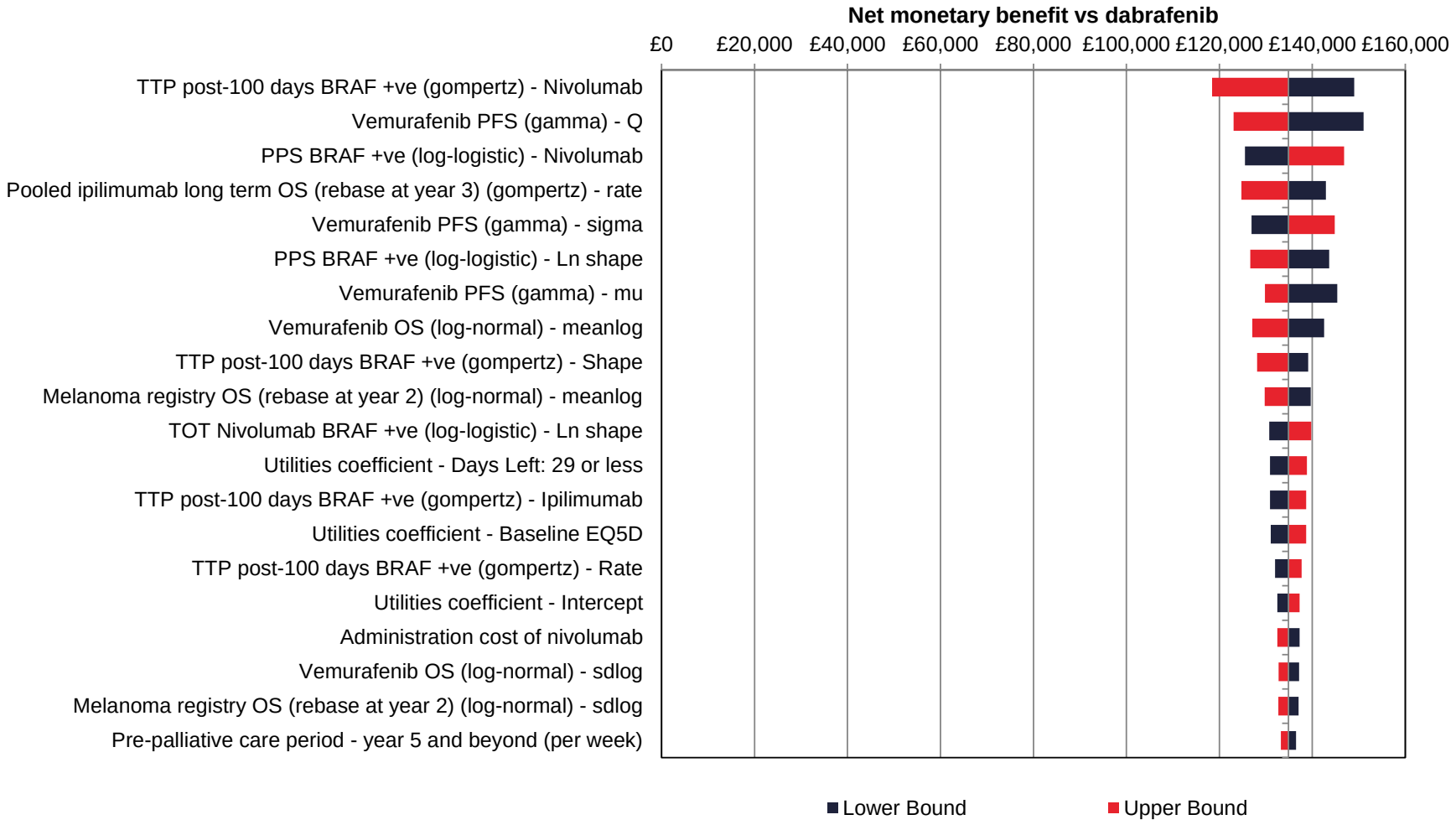
Key: OS, overall survival; PPS, post-progression survival; TTP, time to progression.



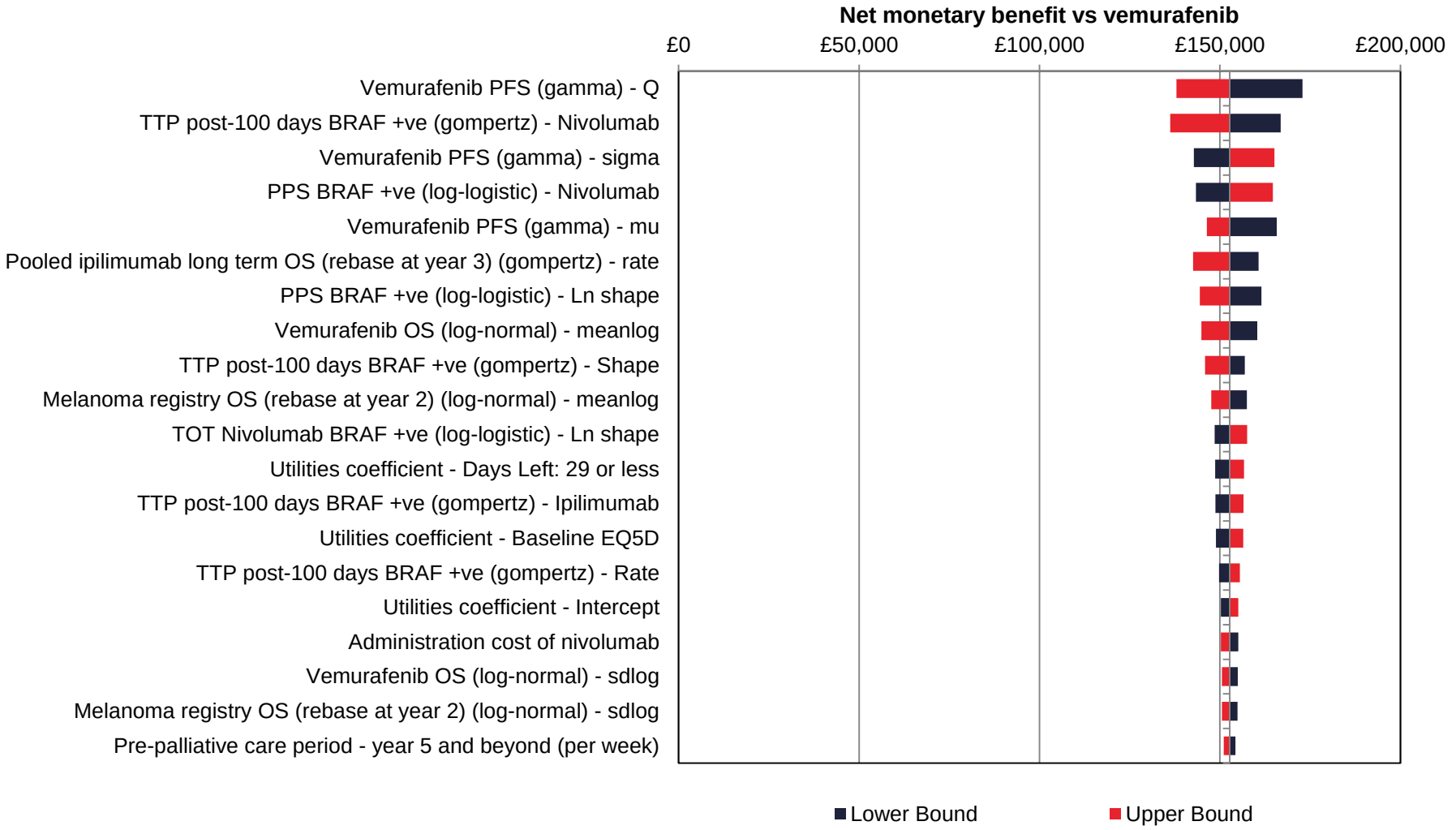
Key: DTIC, dacarbazine; OS, overall survival; PPS, post-progression survival; TOT, time on treatment; TTP, time to progression.

Figure 76: 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 97: Results of scenario analysis – BRAF mutation-negative

Parameter	Base case	Scenario analysis	Base case (list price)				PAS drug prices for comparator treatments			
			Nivolumab vs ipilimumab		Nivolumab vs dacarbazine		Nivolumab vs ipilimumab		Nivolumab vs dacarbazine[a]	
			ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]
Base case	**N/A**	**N/A**	**14,513**	**59,052**	**23,583**	**81,300**	[redacted]	[redacted]	[redacted]	[redacted]
Parametric curves based on indirect comparison										
TTP	Gompertz	Exponential	18,218	41,468	29,706	49,523	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	16,560	48,367	26,636	63,795	[redacted]	[redacted]	[redacted]	[redacted]
		Log-logistic	18,545	40,088	27,083	61,035	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	19,094	38,122	27,317	59,825	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	18,884	38,854	27,261	60,148	[redacted]	[redacted]	[redacted]	[redacted]
PPS	Log-logistic	Exponential	13,355	67,127	23,646	80,918	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	13,188	68,442	23,977	78,723	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz	13,847	63,509	22,268	90,857	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	14,966	56,256	23,246	83,569	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	14,643	58,214	23,435	82,284	[redacted]	[redacted]	[redacted]	[redacted]
Alternative methods for indirect comparison										
Trial evidence	CheckMate 066 and MDX020-010	CheckMate 066 and CA184-024	13,707	64,790	24,393	76,085	[redacted]	[redacted]	[redacted]	[redacted]
PPS	Separate PPS for nivolumab and ipilimumab	Combined PPS for nivolumab and ipilimumab	14,333	60,237	23,500	81,875	[redacted]	[redacted]	[redacted]	[redacted]
Long-term survival										
Registry survival	Log-normal	Exponential	14,513	59,052	23,759	80,080	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	14,513	59,052	23,611	81,103	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Base case (list price)				PAS drug prices for comparator treatments			
			Nivolumab vs ipilimumab		Nivolumab vs dacarbazine		Nivolumab vs ipilimumab		Nivolumab vs dacarbazine[a]	
			ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]
(rebased at 2 years)		Gompertz					[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	14,513	59,052	23,512	81,795	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	14,513	59,052	23,591	81,244	[redacted]	[redacted]	[redacted]	[redacted]
Pooled ipilimumab long-term survival	Gompertz	Exponential	15,006	56,088	24,586	74,788	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	14,316	60,301	23,186	84,044	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	14,354	60,051	23,264	83,496	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	14,348	60,093	23,251	83,588	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	14,347	60,099	23,249	83,600	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment										
TOT curve for nivolumab	Log-logistic	Exponential	12,830	61,876	22,671	84,124	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	14,981	58,264	23,837	80,512	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz	19,167	51,238	26,105	73,486	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	16,376	55,908	24,594	78,156	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	16,324	55,997	24,565	78,245	[redacted]	[redacted]	[redacted]	[redacted]
Duration of treatment	100% discontinue at 2 years	75% discontinue at 2 years[c]	27,852	36,627	30,806	58,875	[redacted]	[redacted]	[redacted]	[redacted]
		50% discontinue at 2 years[c]	41,359	14,202	38,077	36,450	[redacted]	[redacted]	[redacted]	[redacted]
		25% discontinue at 2 years[c]	55,035	-8,223	45,397	14,025	[redacted]	[redacted]	[redacted]	[redacted]
		0% discontinue at 2 years (no treatment continuation rule) [c]	68,883	-30,647	52,766	-8,400	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Base case (list price)				PAS drug prices for comparator treatments			
			Nivolumab vs ipilimumab		Nivolumab vs dacarbazine		Nivolumab vs ipilimumab		Nivolumab vs dacarbazine[a]	
			ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]
	0% discontinue at 2 years have registry OS for life	25% discontinue at 2 years have registry OS for life[d]	16,539	48,101	25,325	70,349	[redacted]	[redacted]	[redacted]	[redacted]
		50% discontinue at 2 years have registry OS for life[d]	19,805	35,594	27,687	57,842	[redacted]	[redacted]	[redacted]	[redacted]
		75% discontinue at 2 years have registry OS for life[d]	25,269	22,405	30,749	44,652	[redacted]	[redacted]	[redacted]	[redacted]
		100% discontinue at 2 years have registry OS for life[d]	34,758	9,849	34,417	32,097	[redacted]	[redacted]	[redacted]	[redacted]
	Maximum treatment duration of 2 years	Maximum treatment duration of 3 years	23,373	44,067	28,388	66,315	[redacted]	[redacted]	[redacted]	[redacted]
		Maximum treatment duration of 4 years	29,786	33,388	31,850	55,636	[redacted]	[redacted]	[redacted]	[redacted]
		Maximum treatment duration of 5 years	34,831	24,980	34,568	47,228	[redacted]	[redacted]	[redacted]	[redacted]
		No maximum treatment duration	68,883	-30,647	52,766	-8,400	[redacted]	[redacted]	[redacted]	[redacted]
Dosing and drug cost										
Method for dosing for nivolumab and ipilimumab	Method of moment (weight based dosing)	Cost per mg	14,317	59,378	21,989	86,206	[redacted]	[redacted]	[redacted]	[redacted]
		Round up to the nearest full vial	13,360	60,970	22,306	85,231	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab dose	Up to 16 doses	Fixed 4 doses	7,593	70,567	23,583	81,300	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Base case (list price)				PAS drug prices for comparator treatments			
			Nivolumab vs ipilimumab		Nivolumab vs dacarbazine		Nivolumab vs ipilimumab		Nivolumab vs dacarbazine[a]	
			ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]	ICER	Incremental net benefit[b]
Utilities										
Utility analysis	CheckMate 066 trial analysis	Ipilimumab NICE TA319 utilities	13,092	68,083	20,446	104,909	[redacted]	[redacted]	[redacted]	[redacted]
General model settings										
Time horizon	40 years	10 years	24,269	23,983	43,308	10,760	[redacted]	[redacted]	[redacted]	[redacted]
		20 years	16,218	49,261	26,991	60,988	[redacted]	[redacted]	[redacted]	[redacted]
		30 years	14,645	58,148	23,855	79,395	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	0.035	0.015	12,746	76,591	19,582	117,018	[redacted]	[redacted]	[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], results for nivolumab vs dacarbazine are different between base case (list price) and PAS-based base case because the cost of subsequent ipilimumab use in both treatment arms; [b], willingness to pay threshold £50,000; [c], 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); [d], in these scenario analyses, all patients still on nivolumab treatments at Year 2 will discontinue treatment, but only a proportion (75% to 0%) will get survival benefit for the nivolumab arm with the reaming patients (25% to 100%) having OS same as the registry OS from Year 2 onwards; Ex-dominated: extended dominated.

Table 98: Results of scenario analysis – BRAF mutation-positive

Parameter	Base case	Scenario analysis	Base case (list price)						PAS drug prices for comparator treatments					
			Nivolumab vs Ipilimumab		Nivolumab vs dabrafenib		Nivolumab vs vemurafenib		Nivolumab vs Ipilimumab		Nivolumab vs dabrafenib		Nivolumab 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	**7,346**	**77,652**	**D**	**134,872**	**D**	**152,684**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric curves based on indirect comparison														
TTP	Gompertz	Exponential	9,125	57,968	D	103,188	D	121,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	8,342	65,721	D	118,061	D	135,874	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-logistic	9,101	57,734	D	115,897	D	133,709	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	9,310	55,778	D	114,702	D	132,515	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	9,232	56,484	D	114,962	D	132,775	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	Log-logistic	Exponential	6,862	86,160	D	123,262	D	141,075	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	6,812	87,168	D	118,158	D	135,971	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz	7,002	83,519	D	140,587	D	158,399	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	7,500	75,177	D	141,924	D	159,737	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	7,370	77,200	D	136,383	D	154,196	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative methods for indirect comparison														
Trial evidence	CheckMate 066 and MDX020-010	CheckMate 066 and CA184-024	7,068	83,171	D	120,551	D	138,364	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	Separate PPS for nivolumab and ipilimumab	Combined PPS for nivolumab and ipilimumab	7,276	78,862	D	135,315	D	153,127	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Base case (list price)						PAS drug prices for comparator treatments					
			Nivolumab vs Ipilimumab		Nivolumab vs dabrafenib		Nivolumab vs vemurafenib		Nivolumab vs Ipilimumab		Nivolumab vs dabrafenib		Nivolumab 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
Long-term survival														
Registry survival (rebased at 2 years)	Log-normal	Exponential	7,346	77,652	D	134,434	D	152,176	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	7,346	77,652	D	135,278	D	153,085	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz							[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	7,346	77,652	D	135,616	D	153,428	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	7,346	77,652	D	134,718	D	152,531	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled ipilimumab long-term survival	Gompertz	Exponential	8,092	67,546	D	114,501	D	132,313	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	7,398	76,874	D	133,305	D	151,118	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	7,402	76,805	D	133,164	D	150,977	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	7,377	77,189	D	133,938	D	151,751	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	7,308	78,243	D	136,064	D	153,876	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment														
TOT curve for nivolumab	Log-logistic	Exponential	3,484	84,788	D	142,009	D	159,821	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	5,662	80,768	D	137,989	D	155,801	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz	9,602	73,504	D	130,724	D	148,537	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Normal	9,540	73,593	D	130,813	D	148,626	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised Gamma	9,430	73,797	D	131,018	D	148,830	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Base case (list price)						PAS drug prices for comparator treatments					
			Nivolumab vs Ipilimumab		Nivolumab vs dabrafenib		Nivolumab vs vemurafenib		Nivolumab vs Ipilimumab		Nivolumab vs dabrafenib		Nivolumab 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
Duration of treatment	100% discontinue at 2 years	75% discontinue at 2 years	17,687	58,544	4,853	115,764	D	133,576						
		50% discontinue at 2 years	28,128	39,436	12,176	96,656	4,988	114,468						
		25% discontinue at 2 years	38,671	20,328	19,549	77,548	12,372	95,360						
		0% discontinue at 2 years (no treatment continuation rule)	49,317	1,220	26,974	58,440	19,808	76,252						
	0% discontinue at 2 years have registry OS for life	25% discontinue at 2 years have registry OS for life	8,238	65,735	D	122,955	D	140,768						
		50% discontinue at 2 years have registry OS for life	9,726	51,706	D	108,926	D	126,739						
		75% discontinue at 2 years have registry OS for life	12,049	37,831	D	95,052	D	112,864						
		100% discontinue at 2 years have registry OS for life	15,759	25,155	D	82,375	D	100,187						
	Maximum treatment duration of 2 years	Maximum treatment duration of 3 years	14,245	64,816	2,425	122,036	D	139,849						
		Maximum treatment duration of 4 years	19,199	55,750	5,912	112,970	D	130,783						
		Maximum treatment duration of 5 years	23,059	48,651	8,615	105,871	1,417	123,684						
		No maximum treatment duration	49,317	1,220	26,974	58,440	19,808	76,252						
Dosing and drug cost														

Parameter	Base case	Scenario analysis	Base case (list price)						PAS drug prices for comparator treatments					
			Nivolumab vs Ipilimumab		Nivolumab vs dabrafenib		Nivolumab vs vemurafenib		Nivolumab vs Ipilimumab		Nivolumab vs dabrafenib		Nivolumab 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
Method for dosing for nivolumab and ipilimumab	Method of moment (weight based dosing)	Cost per mg	7,657	77,085	D	139,379	D	157,191	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Round up to the nearest full vial	6,594	79,021	D	138,471	D	156,283	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab dose	Up to 16 doses	Fixed 4 doses	1,021	89,167	D	134,872	D	152,684	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities														
Utility analysis	CheckMate 066 trial analysis	Ipilimumab NICE TA319 utilities	6,579	88,266	D	155,111	D	172,924	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General model settings														
Time horizon	40 years	10 years	12,760	33,740	D	54,904	D	71,898	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20 years	8,634	60,340	D	102,166	D	119,742	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		30 years	7,559	73,983	D	127,703	D	145,448	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	0.035	0.015	6,601	101,404	D	179,448	D	198,099	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: D, dominant; 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 nivolumab 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 nivolumab being cost effective compared to its comparators, at WTP thresholds of £30,000 and £50,000, are 63% and 95%, respectively, for BRAF mutation-negative patients; and 91% and 99%, 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 nivolumab remains cost effective compared to its comparators for the majority of scenarios tested. Specifically, nivolumab remains cost effective in scenarios for alternative parametric curves for TTP, PPS, TOT and long-term OS, for alternative source and assumptions for ITC analysis, 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 nivolumab 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 a high proportion of patients discontinue nivolumab treatment at Year 2 and are assumed to have an OS that is the same as the long-term registry OS. 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[12]:

- The Markov state-transition method to estimate OS and PFS using TTP, PPS and PrePS;
- The rationale and method of the indirect treatment comparison for establishing comparable efficacy between nivolumab and ipilimumab;
- Extrapolation beyond trial period and the use of external data for long-term survival;
- The modelling of time on treatment for nivolumab and the treatment continuation rule;
- The use of utilities based on progression status and time to death;
- Modelling costs and resource use (excluding drug costs) for advanced melanoma patients; and
- Modelling safety and AEs.

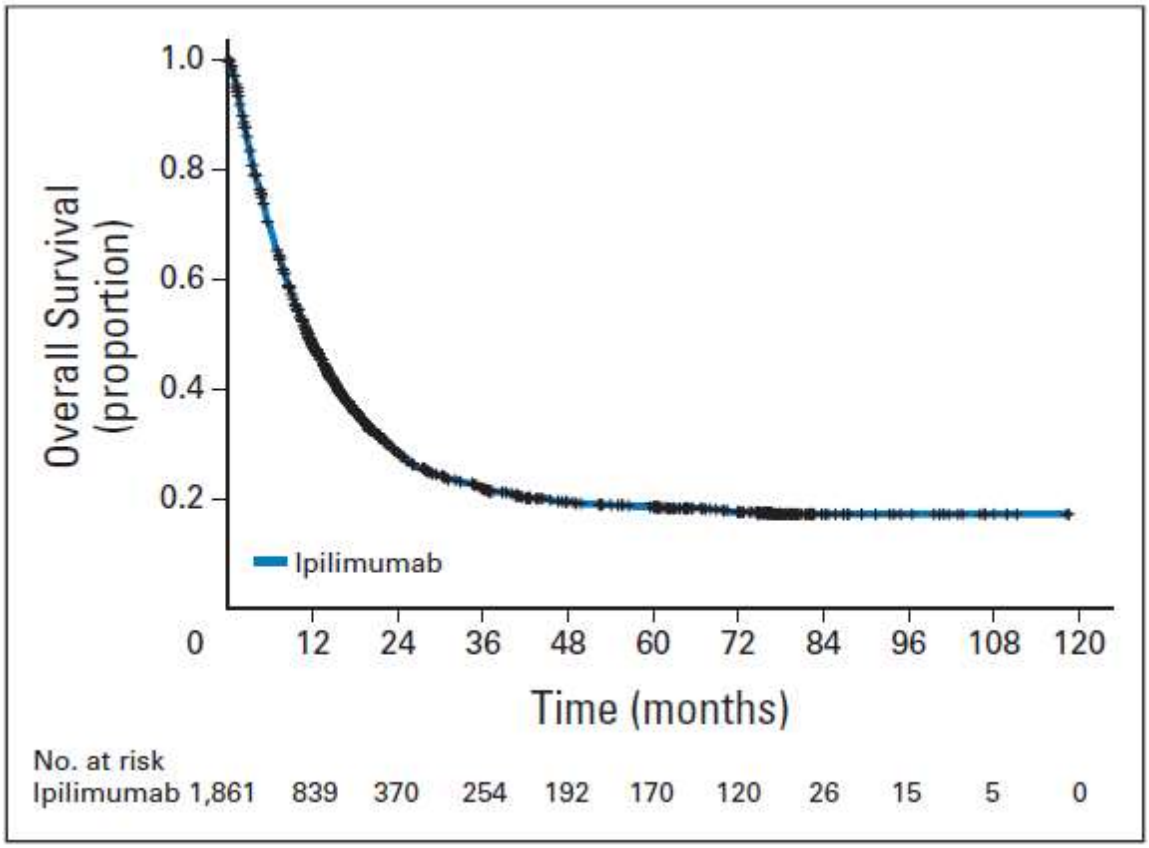
The experts were in agreement with the modelling and indirect comparison methods, and the key feedback for other aspects has been incorporated into the analysis, including:

- 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[51];
- The use of a clinically plausible and practical treatment continuation rule for nivolumab;
- 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 84 compares a range of model results with available corresponding clinical data for validation. Figure 77 presents the OS for ipilimumab based on a pooled analysis of 1,861 patients from 12 trials over a 10-year period.[51] The OS estimated by the model for ipilimumab (as shown in Figure 53 and Figure 57 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. The estimated treatment effect for nivolumab versus ipilimumab is comparable to the observed PFS within the 067 trial.

Figure 77: Pooled OS for ipilimumab[51]



The recent ipilimumab NICE appraisal (TA319[4]) investigated the cost effectiveness of ipilimumab compared to vemurafenib and DTIC for previously untreated advanced melanoma patients. Though the methods and trial data sources used are different, the cost-effectiveness results and conclusions of ipilimumab compared to vemurafenib and DTIC from the PAS-based base case in this analysis are comparable to this recent appraisal.

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 best use the available data and optimally capture the unique characteristics of emerging immunotherapy treatments, including nivolumab, 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 nivolumab and relevant comparators through the use of a bespoke patient-level covariate-adjusted indirect treatment comparison 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[12], 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 nivolumab 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 DTIC and BRAF inhibitors are in line with previous published cost-effectiveness literature.[4]

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 nivolumab 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 nivolumab is cost effective compared to ipilimumab and DTIC 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[74] and these are presented in Table 99. 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.[29]

Table 99: Estimates of incident population

Parameters		**Estimate**	**Source**
Total population of England		53,865,800	England mid-2013 population (ONS)[85]
Annual newly diagnosed of melanoma	Males	0.0210%	Cancer registrations 2012[29]
	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[74]
Percentage increase in incidence per year		3.5%	Decision Resources Malignant Melanoma June 2006[236]
Annual newly diagnosed of advanced melanoma (in 2013)		1,176	Calculated
% of BRAF mutation-positive		48%	Long et al. (2011)[69]
BRAF mutation-negative		612	Calculated
BRAF mutation-positive		565	Calculated
Proportion of patient require subsequent line treatments		21%	Ipilimumab NICE TA268[75]

The number of patients eligible for treatment with nivolumab was calculated as the proportion of malignant melanoma patients with stage IIIc or IV malignant melanoma from the overall incidence.[29]

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.[69] The increase in incidence per year was assumed to be 3.5%.[236]

The total numbers of eligible patients from Year 1 to Year 5 (2016 to 2020) are shown in Table 100.

Table 100: Population eligible for treatment with nivolumab 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 nivolumab.

- It was assumed that all patients are tested for BRAF mutation-status.[74]
- 0% are treated through clinical trials.[74]
- 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.

6.3 Assumptions made about market share in England

The estimated market share of nivolumab and each modelled comparator drug is shown in Table 101. For BRAF mutation-negative patients, the market share of nivolumab is expected to be [redacted] (first line) and [redacted] (subsequent lines) in 2016, rising to [redacted] and [redacted] in 2017. For BRAF mutation-positive patients, the market share is expected to be [redacted] and [redacted] in 2016, rising to [redacted] and [redacted] in 2017. Due to limited forecasts, the market shares projected for 2018 to 2020 are assumed to be the same at those for 2017

The assumed market share in the absence of nivolumab is estimated by increasing the market share of the remaining treatments by the same percentage to reach the overall 100% limit. The estimated total number of new patients treated with nivolumab is [redacted] for first line and subsequent lines, respectively) in 2016 and [redacted] for first line and subsequent lines) in 2020.

Table 101: 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)	678	702	727	752	778
Nivolumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DTIC (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DTIC (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRAF mutation-positive (first line)					
Expected number of BRAF mutation-positive patients (first line)	626	648	671	694	718
Nivolumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab (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]
BRAF mutation-negative (subsequent lines)					
Expected number of BRAF mutation-negative patients (subsequent lines)	142	147	153	158	163
Nivolumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DTIC (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DTIC (patient numbers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRAF mutation-positive (subsequent lines)					
Expected number of BRAF mutation-positive patients (subsequent lines)	131	136	141	146	151
Nivolumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab (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]

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.

The differential costs considered, both budget impact and budget savings, are incorporated as the incremental costs as calculated 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 nivolumab is introduced is estimated to be £106.1 million (£10.7 million for patients treated with nivolumab) and £154.2 million (£72.5 million for patients treated with nivolumab) in the years 2016 and 2020, respectively, in the base case (list price), with net budget impact of £-0.1 million and £21.3 million in 2016 and 2020. Based on base case with PAS assumed for the comparators, the gross budget is estimated to be £74.8 million (£10.1 million for patients treated with nivolumab) and £123.8 million (£68.1 million for patients treated with nivolumab) in 2016 and 2020, with net budget impact of £2.7 million and £32.8 million in year 2016 and 2020.

The detailed net budget impact in the base case (with list price) is shown in Table 103 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 104 and Table 105.

Table 102: Estimated net budget impact over 5 years (BRAF mutation-negative patients) – base case (list price)

	2016	2017	2018	2019	2020
Drug costs	-£534,783	£9,584,448	£16,342,060	£16,909,556	£17,498,240
Drug admin costs	£346,050	£1,536,640	£2,217,961	£2,265,847	£2,324,213
Subsequent ipi costs	£757,980	£750,185	£1,905,840	£3,344,296	£3,440,668
Treatment initiation	£0	£0	£0	£0	£0
Pre-palliative care	£38,842	£268,414	£493,825	£647,897	£794,288
Palliative care	-£48,482	-£255,909	-£268,176	-£249,875	-£244,040
End of life care	-£25,900	-£142,189	-£155,487	-£145,181	-£140,971
AE costs	£5,659	£51,367	£71,723	£72,897	£74,976
Total costs	**£539,364**	**£11,792,956**	**£20,607,747**	**£22,845,437**	**£23,747,374**

Table 103: Estimated net budget impact over 5 years (BRAF mutation-positive patients) – base case (list price)

	2016	2017	2018	2019	2020
Drug costs	-£1,036,418	-£3,643,603	-£2,826,102	-£4,272,308	-£5,249,252
Drug admin costs	£258,027	£1,199,049	£1,617,620	£1,674,236	£1,732,835
Subsequent ipi costs	£116,599	£358,288	£536,204	£1,003,988	£981,156
Treatment initiation	£0	£0	£0	£0	£0
Pre-palliative care	£5,247	£37,722	£114,525	£177,111	£239,666
Palliative care	-£20,944	-£93,641	-£124,896	-£124,751	-£129,133
End of life care	-£8,862	-£41,461	-£63,014	-£62,915	-£64,711
AE costs	£7,140	£33,941	£42,386	£40,832	£41,133
Total costs	**-£679,212**	**-£2,149,704**	**-£703,278**	**-£1,563,807**	**-£2,448,306**

Table 104: Estimated net budget impact over 5 years (BRAF mutation-negative patients) – assuming PAS drug prices for comparator treatments

Table 105: Estimated net budget impact over 5 years (BRAF mutation-positive patients) – assuming PAS drug prices for comparator treatments

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8 Appendices

These are provided as separate documents to the main submission.

Appendix 1: European public assessment report, SmPC/IFU, scientific discussion or drafts (Section 2.2)

Appendix 2: Search strategy for relevant (RCT and non-RCT) studies

Appendix 3: Quality assessment of clinical trials (Section 4.6, Section 4.10 & Section 4.11)

Appendix 4: American Joint Committee on Cancer staging system (Section 3.1)

Appendix 5: Reference list of citations excluded at secondary screening in RCT review (Section 4.1)

Appendix 6: Tools used to assess health-related quality of life (HRQL) (Section 4.7)

Appendix 7: Subgroup analysis for CheckMate 067 and 037

Appendix 8: Survival analyses

Appendix 9: Search strategy for cost-effectiveness studies

Appendix 10: Search strategy for measurement and valuation of health effects (Section 5.4)

Appendix 11: Cost and healthcare resource identification, measurement and valuation (Section 5.5)

Appendix 12: Comparison of modelled and observed OS based on MDX010-20

Appendix 13: Health-related quality of life systematic search results

Appendix 14: Utility analysis using patient-level EQ-5D data from CheckMate 066

Appendix 15: Cost and resource use systematic search results

Appendix 16: OWSA results for PAS-based base case

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Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID845]

Dear [redacted]

The Evidence Review Group, Southampton Health Technology Assessments Centre (SHTAC), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 26th August 2015 by Bristol Myers Squibb Pharmaceuticals. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 1st October 2015. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link: <<Insert NICE DOCS LINK>>.

If you have any further queries on the technical issues raised in this letter then please contact [redacted], Technical Adviser. Any procedural questions should be addressed to [redacted], Project Manager in the first instance.

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation
Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

A1. Please explain whether any of the patients enrolled in the CheckMate 066 trial were from the UK, and if so what proportion (Table 11 mentions 'Europe' and we note that the lead author of the journal publication is from the UK).

A2. In CheckMate 037 and 067, please explain how many UK centres participated, and how many UK patients were enrolled in each of these trials. Please provide baseline characteristics for UK patients enrolled in CheckMate 037, 067, and (if any) 066.

A3. **Priority question:** On pages 98 to 121 of the company's submission, the method of analysing patient-level data is implied in several places but it is not explicitly stated. To avoid any possible ambiguity about the analysis approach, please provide a precise description of how the patient-level data were analysed.

A4. Please explain the criteria for unsuitability to ipilimumab and to BRAF inhibitors (mentioned in various parts of the company submission). What proportion of patients with advanced melanoma would this represent?

A5. Please explain how the survival model estimated the weights to attach to each covariate when fitting survival curves (shown in Table 21 of the company submission appendices). Please provide references to support the use of this methodology.

A6. **Priority question:** Please supply EQ-5D index utility score data for the respective trial arms in the CheckMate 066 and the CheckMate 037 trials for the baseline and follow-up visits, and any statistical significance testing of these. Please also supply EORTC QLQ-C30 score data for the respective trial arms in the CheckMate 066 trial and the CheckMate 037 for the baseline and follow-up visits, and any statistical significance testing of these.

A7. The company's submission page 47 states that HRQoL analyses are not currently available for CheckMate 067. Please specify when these will be available.

A8. **Priority question:** The company's submission states that the OS data in the CheckMate 067 trial are not yet available and therefore this study is not included in the direct or indirect estimation of treatment effects (page 94). Please clarify when OS data from this trial will be available.

A9. In addition, the company's submission states that OS data for the CheckMate 066 trial are relatively immature. Therefore, rather than making survival extrapolations based on OS, an alternative approach was taken using time to progression, pre-progression survival, and post-progression survival instead of OS and TTP. It is not stated whether this approach was possible for the CheckMate 067 trial, which would thus allow this trial to be used in the analysis and therefore obviate the need for an

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indirect comparison of ipilimumab and nivolumab. Please explain whether this is possible, and if so provide an analysis of cost effectiveness using this trial.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please clarify how the utility values have been calculated. In addition, please explain the difference between the baseline EQ-5D baseline value of 0.6030 and that of 0.72 (both shown in Table 66) and state which of these has been used in the calculation of the utility values.

B2. **Priority question:** Please provide an analysis comparing nivolumab with DTIC using the Checkmate 066 trial data only, without adjusting survival curves for covariates.

B3. The utility decrements listed in Table 65 are reported to be from Beusterien et al (2009) but we are unable to find these estimates in that publication. Please clarify how these decrements have been derived.

B4. If possible, please provide an analysis that shows the utility data from checkmate 066 tabulated in the following format: mean utility for patients treated with nivolumab who have not progressed; mean utility for patients treated with nivolumab who have progressed; mean utility for patients treated with DTIC who have not progressed; mean utility for patients treated with DTIC who have progressed.

B5. Please clarify how the numbers of adverse events from checkmate 066 in Table 61 have been derived and how they differ from those presented in Table 47.

Section C: Textual clarifications and additional points

None

Single Technology Appraisal (STA)
Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID845]

Company response to clarification questions - 1st October 2015

Section A: Clarification on effectiveness data

A1. Please explain whether any of the patients enrolled in the CheckMate 066 trial were from the UK, and if so what proportion (Table 11 mentions 'Europe' and we note that the lead author of the journal publication is from the UK).

No UK trial centres or UK patients participated in the Checkmate 066 trial, although James Larkin from the Royal Marsden Hospital was involved in designing the trial. The lead author of the journal publication, Caroline Robert, is French.

A2. In CheckMate 037 and 067, please explain how many UK centres participated, and how many UK patients were enrolled in each of these trials. Please provide baseline characteristics for UK patients enrolled in CheckMate 037, 067, and (if any) 066.

There were 5 UK trial centres in Checkmate 037 and 43 UK patients were randomised to treatment (see Table S.2.1. Checkmate 037 CSR). Demographic and baseline characteristics for the randomised UK subjects are provided in Appendix A of this response.

7 UK trial centres participated in the Checkmate 067 trial. 93 UK patients were randomised to treatment (from a total number randomised of 945, see Table S.2.1. Checkmate 067 CSR). Demographic and baseline characteristics for the randomised UK subjects are provided in Appendix B of this response.

A3. Priority question: On pages 98 to 121 of the company's submission, the method of analysing patient-level data is implied in several places but it is not explicitly stated. To avoid any possible ambiguity about the analysis approach, please provide a precise description of how the patient-level data were analysed.

Section 4.10 of the company's submission describes the strategy and analyses performed to construct treatment comparisons with palliative chemotherapy, ipilimumab and BRAF inhibitors. There are multiple occasions where patient level data were analysed using different data, models/methods and for different endpoints. These are referred to in Section 12 of the company's submission, but are also summarised more explicitly in Table 1 below.

The three types of patient level data analyses used are parametric survival modelling, Cox proportional hazards regression modelling, and Kaplan-Meier techniques. The parametric and Cox survival models were adjusted for treatment, trial and other covariates. The covariates included in the models are summarised in Table 27 of the company's submission.

Parametric survival modelling was performed using R, and specifically the function 'flexsurvreg'. Parametric survival modelling included separate analyses for 6 different parametric distributions; exponential, Weibull, log-Normal, log-logistic, Gompertz, and generalised gamma. The Cox proportional hazards modelling was performed in SAS using the procedure PHREG. The Kaplan-Meier analyses were performed in SAS using the procedure LIFETEST.

Pseudo patient level data analyses were performed for the BRAF inhibitor data. The pseudo patient level data was created by digitisation of published Kaplan-Meier curves. Parametric survival modelling was then performed using R, and specifically the function 'flexsurvreg'.

Table 1. Summary of patient level data analyses

Treatments included	Trials included	Endpoint	Method	Purpose	Reference in company's submission
Nivolumab DTIC Ipilimumab GP100	CheckMate 066 MDX010-20	TTP	KM	To evaluate strategy for PM for TTP	Figures 28, 29, 30
Nivolumab DTIC Ipilimumab GP100	CheckMate 066 MDX010-20	TTP pre 100 days	CPH	To estimate TTP in a non-parametric way (given the KM shape) pre 100 days	Table 30
Nivolumab DTIC Ipilimumab GP100	CheckMate 066 MDX010-20	TTP post 100 days	PM	To estimate TTP post 100 days, enabling extrapolations of survival curves	Figure 31
Nivolumab DTIC Ipilimumab GP100	CheckMate 066 MDX010-20	PostPS	KM	To evaluate strategy for PM for PostPS	Figure 32
Nivolumab DTIC Ipilimumab GP100	CheckMate 066 MDX010-20	PostPS	PM	To estimate PostPS, enabling extrapolations of survival curves	Figure 33
Nivolumab DTIC Ipilimumab GP100	CheckMate 066 MDX010-20	PrePS	KM	To evaluate strategy for PM for PrePS	Figure 34
Nivolumab DTIC Ipilimumab GP100	CheckMate 066 MDX010-20	PrePS	CPH	To estimate PrePS in a non-parametric way (given the KM shape and lack of events)	Table 35
Nivolumab DTIC	CheckMate 066	TTP post 100 days	CPH	To estimate HR for use in an adjusted indirect comparison of nivolumab versus ipilimumab	Table 36
Nivolumab DTIC	CheckMate 066	PostPS	CPH	To estimate HR for use in an adjusted indirect comparison of nivolumab versus ipilimumab	Table 36
Nivolumab DTIC	CheckMate 066	OS	CPH	To estimate HR for use in an adjusted indirect comparison of nivolumab versus ipilimumab	Table 36

Treatments included	Trials included	Endpoint	Method	Purpose	Reference in company's submission
Nivolumab DTIC	CheckMate 066	PFS	CPH	To estimate HR for use in an adjusted indirect comparison of nivolumab versus ipilimumab	Table 36
Ipilimumab GP100	MDX010-20	TTP post 100 days	CPH	To estimate HR for use in an adjusted indirect comparison of nivolumab versus ipilimumab	Table 36
Ipilimumab GP100	MDX010-20	PostPS	CPH	To estimate HR for use in an adjusted indirect comparison of nivolumab versus ipilimumab	Table 36
Ipilimumab GP100	MDX010-20	OS	CPH	To estimate HR for use in an adjusted indirect comparison of nivolumab versus ipilimumab	Table 36
Ipilimumab GP100	MDX010-20	PFS	CPH	To estimate HR for use in an adjusted indirect comparison of nivolumab versus ipilimumab	Table 36
Vemurafenib	BRIM-3[a]	OS	PM	To estimate OS and extrapolations for BRAF inhibitors	Figure 38
Vemurafenib	BRIM-3[a]	PFS	PM	To estimate PFS and extrapolations for BRAF inhibitors	Figure 39

Key: CPH, Cox proportional hazards modelling; HR, hazard ratio; KM, Kaplan Meier; OS, overall survival; PFS, progression free survival; PM, parametric modelling, PostPS, post progression survival; PrePS, pre progression survival; TTP, time to progression
Notes: [a], pseudo patient level data created using digitization of published KM curves

A4. Please explain the criteria for unsuitability to ipilimumab and to BRAF inhibitors (mentioned in various parts of the company submission). What proportion of patients with advanced melanoma would this represent?

A patient's suitability to ipilimumab will be based on clinical assessment, including the patient's overall fitness and the speed and extent of the disease. It is generally accepted that in order to gain the maximum benefit from ipilimumab patients should be fit enough to receive all four cycles over a 12 week period. If clinical assessment is such that the patients are likely to deteriorate quickly over the next 12 weeks, then patients are less likely to be suitable for treatment with ipilimumab, and an alternative treatment choice may be made.

Patients will be unsuitable for treatment with BRAF inhibitors if, at a molecular level, their melanoma is not driven by a BRAF mutation. BRAF inhibitors are only effective in this circumstance, which accounts for approximately 50% of the melanoma population.

As stated in the company's submission, as both the BRAF inhibitors (dabrafenib, vemurafenib) and ipilimumab are licensed and recommended for use in both the first- and second-line setting in England, patients with BRAF mutation-positive melanoma who fail to respond to BRAF inhibitor therapy can be switched to ipilimumab, and vice versa.

For the remaining 50% of the advanced melanoma population who are BRAF mutation-negative (wild-type), BRAF inhibitors are not appropriate treatment options. Of these, UK clinicians participating in a BMS-led scientific advisory board meeting concluded that 0%-20% would not be suitable for ipilimumab either, and might therefore receive palliative chemotherapy instead.

A5. Please explain how the survival model estimated the weights to attach to each covariate when fitting survival curves (shown in Table 21 of the company submission appendices). Please provide references to support the use of this methodology.

When producing predicted survival curves to assess model fit (as displayed in figure 31 of the company's submission for TTP post 100 days and figure 33 for PostPS), the mean observed covariate values observed in the trials were applied to the fitted parametric models. As all covariates were dichotomous, the values used in the predictions were the proportions (0 to 1) for the non-reference category of the covariate. The actual values used in these models are shown in tables 2 and 3 below. Separate covariate proportions are used by trial, treatment, and outcome. The covariates were the observed proportions of each covariate for the patients included in the analysis (of TTP post 100 days and, separately, PostPS) for the given trial and treatment group.

Table 2. Covariate proportions used for model parametric model fit assessment for TTP post 100 days

Covariate	Levels	Nivol-umab	DTIC	Ipilim-umab	Gp100
Treatment	Ipilimumab vs palliative chemotherapy	0	0	1	0
Treatment	Nivolumab vs palliative chemotherapy	1	0	0	0
Trial	CheckMate 066 vs MDX010-20	1	1	0	0
Gender	Male vs female	0.6204	0.5455	0.5724	0.6522
Age group	<65 vs ≥65	0.4722	0.5455	0.6645	0.6087
LDH	>ULN vs ≤ULN	0.2685	0.2727	0.2566	0.2174
Baseline ECOG	0 vs ≥1	0.7315	0.6212	0.5921	0.6522
M stage	M1c vs 'M0 or M1a or M1b'	0.5556	0.6061	0.6711	0.6957
History of brain metastases	Yes vs no	0.0370	0.0758	0.0987	0.1304

Covariate	Levels	Nivol-umab	DTIC	Ipilim-umab	Gp100
Use of subsequent ipilimumab (for the PPS outcome only)	Yes vs no	0	0	0	0
Key: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; NA, not applicable, ULN, upper limit of normal range. **Notes:** The underlined covariate levels indicate which were used as reference categories in the survival models.					

Table 3. Covariate proportions used for model parametric model fit assessment for PostPS

Covariate	Levels	Nivol-umab	DTIC	Ipilim-umab	Gp100
Treatment	Ipilimumab vs palliative chemotherapy	0	0	1	0
Treatment	Nivolumab vs palliative chemotherapy	1	0	0	0
Trial	CheckMate 066 vs MDX010-20	1	1	0	0
Gender	Male vs female	0.5161	0.6159	0.5979	0.5300
Age group	<65 vs ≥65	0.5699	0.4565	0.7311	0.7100
LDH	>ULN vs ≤ULN	0.4194	0.3188	0.3133	0.3100
Baseline ECOG	0 vs ≥1	0.7097	0.6739	0.6371	0.5900
M stage	M1c vs 'M0 or M1a or M1b'	0.6022	0.6377	0.6919	0.6700
History of brain metastases	Yes vs no	0.0215	0.0507	0.1018	0.1700
Use of subsequent ipilimumab	Yes vs no	0.4624	0.4855	0	0
Key: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; NA, not applicable, ULN, upper limit of normal range. **Notes:** The underlined covariate levels indicate which were used as reference categories in the survival models.					

When including the survival curves in the economic model, the baseline characteristics for CheckMate-066, pooled across treatment arms were applied for both TTP post 100 days and PostPS as shown in Table 4 below.

Table 4. Covariate proportions used for model parametric model projection in economic model for TTP post 100 days and PostPS

Covariate	Levels	Nivolumab	Ipilimumab	Palliative chemotherapy
Treatment	Ipilimumab vs palliative chemotherapy	0	1	0
Treatment	Nivolumab vs palliative chemotherapy	1	0	0
Trial	CheckMate 066 vs MDX010-20	1	1	1
Gender	Male vs female	0.5885	0.5885	0.5885
Age group	<65 vs ≥65	0.4785	0.4785	0.4785
LDH	>ULN vs ≤ULN	0.3844	0.3844	0.3844
Baseline ECOG	0 vs ≥1	0.6451	0.6451	0.6451
M stage	M1c vs 'M0 or M1a or M1b'	0.6100	0.6100	0.6100
History of brain metastases	Yes vs no	0.0359	0.0359	0.0359
Use of subsequent ipilimumab (for the PostPS outcome only)	Yes vs no	0.2967	0.2967	0.2967

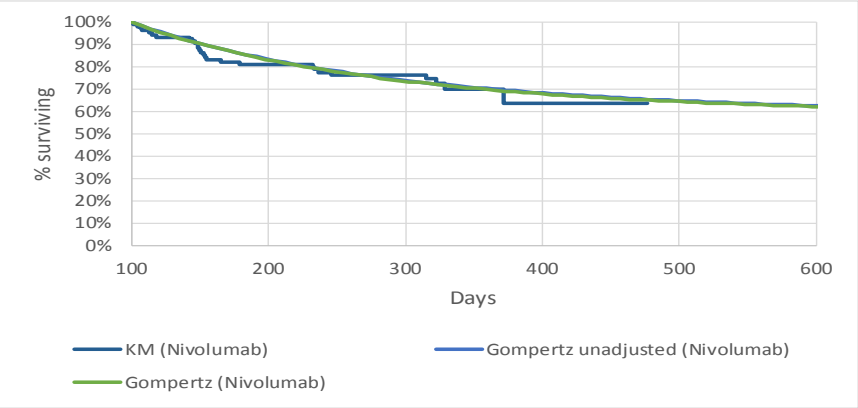
Key: ECOG, Eastern Cooperative Oncology Group score; LDH, lactate dehydrogenase; NA, not applicable, ULN, upper limit of normal range.
Notes: The underlined covariate levels indicate which were used as reference categories in the survival models.

The use of the mean of covariates method to form parametric model predictions has been identified as problematic in some cases[1]. We have adopted the mean of covariates method for our model as we needed to utilise our covariate adjusted models to adjust our models to the population identified for the BRAF inhibitors for that particular comparison, and for that comparison the alternative methodology (corrected group prognosis method) is not possible given the lack of data for the exact distribution of patients for each of the covariates in the BRIM-3 trial.

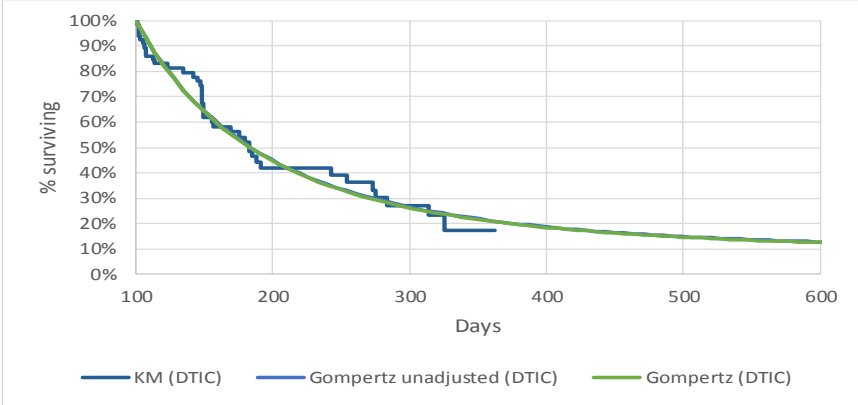
Within our analysis the use of the mean of covariates method has not been shown to be problematic, evidenced by the good fit of the curves compared to the KM data. In addition Figures 1 and 2 below present both the adjusted and covariate-unadjusted curves for the selected models for TTP post 100 days and PostPS. The absence of major differences between these curves gives us additional confidence in the application of the mean of covariates method for our analyses.

Figure 1. Parametric models for TTP post 100 days both unadjusted and adjusted for covariates

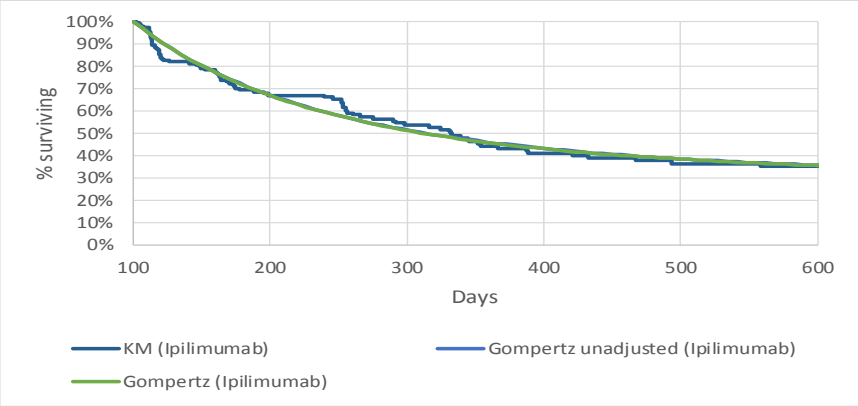
Time to progression post 100 days (day 0=day 100) - Nivolumab



Time to progression post 100 days (day 0=day 100) - DTIC



Time to progression post 100 days (day 0=day 100) - Ipilimumab



Time to progression post 100 days (day 0=day 100) - GP100

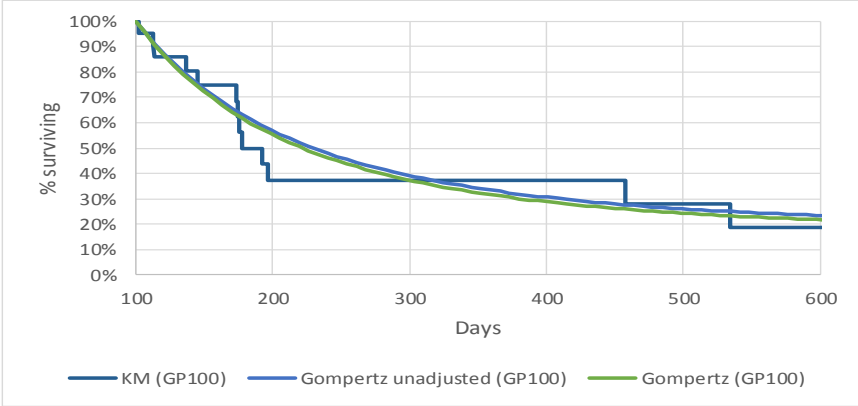
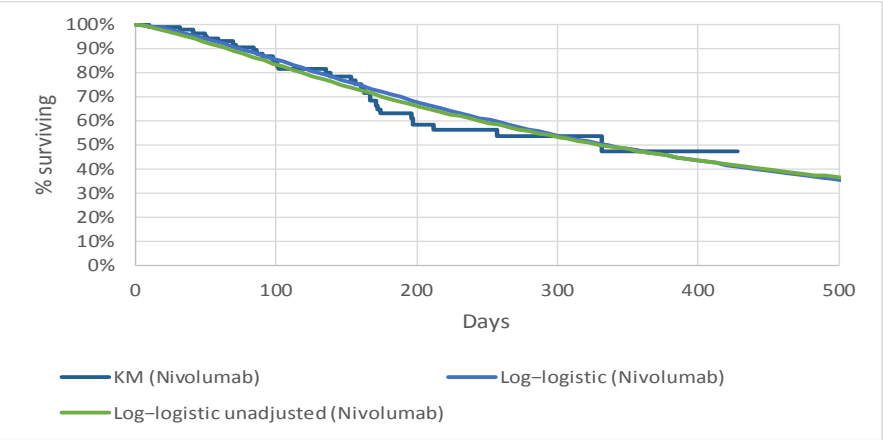
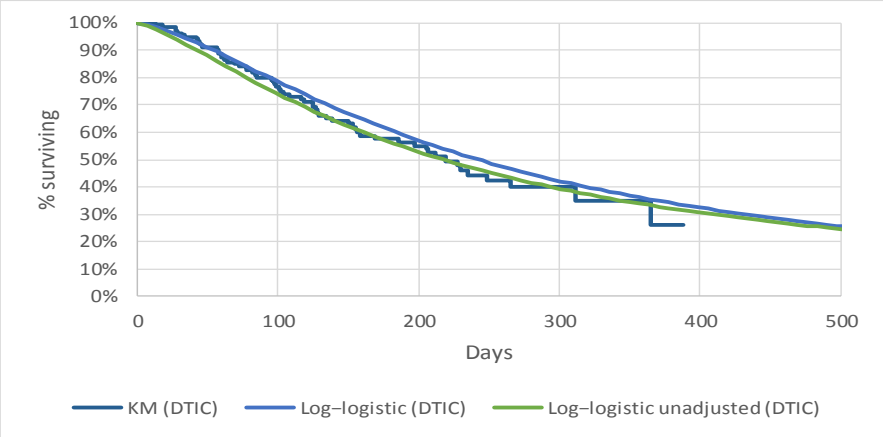


Figure 2. Parametric models for PostPS both unadjusted and adjusted for covariates

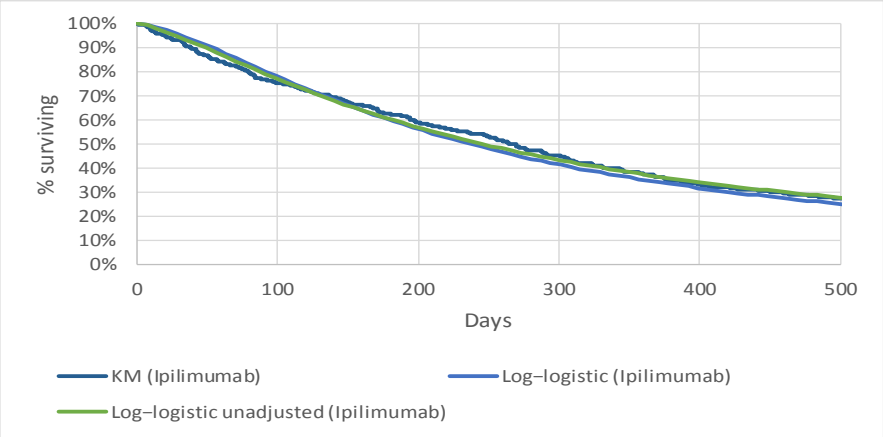
Post progression survival - Nivolumab



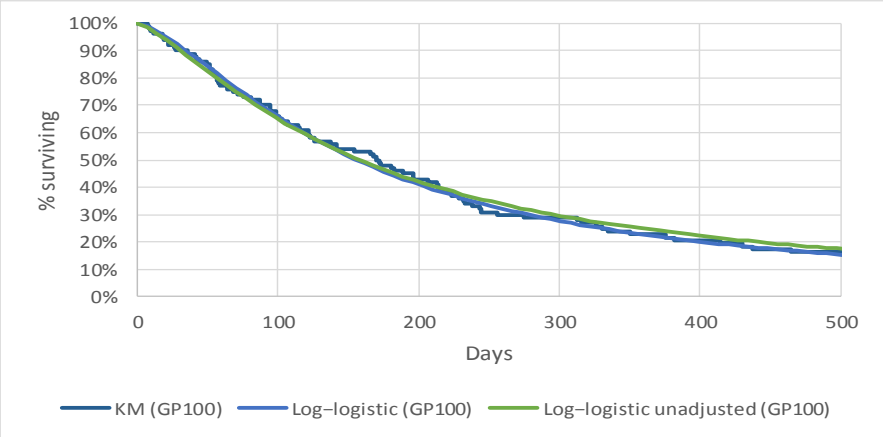
Post progression survival - DTIC



Post progression survival - Ipilimumab



Post progression survival - GP100



A6. Priority question: Please supply EQ-5D index utility score data for the respective trial arms in the CheckMate 066 and the CheckMate 037 trials for the baseline and follow-up visits, and any statistical significance testing of these. Please also supply EORTC QLQ-C30 score data for the respective trial arms in the CheckMate 066 trial and the CheckMate 037 for the baseline and follow-up visits, and any statistical significance testing of these.

Utility score data from Checkmate 066 are provided herewith and were reported in the poster authored by Long et al, included in the company's submission. Further detail is provided below as requested.

CheckMate 066 EQ-5D Utility Index
The mean (SD) EQ-5D utility score was higher at baseline for nivolumab (0.778 [0.215]) than for dacarbazine (0.711 [0.310]), and remained consistently higher over time versus dacarbazine. Significant improvements were observed in the nivolumab treatment group through to week 49, with the most significant improvements ($p<0.001$) observed at week 13 (mean=0.075; n=105), week 25 (mean=0.076; n=72), and week 37 (mean=0.084; n=53). There were no significant improvements observed for the dacarbazine treatment group at any time point during the study. Of note, improvement for nivolumab at week 37 was greater than the MID for this scale (0.08), indicating clinically meaningful improvement. The EQ-5D utility index means by treatment arm and the EQ-5D change from baseline means are presented below in Figure 3 and Figure 4, respectively.

Figure 3. EQ-5D Utility Index: Means and Standard Errors Over Time by Treatment Arm: All Randomised Subjects Population

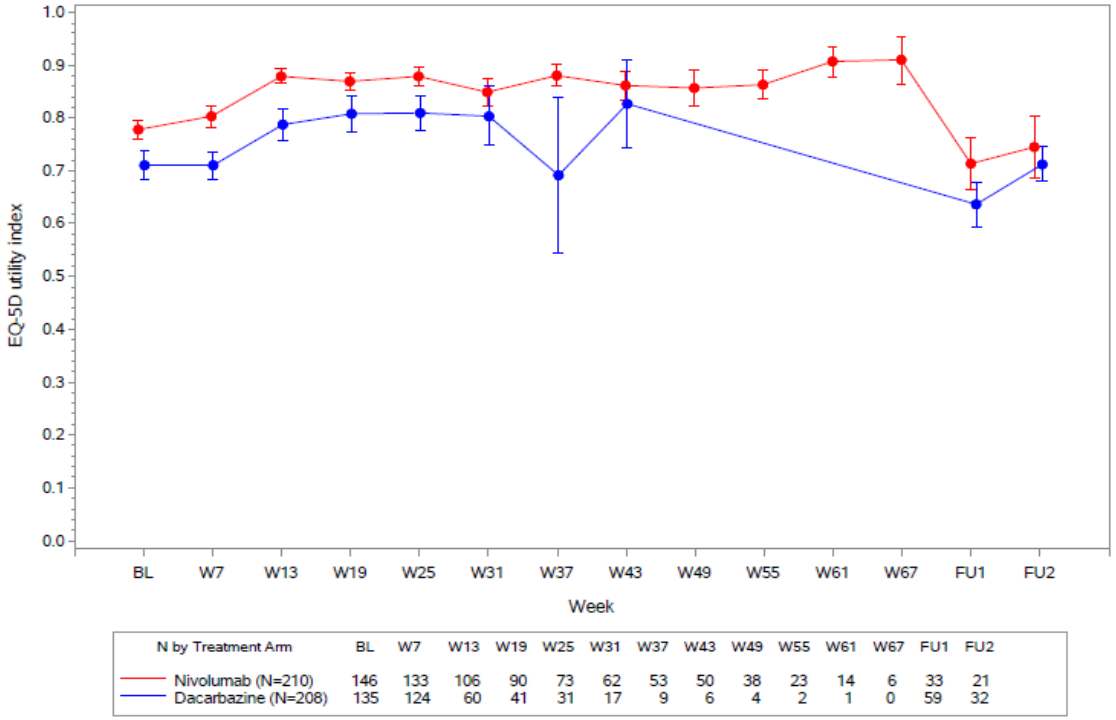
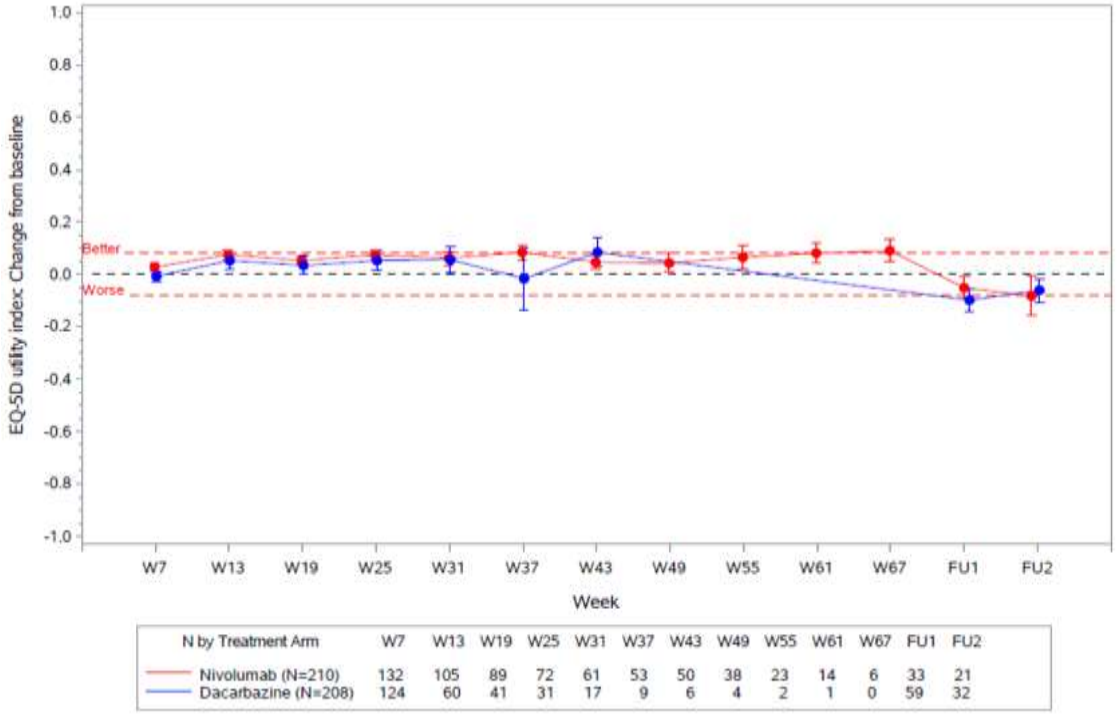


Figure 4. EQ-5D Utility Index: Change From Baseline Means and Standard Errors Over Time by Treatment Arm according to MID: All Randomised Subjects Population



CheckMate 066 EORTC-QLQC30 Global Health Status/QoL

Mean (SD) global health status/QoL at baseline was 68.9 (20.2) for nivolumab and 66.2 (25.1) for dacarbazine. Mean changes from baseline that occurred starting at week 7 were modest, with a trend towards improvement in both treatment groups, but these improvements were neither statistically significant nor clinically meaningful within each treatment group At week 25, global health status/QoL showed a trend towards worsening in the dacarbazine group (mean=-1.6; SD=20.3); however, the change from baseline was neither statistically significant nor clinically meaningful. Mean scores and changes from baseline for the global health status/QoL scale are summarised in Figure 5 and Figure 6, respectively.

Figure 5. EORTC QLQ-C30 Global Health Status/QoL Means and Standard Errors Over Time by Treatment Arm: All Randomised Subjects Population

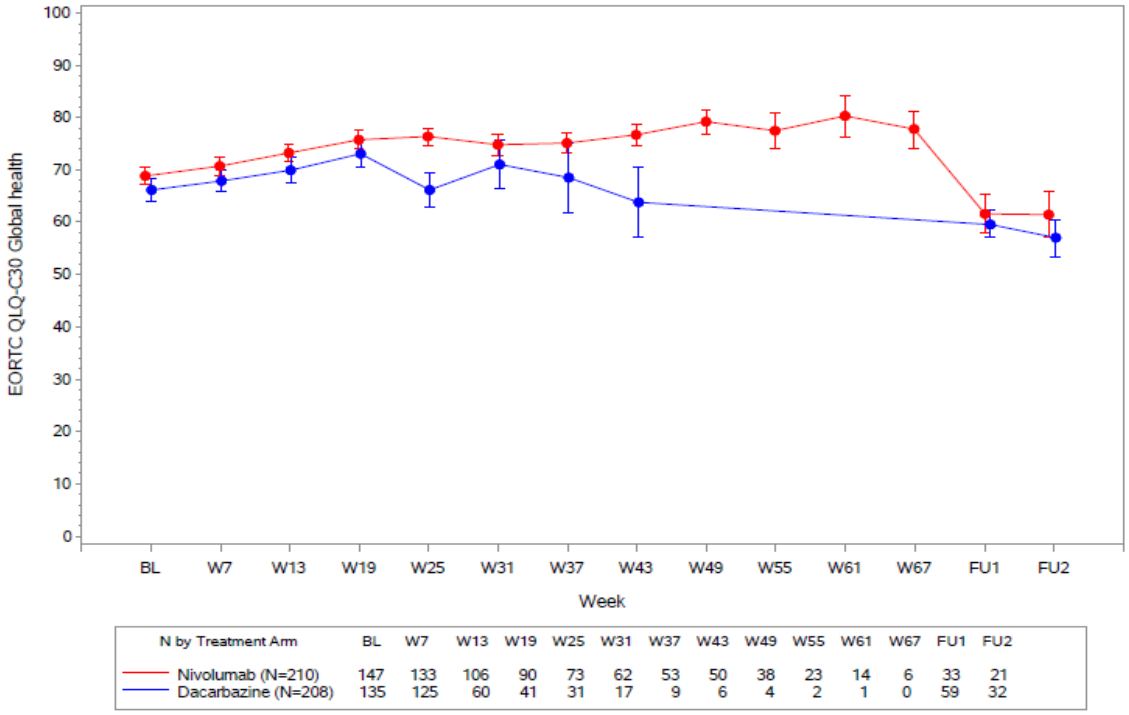
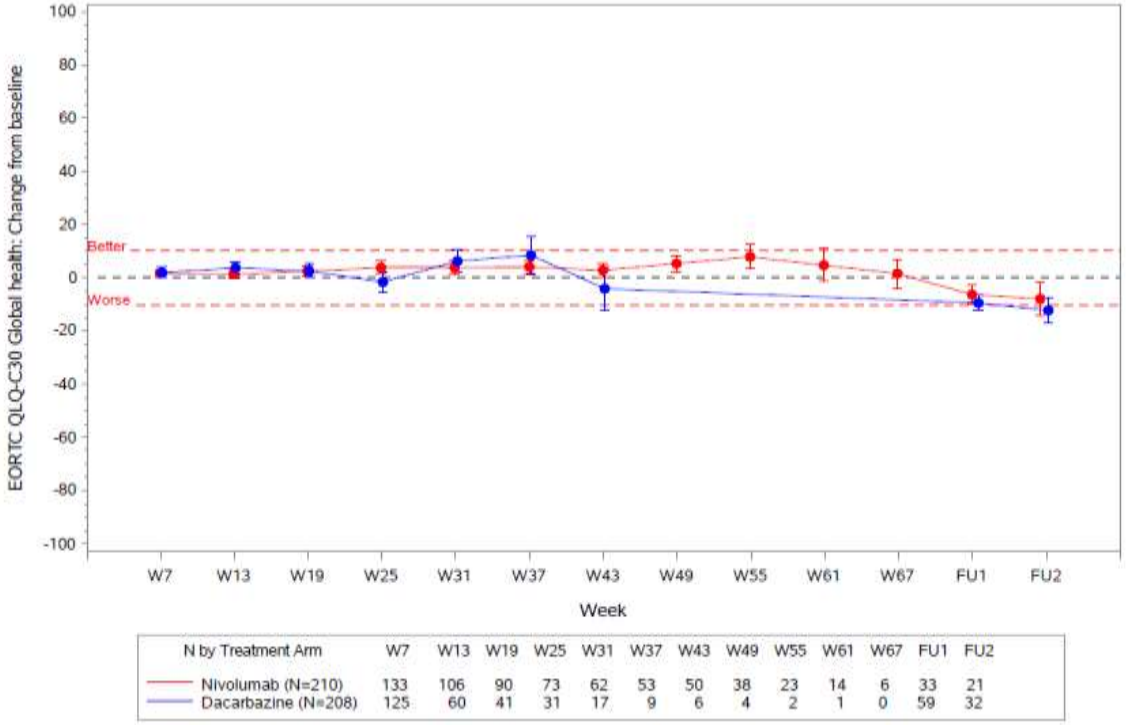


Figure 6. EORTC QLQ-C30 Global Health Status/QoL: Change From Baseline Means and Standard Errors Over Time by Treatment Arm according to MID: All Randomised Subjects Population



CheckMate 066 EORTC-QLQ C30 Symptom Scales

Symptom burden remained relatively stable over time in the two treatment groups, but there were some statistically significant and clinically meaningful changes observed (Table 5). The nivolumab treatment arm experienced statistically significant improvement in insomnia and appetite loss; the improvement in insomnia was clinically meaningful at weeks 55 and 61. The dacarbazine treatment arm also showed some statistically significant improvements in insomnia

and pain; although the improvement in pain was clinically meaningful at week 31, this result should be interpreted with caution given the high attrition rate for dacarbazine by this time point. The dacarbazine arm showed significant deterioration at week 7 in fatigue and dyspnoea; however, this deterioration was not clinically meaningful. At both follow-up visits, both treatment arms experienced significant and/or clinically meaningful deterioration in symptoms.

Table 5. Statistically Significant or Clinically Meaningful Changes From Baseline for EORTC QLQ-C30 Symptom Scales

Subscale	Mean Change From Baseline							
	Week 7	Week 13	Week 19	Week 31	Week 55	Week 61	Follow-up 1	Follow-up 2
Fatigue	DTIC: 3.6*						NIVO: 15.8*† DTIC: 13.7*†	NIVO: 20.1*† DTIC: 15.6*†
Nausea and vomiting							DTIC: 4.0*	DTIC: 6.2*
Pain			DTIC: -4.9*	DTIC: -10.8†			NIVO: 7.6* DTIC: 9.9*	DTIC: 10.4*†
Dyspnoea	DTIC: 4.5*							
Insomnia	DTIC: -4.0*	NIVO: -5.0*			NIVO: -11.6*†	NIVO: -16.7†	DTIC: 7.9*	NIVO: 12.7† DTIC: 10.4†
Appetite loss		NIVO: -6.9*					NIVO: 10.1*† DTIC: 10.7*†	NIVO: 23.8*†
Constipation							DTIC: 9.6*	
Diarrhoea								NIVO: 19.0†
Financial difficulties							DTIC: 9.0*	

*Statistically significant change within treatment arm
†Clinically meaningful change based on MID (10 point change)
Note: Mean change scores are only presented where statistically significant or clinically meaningful changes were observed within treatment arm(s)
Nivo=nivolumab; DTIC=dacarbazine

Full quality of life data from Checkmate 037 is not yet available. Some very preliminary analyses have been undertaken in a small cohort of patients used for the ORR analysis. The complete analyses will be conducted on the final OS data cut towards the beginning of 2016 and will coincide with the complete final OS analysis. The preliminary information currently available is provided in

Table 1 and Table 2 below.

Table 1. Descriptive statistics for the EQ-5D Utility Index using the ORR sample randomised to treatment

	Overall (N=167)		Nivolumab 3 mg/kg (N=120)		Investigator's Choice (N=47)	
	Timepoint	Change from	Timepoint	Change from	Timepoint	Change from
EQ-5D Utility Score (UK): Baseline						
N	105	---	80	---	25	---
Median (Q1 - Q3)	0.796 (0.691, 1.000)	---	0.796 (0.691, 1.000)	---	0.725 (0.691, 0.883)	---
Mean (SD)	0.782 (0.212)	---	0.776 (0.232)	---	0.802 (0.130)	---
Minimum - Maximum	-0.005 - 1.000	---	-0.005 - 1.000	---	0.620 - 1.000	---
Missing	62 (37.1%)	---	40 (33.3%)	---	22 (46.8%)	---
95% CI	(0.741, 0.823)	---	(0.724, 0.827)	---	(0.749, 0.856)	---
EQ-5D Utility Score (UK): Week 3						
N	22	22	---	---	22	22
Median (Q1 - Q3)	0.796 (0.691, 0.883)	0.000 (-0.069, 0.000)	---	---	0.796 (0.691, 0.883)	0.000 (-0.069, 0.000)
Mean (SD)	0.795 (0.132)	-0.022 (0.101)	---	---	0.795 (0.132)	-0.022 (0.101)
Minimum - Maximum	0.587 - 1.000	-0.263 - 0.204	---	---	0.587 - 1.000	-0.263 - 0.204
Missing	145 (86.8%)	145 (86.8%)	---	---	25 (53.2%)	25 (53.2%)
95% CI	(0.736, 0.853)	(-0.066, 0.023)	---	---	(0.736, 0.853)	(-0.066, 0.023)
EQ-5D Utility Score (UK): Week 4						
N	77	77	77	77	---	---
Median (Q1 - Q3)	0.796 (0.689, 1.000)	0.000 (-0.036, 0.036)	0.796 (0.689, 1.000)	0.000 (-0.036, 0.036)	---	---
Mean (SD)	0.755 (0.282)	-0.014 (0.230)	0.755 (0.282)	-0.014 (0.230)	---	---

	Overall (N=167)		Nivolumab 3 mg/kg (N=120)		Investigator's Choice (N=47)	
	Timepoint	Change from	Timepoint	Change from	Timepoint	Change from
Minimum - Maximum	-0.215 - 1.000	-0.689 - 0.765	-0.215 - 1.000	-0.689 - 0.765	---	---
Missing	90 (53.9%)	90 (53.9%)	43 (35.8%)	43 (35.8%)	---	---
95% CI	(0.691, 0.819)	(-0.066, 0.039)	(0.691, 0.819)	(-0.066, 0.039)	---	---
EQ-5D Utility Score (UK): Week 6						
N	20	20	---	---	20	20
Median (Q1 - Q3)	0.796 (0.691, 1.000)	0.000 (-0.094, 0.107)	---	---	0.796 (0.691, 1.000)	0.000 (-0.094, 0.107)
Mean (SD)	0.797 (0.186)	-0.013 (0.186)	---	---	0.797 (0.186)	-0.013 (0.186)
Minimum - Maximum	0.293 - 1.000	-0.590 - 0.275	---	---	0.293 - 1.000	-0.590 - 0.275
Missing	147 (88.0%)	147 (88.0%)	---	---	27 (57.4%)	27 (57.4%)
95% CI	(0.710, 0.884)	(-0.100, 0.074)	---	---	(0.710, 0.884)	(-0.100, 0.074)
EQ-5D Utility Score (UK): Week 8						
N	68	68	68	68	---	---
Median (Q1 - Q3)	0.804 (0.691, 1.000)	0.000 (-0.062, 0.117)	0.804 (0.691, 1.000)	0.000 (-0.062, 0.117)	---	---
Mean (SD)	0.783 (0.253)	0.003 (0.237)	0.783 (0.253)	0.003 (0.237)	---	---
Minimum - Maximum	-0.181 - 1.000	-0.730 - 0.765	-0.181 - 1.000	-0.730 - 0.765	---	---
Missing	99 (59.3%)	99 (59.3%)	52 (43.3%)	52 (43.3%)	---	---
95% CI	(0.721, 0.844)	(-0.054, 0.060)	(0.721, 0.844)	(-0.054, 0.060)	---	---
EQ-5D Utility Score (UK): Week 9						
N	10	10	---	---	10	10

	Overall (N=167)		Nivolumab 3 mg/kg (N=120)		Investigator's Choice (N=47)	
	Timepoint	Change from	Timepoint	Change from	Timepoint	Change from
Median (Q1 - Q3)	0.691 (0.656, 0.812)	-0.053 (-0.158, 0.000)	---	0.691 (0.656, 0.812)	-0.053 (-0.158, 0.000)	
Mean (SD)	0.757 (0.143)	-0.071 (0.107)	---	0.757 (0.143)	-0.071 (0.107)	
Minimum - Maximum	0.620 - 1.000	-0.263 - 0.087	---	0.620 - 1.000	-0.263 - 0.087	
Missing	157 (94.0%)	157 (94.0%)	---	37 (78.7%)	37 (78.7%)	
95% CI	(0.655, 0.860)	(-0.148, 0.005)	---	(0.655, 0.860)	(-0.148, 0.005)	
EQ-5D Utility Score (UK): Week 12						
N	65	65	56	56	9	9
Median (Q1 - Q3)	0.848 (0.725, 1.000)	0.000 (0.000, 0.087)	0.848 (0.725, 1.000)	0.000 (0.000, 0.102)	0.796 (0.725, 1.000)	0.000 (-0.071, 0.000)
Mean (SD)	0.837 (0.160)	0.039 (0.201)	0.837 (0.162)	0.048 (0.206)	0.839 (0.159)	-0.014 (0.165)
Minimum - Maximum	0.362 - 1.000	-0.452 - 0.912	0.362 - 1.000	-0.452 - 0.912	0.620 - 1.000	-0.275 - 0.275
Missing	102 (61.1%)	102 (61.1%)	64 (53.3%)	64 (53.3%)	38 (80.9%)	38 (80.9%)
95% CI	(0.798, 0.877)	(-0.010, 0.089)	(0.794, 0.880)	(-0.007, 0.103)	(0.717, 0.962)	(-0.141, 0.113)
EQ-5D Utility Score (UK): Week 15						
N	6	6	---	---	6	6
Median (Q1 - Q3)	0.863 (0.691, 1.000)	0.000 (0.000, 0.036)	---	---	0.863 (0.691, 1.000)	0.000 (0.000, 0.036)
Mean (SD)	0.851 (0.164)	0.025 (0.065)	---	---	0.851 (0.164)	0.025 (0.065)
Minimum - Maximum	0.689 - 1.000	-0.036 - 0.150	---	---	0.689 - 1.000	-0.036 - 0.150
Missing	161 (96.4%)	161 (96.4%)	---	---	41 (87.2%)	41 (87.2%)
95% CI	(0.679, 1.023)	(-0.044, 0.094)	---	---	(0.679, 1.023)	(-0.044, 0.094)
EQ-5D Utility Score (UK): Week 16						
N	49	49	49	49	---	---

	Overall (N=167)		Nivolumab 3 mg/kg (N=120)		Investigator's Choice (N=47)	
	Timepoint	Change from	Timepoint	Change from	Timepoint	Change from
Median (Q1 - Q3)	0.850 (0.725, 1.000)	0.000 (0.000, 0.117)	0.850 (0.725, 1.000)	0.000 (0.000, 0.117)	---	---
Mean (SD)	0.837 (0.212)	0.044 (0.259)	0.837 (0.212)	0.044 (0.259)	---	---
Minimum - Maximum	-0.074 - 1.000	-0.765 - 0.801	-0.074 - 1.000	-0.765 - 0.801	---	---
Missing	118 (70.7%)	118 (70.7%)	71 (59.2%)	71 (59.2%)	---	---
95% CI	(0.776, 0.898)	(-0.030, 0.119)	(0.776, 0.898)	(-0.030, 0.119)	---	---
EQ-5D Utility Score (UK): Week 18						
N	6	6	---	---	6	6
Median (Q1 - Q3)	0.771 (0.689, 1.000)	0.000 (-0.036, 0.000)	---	---	0.771 (0.689, 1.000)	0.000 (-0.036, 0.000)
Mean (SD)	0.820 (0.147)	-0.012 (0.019)	---	---	0.820 (0.147)	-0.012 (0.019)
Minimum - Maximum	0.689 - 1.000	-0.036 - 0.002	---	---	0.689 - 1.000	-0.036 - 0.002
Missing	161 (96.4%)	161 (96.4%)	---	---	41 (87.2%)	41 (87.2%)
95% CI	(0.666, 0.974)	(-0.031, 0.008)	---	---	(0.666, 0.974)	(-0.031, 0.008)
EQ-5D Utility Score (UK): Week 20						
N	45	45	45	45	---	---
Median (Q1 - Q3)	1.000 (0.725, 1.000)	0.000 (0.000, 0.123)	1.000 (0.725, 1.000)	0.000 (0.000, 0.123)	---	---
Mean (SD)	0.850 (0.202)	0.062 (0.264)	0.850 (0.202)	0.062 (0.264)	---	---
Minimum - Maximum	0.055 - 1.000	-0.672 - 0.888	0.055 - 1.000	-0.672 - 0.888	---	---
Missing	122 (73.1%)	122 (73.1%)	75 (62.5%)	75 (62.5%)	---	---
95% CI	(0.789, 0.911)	(-0.017, 0.142)	(0.789, 0.911)	(-0.017, 0.142)	---	---
EQ-5D Utility Score (UK): Week 21						
N	5	5	---	---	5	5

	Overall (N=167)		Nivolumab 3 mg/kg (N=120)		Investigator's Choice (N=47)	
	Timepoint	Change from	Timepoint	Change from	Timepoint	Change from
Median (Q1 - Q3)	0.883 (0.812, 1.000)	0.000 (0.000, 0.033)	---	---	0.883 (0.812, 1.000)	0.000 (0.000, 0.033)
Mean (SD)	0.877 (0.132)	0.024 (0.038)	---	---	0.877 (0.132)	0.024 (0.038)
Minimum - Maximum	0.689 - 1.000	0.000 - 0.087	---	---	0.689 - 1.000	0.000 - 0.087
Missing	162 (97.0%)	162 (97.0%)	---	---	42 (89.4%)	42 (89.4%)
95% CI	(0.713, 1.041)	(-0.023, 0.071)	---	---	(0.713, 1.041)	(-0.023, 0.071)
EQ-5D Utility Score (UK): Week 24						
N	29	29	26	26	3	3
Median (Q1 - Q3)	0.796 (0.725, 1.000)	0.000 (-0.071, 0.107)	0.822 (0.725, 1.000)	0.000 (-0.071, 0.107)	0.796 (0.796, 1.000)	0.107 (-0.204, 0.150)
Mean (SD)	0.841 (0.140)	0.029 (0.169)	0.838 (0.144)	0.031 (0.170)	0.864 (0.118)	0.018 (0.193)
Minimum - Maximum	0.620 - 1.000	-0.209 - 0.532	0.620 - 1.000	-0.209 - 0.532	0.796 - 1.000	-0.204 - 0.150
Missing	138 (82.6%)	138 (82.6%)	94 (78.3%)	94 (78.3%)	44 (93.6%)	44 (93.6%)
95% CI	(0.787, 0.894)	(-0.035, 0.093)	(0.780, 0.896)	(-0.038, 0.099)	(0.571, 1.157)	(-0.462, 0.498)

Table 2. Descriptive statistics for EORTC QLQ-C30 Global Health Status/Quality of Life using the ORR sample randomised to treatment

	Overall (N=167)		Nivolumab 3 mg/kg (N=120)		Investigator's Choice (N=47)	
	Timepoint	Change from Baseline	Timepoint	Change from Baseline	Timepoint	Change from Baseline
EORTC QLQC C-30 Global Health Status: Baseline						
N	105	---	80	---	25	---
Median (Q1 - Q3)	75.0 (50.0, 83.3)	---	75.0 (58.3, 83.3)	---	66.7 (50.0, 83.3)	---
Mean (SD)	69.3 (21.3)	---	70.3 (21.9)	---	66.0 (19.1)	---
Minimum - Maximum	0.0 - 100.0	---	0.0 - 100.0	---	25.0 - 100.0	---
Missing	62 (37.1%)	---	40 (33.3%)	---	22 (46.8%)	---
95% CI	(65.2, 73.4)	---	(65.4, 75.2)	---	(58.1, 73.9)	---
EORTC QLQC C-30 Global Health Status: Week 3						
N	22	22	---	---	22	22

	Overall (N=167)		Nivolumab 3 mg/kg (N=120)		Investigator's Choice (N=47)	
	Timepoint	Change from Baseline	Timepoint	Change from Baseline	Timepoint	Change from Baseline
Median (Q1 - Q3)	62.5 (50.0, 83.3)	0.0 (-8.3, 8.3)	---	---	62.5 (50.0, 83.3)	0.0 (-8.3, 8.3)
Mean (SD)	64.4 (22.1)	-3.0 (13.3)	---	---	64.4 (22.1)	-3.0 (13.3)
Minimum - Maximum	25.0 - 100.0	-41.7 - 16.7	---	---	25.0 - 100.0	-41.7 - 16.7
Missing	145 (86.8%)	145 (86.8%)	---	---	25 (53.2%)	25 (53.2%)
95% CI	(54.6, 74.2)	(-8.9, 2.8)	---	---	(54.6, 74.2)	(-8.9, 2.8)
EORTC QLQC C-30 Global Health Status: Week 4						
N	77	77	77	77	---	
Median (Q1 - Q3)	66.7 (58.3, 83.3)	0.0 (-8.3, 8.3)	66.7 (58.3, 83.3)	0.0 (-8.3, 8.3)	---	
Mean (SD)	69.4 (17.4)	-0.4 (18.0)	69.4 (17.4)	-0.4 (18.0)	---	
Minimum - Maximum	33.3 - 100.0	-50.0 - 66.7	33.3 - 100.0	-50.0 - 66.7	---	
Missing	90 (53.9%)	90 (53.9%)	43 (35.8%)	43 (35.8%)	---	
95% CI	(65.4, 73.3)	(-4.5, 3.7)	(65.4, 73.3)	(-4.5, 3.7)	---	
EORTC QLQC C-30 Global Health Status: Week 6						
N	20	20	---	---	20	
Median (Q1 - Q3)	58.3 (41.7, 75.0)	-8.3 (-16.7, 0.0)	---	---	58.3 (41.7, 75.0)	
Mean (SD)	60.0 (19.2)	-7.1 (12.2)	---	---	60.0 (19.2)	
Minimum - Maximum	33.3 - 91.7	-25.0 - 16.7	---	---	33.3 - 91.7	
Missing	147 (88.0%)	147 (88.0%)	---	---	27 (57.4%)	
95% CI	(51.0, 69.0)	(-12.8, -1.4)	---	---	(51.0, 69.0)	
EORTC QLQC C-30 Global Health Status: Week 8						
N	68	68	68	68	---	---
Median (Q1 - Q3)	66.7 (58.3, 83.3)	0.0 (-16.7, 8.3)	66.7 (58.3, 83.3)	0.0 (-16.7, 8.3)	---	---
Mean (SD)	68.0 (20.8)	-2.7 (24.5)	68.0 (20.8)	-2.7 (24.5)	---	---
Minimum - Maximum	16.7 - 100.0	-66.7 - 66.7	16.7 - 100.0	-66.7 - 66.7	---	---
Missing	99 (59.3%)	99 (59.3%)	52 (43.3%)	52 (43.3%)	---	---
95% CI	(63.0, 73.0)	(-8.6, 3.2)	(63.0, 73.0)	(-8.6, 3.2)	---	---
EORTC QLQC C-30 Global Health Status: Week 9						
N	10	10	---	---	10	10
Median (Q1 - Q3)	50.0 (41.7, 66.7)	-4.2 (-8.3, 0.0)	---	---	50.0 (41.7, 66.7)	-4.2 (-8.3, 0.0)
Mean (SD)	56.7 (24.8)	-4.2 (9.8)	---	---	56.7 (24.8)	-4.2 (9.8)
Minimum - Maximum	33.3 - 100.0	-16.7 - 16.7	---	---	33.3 - 100.0	-16.7 - 16.7
Missing	157 (94.0%)	157 (94.0%)	---	---	37 (78.7%)	37 (78.7%)
95% CI	(38.9, 74.4)	(-11.2, 2.9)	---	---	(38.9, 74.4)	(-11.2, 2.9)
EORTC QLQC C-30 Global Health Status: Week 12						

	Overall (N=167)		Nivolumab 3 mg/kg (N=120)		Investigator's Choice (N=47)	
	Timepoint	Change from Baseline	Timepoint	Change from Baseline	Timepoint	Change from Baseline
N	65	65	56	56	9	9
Median (Q1 - Q3)	75.0 (58.3, 83.3)	0.0 (-8.3, 8.3)	83.3 (66.7, 83.3)	0.0 (-8.3, 8.3)	58.3 (58.3, 66.7)	8.3 (-8.3, 8.3)
Mean (SD)	72.8 (19.3)	1.7 (20.1)	74.1 (19.0)	1.6 (20.9)	64.8 (20.3)	1.9 (14.9)
Minimum - Maximum	16.7 - 100.0	-58.3 - 66.7	16.7 - 100.0	-58.3 - 66.7	33.3 - 100.0	-25.0 - 16.7
Missing	102 (61.1%)	102 (61.1%)	64 (53.3%)	64 (53.3%)	38 (80.9%)	38 (80.9%)
95% CI	(68.0, 77.6)	(-3.3, 6.6)	(69.0, 79.2)	(-4.0, 7.2)	(49.2, 80.4)	(-9.6, 13.3)
EORTC QLQC C-30 Global Health Status: Week 15						
N	6	6	---	---	6	6
Median (Q1 - Q3)	62.5 (50.0, 100.0)	4.2 (0.0, 16.7)	---	---	62.5 (50.0, 100.0)	4.2 (0.0, 16.7)
Mean (SD)	70.8 (23.4)	5.6 (10.1)	---	---	70.8 (23.4)	5.6 (10.1)
Minimum - Maximum	50.0 - 100.0	-8.3 - 16.7	---	---	50.0 - 100.0	-8.3 - 16.7
Missing	161 (96.4%)	161 (96.4%)	---	---	41 (87.2%)	41 (87.2%)
95% CI	(46.3, 95.4)	(-5.0, 16.1)	---	---	(46.3, 95.4)	(-5.0, 16.1)
EORTC QLQC C-30 Global Health Status: Week 16						
N	49	49	49	49	---	---
Median (Q1 - Q3)	83.3 (66.7, 83.3)	0.0 (-8.3, 8.3)	83.3 (66.7, 83.3)	0.0 (-8.3, 8.3)	---	---
Mean (SD)	76.7 (17.5)	2.6 (21.9)	76.7 (17.5)	2.6 (21.9)	---	---
Minimum - Maximum	8.3 - 100.0	-66.7 - 66.7	8.3 - 100.0	-66.7 - 66.7	---	---
Missing	118 (70.7%)	118 (70.7%)	71 (59.2%)	71 (59.2%)	---	---
95% CI	(71.7, 81.7)	(-3.7, 8.8)	(71.7, 81.7)	(-3.7, 8.8)	---	---
EORTC QLQC C-30 Global Health Status: Week 18						
N	6	6	---	---	6	6
Median (Q1 - Q3)	58.3 (41.7, 100.0)	0.0 (-8.3, 8.3)	---	---	58.3 (41.7, 100.0)	0.0 (-8.3, 8.3)
Mean (SD)	66.7 (27.4)	1.4 (9.7)	---	---	66.7 (27.4)	1.4 (9.7)
Minimum - Maximum	41.7 - 100.0	-8.3 - 16.7	---	---	41.7 - 100.0	-8.3 - 16.7
Missing	161 (96.4%)	161 (96.4%)	---	---	41 (87.2%)	41 (87.2%)
95% CI	(37.9, 95.4)	(-8.8, 11.6)	---	---	(37.9, 95.4)	(-8.8, 11.6)
EORTC QLQC C-30 Global Health Status: Week 20						
N	45	45	45	45	---	---
Median (Q1 - Q3)	83.3 (66.7, 83.3)	0.0 (-8.3, 8.3)	83.3 (66.7, 83.3)	0.0 (-8.3, 8.3)	---	---
Mean (SD)	76.3 (13.4)	1.9 (20.6)	76.3 (13.4)	1.9 (20.6)	---	---
Minimum - Maximum	33.3 - 100.0	-66.7 - 50.0	33.3 - 100.0	-66.7 - 50.0	---	---
Missing	122 (73.1%)	122 (73.1%)	75 (62.5%)	75 (62.5%)	---	---
95% CI	(72.3, 80.3)	(-4.3, 8.1)	(72.3, 80.3)	(-4.3, 8.1)	---	---

	Overall (N=167)		Nivolumab 3 mg/kg (N=120)		Investigator's Choice (N=47)	
	Timepoint	Change from Baseline	Timepoint	Change from Baseline	Timepoint	Change from Baseline
EORTC QLQC C-30 Global Health Status: Week 21						
N	5	5	---	---	5	5
Median (Q1 - Q3)	66.7 (50.0, 100.0)	0.0 (0.0, 16.7)	---	---	66.7 (50.0, 100.0)	0.0 (0.0, 16.7)
Mean (SD)	73.3 (25.3)	6.7 (9.1)	---	---	73.3 (25.3)	6.7 (9.1)
Minimum - Maximum	50.0 - 100.0	0.0 - 16.7	---	---	50.0 - 100.0	0.0 - 16.7
Missing	162 (97.0%)	162 (97.0%)	---	---	42 (89.4%)	42 (89.4%)
95% CI	(41.9, 104.7)	(-4.7, 18.0)	---	---	(41.9, 104.7)	(-4.7, 18.0)
EORTC QLQC C-30 Global Health Status: Week 24						
N	29	29	26	26	3	3
Median (Q1 - Q3)	66.7 (66.7, 83.3)	0.0 (-8.3, 8.3)	75.0 (66.7, 83.3)	0.0 (-8.3, 16.7)	58.3 (58.3, 100.0)	8.3 (0.0, 8.3)
Mean (SD)	74.4 (14.6)	2.9 (18.8)	74.7 (13.8)	2.6 (19.8)	72.2 (24.1)	5.6 (4.8)
Minimum - Maximum	50.0 - 100.0	-33.3 - 50.0	50.0 - 100.0	-33.3 - 50.0	58.3 - 100.0	0.0 - 8.3
Missing	138 (82.6%)	138 (82.6%)	94 (78.3%)	94 (78.3%)	44 (93.6%)	44 (93.6%)
95% CI	(68.9, 80.0)	(-4.3, 10.0)	(69.1, 80.3)	(-5.4, 10.6)	(12.5, 132.0)	(-6.4, 17.5)

A7. The company's submission page 47 states that HRQoL analyses are not currently available for CheckMate 067. Please specify when these will be available.

Analysis of HRQoL data from Checkmate 067 is currently ongoing. It is expected that partial results will be available [redacted]

A8. Priority question: The company's submission states that the OS data in the CheckMate 067 trial are not yet available and therefore this study is not included in the direct or indirect estimation of treatment effects (page 94). Please clarify when OS data from this trial will be available.

OS data from Checkmate 067 will not be available until the number of pre-specified events (deaths) has been reached. This is not expected to be until the fourth quarter of 2016.

A9. Priority question: In addition, the company's submission states that OS data for the CheckMate 066 trial are relatively immature. Therefore, rather than making survival extrapolations based on OS, an alternative approach was taken using time to progression, preprogression survival, and post-progression survival instead of OS and TTP. It is not stated whether this approach was possible for the CheckMate 067 trial, which would thus allow this trial to be used in the analysis and therefore obviate the need for an indirect comparison of ipilimumab and nivolumab. Please explain whether this is possible, and if so provide an analysis of cost effectiveness using this trial.

The proposed time to progression (TTP), preprogression survival (PrePS), and post-progression survival (PPS) method requires patient-level trial data to be available which has both PFS and OS events, where PFS events (including both progression events and death events without progression being observed) were used for fitting TTP and PrePS, and PFS and OS events combined (i.e., in order to derived time from progression to death for each individual patient whose progressing being observed) was used for fitting PPS. Within the model, the fitted TTP,

PrePS and PPS were used together to estimate PFS and short-term OS (note, long-term OS is based on registry data[2] or pooled ipilimumab study[3]). Therefore, the trials used for this approach require both PFS and OS events to be available.

It is not therefore possible to apply the proposed TTP/PrePS/PPS approach using Checkmate 067 trial data as OS data is not available within the Checkmate 067 trial. This means it is not possible to derive the time from progression to death for patients in Checkmate 067 trial and hence PPS for nivolumab and ipilimumab cannot be estimated.

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please clarify how the utility values have been calculated. In addition, please explain the difference between the baseline EQ-5D baseline value of 0.6030 and that of 0.72 (both shown in Table 66) and state which of these has been used in the calculation of the utility values.

The value of 0.6030 reported in Table 66 of the company's submission is the estimated coefficient for the baseline EQ-5D covariate in the fitted statistical model, i.e., the effect of a change in the baseline EQ-5D of observed patients on the estimated utilities. This value is applied similarly to the other estimated coefficients reported in Table 66, such as the value of -0.0741 for post-progression and -0.0233 for "<30 days to death" (i.e., patients who are in the post-progression state have a reduction in utility of 0.0741 and patients who are less than 30 days to death have a reduction in utility of -0.0233).

The observed baseline EQ-5D value of 0.72 (i.e., EQ-5D observed at the start of randomisation) needs to be multiplied by the coefficient 0.6030 to contribute to the calculation of utilities for all modelled health states (e.g., "pre-progression + days left >= 30 days").

The calculation of utility values for the 4 modelled health states is presented below based on the coefficients from the fitted statistical model and baseline EQ-5D value reported in Table 66 of the company's submission.

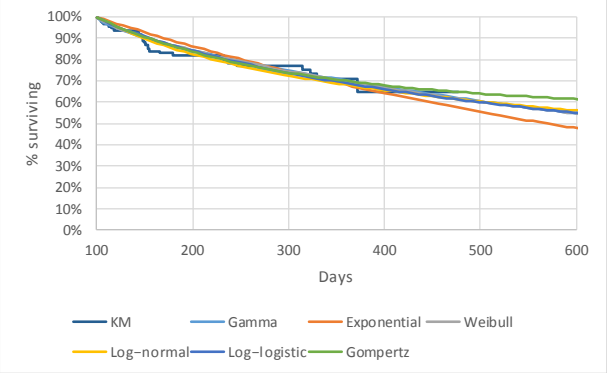
Pre-progression + days left >= 30 days	0.8018 = 0.3676 + 0.6030 * 0.72
Pre-progression + days left <30 days	0.7795 = 0.3676 + 0.6030 * 0.72 - 0.0223
Post-progression + days left >= 30 days	0.7277 = 0.3676 + 0.6030 * 0.72 - 0.0741
Post-progression + days left <30 days	0.7054 = 0.3676 + 0.6030 * 0.72 - 0.0223 - 0.0741

B2. Priority question: Please provide an analysis comparing nivolumab with DTIC using the Checkmate 066 trial data only, without adjusting survival curves for covariates.

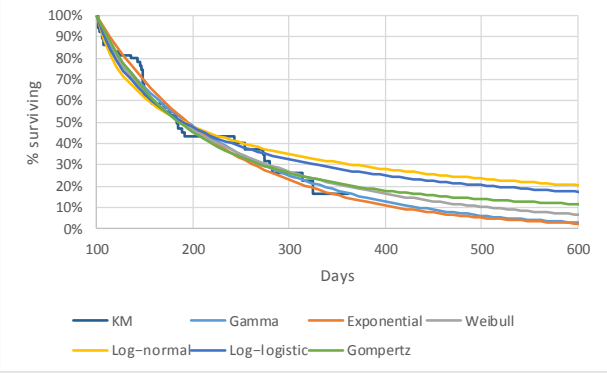
An analysis comparing nivolumab and DTIC using the Checkmate 066 trial data only was performed to estimate the cost-effectiveness of nivolumab versus DTIC in the BRAF mutation-negative patients.

Similar statistical models as used in the original submissions were fitted using patient-level data from Checkmate 066 trial for time to progression (TTP) for the post-100 days for the for post progression survival (PPS) without adjusting for covariates (i.e., the only covariate included is the treatment arm). The fitted curves and the Akaike information criteria (AIC) and Bayesian information criteria (BIC) values are presented below.

Time to progression post 100 days (day 0=day 100) - NIVO



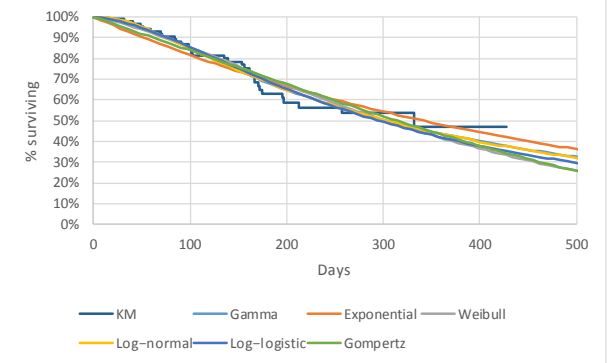
Time to progression post 100 days (day 0=day 100) - DTIC



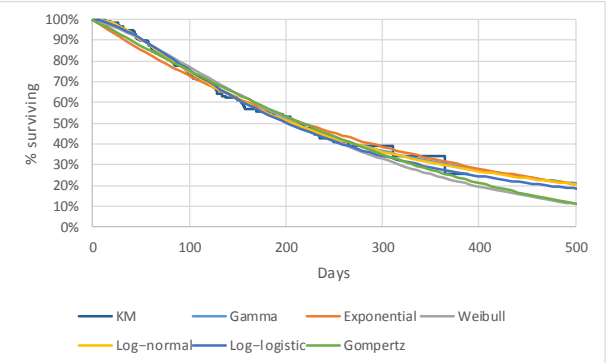
AIC and BIC for TTP post-100 days using Checkmate 066 trial data only:

Model	AIC	BIC
Exponential	894.73	901.12
Generalised Gamma	892.51	905.28
Gompertz	892.91	902.49
Log-logistic	895.05	904.63
Log-normal	897.87	907.45
Weibull	**891.02**	**900.60**

Post progression survival - NIVO



Post progression survival - DTIC



AIC and BIC for PPS days using Checkmate 066 trial data only:

Model	AIC	BIC
Exponential	1342.21	1349.12
Generalised Gamma	1327.93	1341.77
Gompertz	1341.52	1351.90
Log-logistic	1328.29	1338.67
Log-normal	**1325.94**	**1336.32**
Weibull	1333.79	1344.17

These fitted curves based on Checkmate 066 trial data only have been applied to the nivolumab and DTIC arms of the original cost-effectiveness model. The results, expressed as incremental cost-effectiveness ratio (ICER) for nivolumab vs DTIC, are presented below for this new analysis (base case and 10 scenarios depending on TTP and PPS parametric curves being selected). The detailed cost-effectiveness results for the base case are also presented. The results are presented using the model with list price for all treatment drugs. The corresponding results from the original submission are also presented for comparison purpose, which shows that the results from this new analysis are similar to the original results and there is no change in the cost-effectiveness conclusions.

ICER for nivolumab vs DTC base on the new analysis and the original results (drug prices based on list price):

Scenario	**ICER (new analysis)**	**ICER (original model)**
Base case (TTP – gompertz; PPS – Log-logistic)	**£24,251**	**£23,583**
TTP - Exponential	£30,849	£29,706
TTP - Weibull	£28,335	£26,636
TTP - Log-logistic	£27,934	£27,083
TTP - Log-normal	£27,541	£27,317
TTP - Generalised Gamma	£28,548	£27,261
PPS - Exponential	£23,927	£23,646
PPS - Weibull	£26,489	£23,977
PPS - Gompertz	£27,743	£22,268
PPS - Log-normal	£24,084	£23,246
PPS - Generalised Gamma	£23,978	£23,435

Base case results – new analysis (drug prices based on list price)

Technology	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Dacarbazine	[redacted]	1.09			
Nivolumab	[redacted]	4.09	£72,738	3.00	£24,251
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Base case results – original model (drug prices based on list price)

Technology	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**

Dacarbazine	[redacted]	1.23			
Nivolumab	[redacted]	4.31	£72,578	3.08	£23,583
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

B3. The utility decrements listed in Table 65 are reported to be from Beusterien et al (2009) but we are unable to find these estimates in that publication. Please clarify how these decrements have been derived.

Table 8 below shows the assumptions made to estimate the utility decrements for each of the defined AEs category used in the model. All estimates were based on utilities reported in the last column of Table 1 in Beusterien et al 2009[4].

Table 8. Assumptions made to estimate utility decrements

	Model inputs	**Assumptions**
Endocrine disorder (any grade)	-0.11	UK decrement for 1-day in-/outpatient stay for severe toxicity (grade III/IV)
Diarrhoea (Grade 2+)	-0.06	UK decrement for Grade I/II diarrhoea
Other AEs (Grade 3+)	-0.12	Assumes 50:50 split between UK decrement for 1-day in-/outpatient stay for severe toxicity (grade III/IV) & 2–5-day hospitalisation for severe toxicity (grade III/IV)

As there is no exact match reported by Beusterien et al for the definitions of AEs in the model (regarding types and grades of AEs) the utility decrements used were chosen based on clinical opinion received as part of the work for the company's submission of ipilimumab to NICE (TA268).

B4. If possible, please provide an analysis that shows the utility data from checkmate 066 tabulated in the following format: mean utility for patients treated with nivolumab who have not progressed; mean utility for patients treated with nivolumab who have progressed; mean utility for patients treated with DTIC who have not progressed; mean utility for patients treated with DTIC who have progressed.

Table 9 below shows the mean utility results requested based on treatment arm and progression status from Checkmate 066.

Table 9. Mean utility according to treatment arm and progression status

	Utility
Mean utility for patients treated with nivolumab who have not progressed	0.7892
Mean utility for patients treated with nivolumab who have progressed	0.7548
Mean utility for patients treated with DTIC who have not progressed	0.6963
Mean utility for patients treated with DTIC who have progressed	0.6565

Utilities based on both progression status and time to death (less than 30 days to death or not) were used in the base case model, because both progression status and time to death were significant predictors of utilities in the fitted statistical model (using a significance cut-off of 0.1) and the use of time to death utilities, especially in oncology modelling where progression may not capture the full impact of disease on the patient, were supported within the recent ipilimumab NICE submission (NICE TA319[5]) and literature (Hatswell et al 2014[6]).

B5. Please clarify how the numbers of adverse events from Checkmate 066 in Table 61 have been derived and how they differ from those presented in Table 47.

The number of adverse events from Checkmate 066 reported in Table 61 of the company's submission (the cost-effectiveness section) was based on an ad hoc analysis performed using patient-level safety data collected in Checkmate 066 trial, based on a bespoke categorisation and definition of AEs (i.e., the use of any grade endocrine disorder, grade 2+ diarrhoea, and grade 3+ other AEs, and without setting a threshold for the AEs to be included) that best represent AEs considered relevant to the decision problem. The number of adverse events reported in Table 47 (the clinical effectiveness section) was directly taken from the Checkmate 066 CSR[7] and Robert et al 2015[8].

The reason the number of AEs are different between Table 61 and Table 47 is that: 1) different categorisations of AEs were used; and 2) no threshold is set when including AEs in Table 61 (i.e., all AEs were included), and threshold is set when including AEs in the Checkmate 066 CSR and Robert et al (i.e., AEs listed were reported in at least 10% of patients based on any grade of AEs in either study group in Robert et al).

For example, Table 61 reported 4.4% and 3.4% for grade 2+ diarrhoea for nivolumab and DTIC, and Robert et al reported 16.0% and 15.5% for any grade, and 1.0% and 0.5% for grade 3+. The differences here is mainly due to the definition with the ad hoc analysis including grade 2+ AEs which were not reported in the Checkmate 066 CSR or Robert et al.

The reason for doing the ad hoc analysis using patient-level trial data was that during the clinical advisory board the clinicians stated that the reporting of adverse events in the CSR did not capture all adverse events of relevance to clinical practice. The clinicians put forward an alternative definition of adverse events to best capture those with a large impact on resource use and / or the quality of life of patients.

References

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3. 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.
4. 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.
5. 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.
6. 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.
7. Bristol-Myers Squibb Company. A Phase III, randomized, double-blind study of BMS-936558 (nivolumab) versus dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma. (CA209066). 2014. Data on File.
8. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015; 372(4):320-30.

Appendix 1: Question A2. Demographic and Baseline characteristics of UK subjects in Checkmate 067

Demographic and Baseline Characteristics Summary
All Randomized Subjects from United Kingdom

	Nivolumab N = 27	Nivolumab + Ipilimumab N = 30	Ipilimumab N = 36	Total N = 93
AGE (YEARS)				
N	27	30	36	93
MEAN	57.6	54.9	60.3	57.8
MEDIAN	58.0	57.0	62.5	59.0
MIN , MAX	29 , 80	25 , 78	18 , 83	18 , 83
STANDARD DEVIATION	13.96	14.14	13.01	13.70
AGE CATEGORIZATION I (%)				
< 65	17 (63.0)	21 (70.0)	19 (52.8)	57 (61.3)
>= 65	10 (37.0)	9 (30.0)	17 (47.2)	36 (38.7)
AGE CATEGORIZATION II (%)				
< 65	17 (63.0)	21 (70.0)	19 (52.8)	57 (61.3)
>= 65 AND < 75	7 (25.9)	7 (23.3)	13 (36.1)	27 (29.0)
>= 75	3 (11.1)	2 (6.7)	4 (11.1)	9 (9.7)
GENDER (%)				
MALE	21 (77.8)	18 (60.0)	21 (58.3)	60 (64.5)
FEMALE	6 (22.2)	12 (40.0)	15 (41.7)	33 (35.5)
RACE (%)				
WHITE	27 (100.0)	30 (100.0)	36 (100.0)	93 (100.0)
BLACK OR AFRICAN AMERICAN	0	0	0	0
ASIAN	0	0	0	0
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0
OTHER	0	0	0	0

Demographic and Baseline Characteristics Summary
All Randomized Subjects from United Kingdom

	Nivolumab N = 27	Nivolumab + Ipilimumab N = 30	Ipilimumab N = 36	Total N = 93
BASELINE LDH				
<= ULN	17 (63.0)	14 (46.7)	20 (55.6)	51 (54.8)
> ULN	9 (33.3)	16 (53.3)	15 (41.7)	40 (43.0)
<= 2*ULN	22 (81.5)	23 (76.7)	31 (86.1)	76 (81.7)
> 2*ULN	4 (14.8)	7 (23.3)	4 (11.1)	15 (16.1)
NOT REPORTED	1 (3.7)	0	1 (2.8)	2 (2.2)
HISTORY OF BRAIN METASTASES				
YES	0	1 (3.3)	1 (2.8)	2 (2.2)
NO	27 (100.0)	29 (96.7)	35 (97.2)	91 (97.8)
SMOKING STATUS				
YES	12 (44.4)	13 (43.3)	18 (50.0)	43 (46.2)
NO	14 (51.9)	17 (56.7)	17 (47.2)	48 (51.6)
UNKNOWN	1 (3.7)	0	1 (2.8)	2 (2.2)
WEIGHT (KG)				
N	27	30	36	93
MEAN	87.30	80.94	83.10	83.62
MEDIAN	84.50	79.70	83.35	83.00
MIN , MAX	53.5 , 129.3	56.0 , 124.2	45.1 , 117.2	45.1 , 129.3
Q1 , Q3	74.40 , 106.30	68.30 , 86.80	70.65 , 93.60	69.20 , 92.80
STANDARD DEVIATION	19.611	18.674	16.604	18.164

Demographic and Baseline Characteristics Summary
All Randomized Subjects from United Kingdom

	Nivolumab N = 27	Nivolumab + Ipilimumab N = 30	Ipilimumab N = 36	Total N = 93
PERFORMANCE STATUS (ECOG) [%]				
0	20 (74.1)	16 (53.3)	20 (55.6)	56 (60.2)
1	7 (25.9)	14 (46.7)	16 (44.4)	37 (39.8)
2	0	0	0	0
PD-L1 STATUS (IVRS)				
POSITIVE	15 (55.6)	12 (40.0)	19 (52.8)	46 (49.5)
NEGATIVE/INDETERMINATE	12 (44.4)	18 (60.0)	17 (47.2)	47 (50.5)
M STAGE AT STUDY ENTRY (IVRS)				
M0/M1A/M1B	7 (25.9)	11 (36.7)	12 (33.3)	30 (32.3)
M1C	20 (74.1)	19 (63.3)	24 (66.7)	63 (67.7)
M STAGE AT STUDY ENTRY (CRF)				
M0/M1A/M1B	10 (37.0)	11 (36.7)	10 (27.8)	31 (33.3)
M1C	17 (63.0)	19 (63.3)	26 (72.2)	62 (66.7)
AJCC STAGE AT STUDY ENTRY				
STAGE III	0	1 (3.3)	1 (2.8)	2 (2.2)
STAGE IV	27 (100.0)	29 (96.7)	35 (97.2)	91 (97.8)

Demographic and Baseline Characteristics Summary
All Randomized Subjects from United Kingdom

	Nivolumab N = 27	Nivolumab + Ipilimumab N = 30	Ipilimumab N = 36	Total N = 93
BRAF STATUS (IVRS)				
MUTANT	10 (37.0)	10 (33.3)	13 (36.1)	33 (35.5)
WILDTYPE	17 (63.0)	20 (66.7)	23 (63.9)	60 (64.5)
BRAF STATUS (CRF)				
MUTANT	10 (37.0)	10 (33.3)	14 (38.9)	34 (36.6)
WILDTYPE	17 (63.0)	20 (66.7)	22 (61.1)	59 (63.4)
BRAF MUTATION TEST				
COBAS+THXID	14 (51.9)	20 (66.7)	23 (63.9)	57 (61.3)
OTHER	9 (33.3)	2 (6.7)	5 (13.9)	16 (17.2)
UNKNOWN	4 (14.8)	8 (26.7)	8 (22.2)	20 (21.5)

Appendix 2: Question A2. Demographic and Baseline characteristics of UK subjects in Checkmate 037

Demographic and Baseline Characteristics Summary
All Randomized Subjects from United Kingdom

	NIVOLUMAB N = 32	INVESTIGATOR'S CHOICE N = 11	Total N = 43
AGE (YEARS)			
N	32	11	43
Mean	56.1	59.8	57.1
Standard Deviation	12.1	10.1	11.6
Median	57.0	61.0	58.0
Min, Max	25.0, 82.0	42.0, 78.0	25.0, 82.0
GENDER (%)			
FEMALE	12 (37.5)	6 (54.5)	18 (41.9)
MALE	20 (62.5)	5 (45.5)	25 (58.1)
RACE (%)			
WHITE	31 (96.9)	11 (100.0)	42 (97.7)
BLACK OR AFRICAN AMERICAN	0	0	0
ASIAN	1 (3.1)	0	1 (2.3)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
OTHER	0	0	0
NOT REPORTED	0	0	0
PERFORMANCE STATUS (ECOG) (%)			
0	12 (37.5)	3 (27.3)	15 (34.9)
1	20 (62.5)	7 (63.6)	27 (62.8)
2	0	1 (9.1)	1 (2.3)

(A) Excluding immunotherapy and B-RAF inhibitor
(B) Excluding prior anti-CTLA4
(C) Subjects may have lesions at more than one site
(D) Includes both target and non-target lesions
PROGRAM SOURCE: /gbs/prod/clin/programs/ca/209/mma-nice/20150923/rpt/rt-dm-sumall037-v01.sas 29SEP15 11:25

Demographic and Baseline Characteristics Summary
All Randomized Subjects from United Kingdom

	NIVOLUMAB N = 32	INVESTIGATOR'S CHOICE N = 11	Total N = 43
M STAGE AT STUDY ENTRY			
M0	1 (3.1)	0	1 (2.3)
M1A	3 (9.4)	2 (18.2)	5 (11.6)
M1B	2 (6.3)	0	2 (4.7)
M1C	26 (81.3)	9 (81.8)	35 (81.4)
M STAGE AT INITIAL DIAGNOSIS			
M0	19 (59.4)	8 (72.7)	27 (62.8)
M1A	2 (6.3)	0	2 (4.7)
M1B	1 (3.1)	0	1 (2.3)
M1C	3 (9.4)	1 (9.1)	4 (9.3)
UNKNOWN	7 (21.9)	2 (18.2)	9 (20.9)
BASELINE LDH			
<= ULN	17 (53.1)	4 (36.4)	21 (48.8)
> ULN	15 (46.9)	7 (63.6)	22 (51.2)
<= 2*ULN	27 (84.4)	7 (63.6)	34 (79.1)
> 2*ULN	5 (15.6)	4 (36.4)	9 (20.9)

(A) Excluding immunotherapy and B-RAF inhibitor
(B) Excluding prior anti-CTLA4
(C) Subjects may have lesions at more than one site
(D) Includes both target and non-target lesions

PROGRAM SOURCE: /gbs/prod/clin/programs/ca/209/mma-nice/20150923/rpt/rt-dm-sumall037-v01.sas 29SEP15 11:25

Demographic and Baseline Characteristics Summary
All Randomized Subjects from United Kingdom

	NIVOLUMAB N = 32	INVESTIGATOR'S CHOICE N = 11	Total N = 43
HISTORY OF BRAIN METASTASES			
YES	2 (6.3)	1 (9.1)	3 (7.0)
NO	30 (93.8)	10 (90.9)	40 (93.0)
TIME FROM INITIAL DIAGNOSIS (YEARS)			
N	32	11	43
Median	4.5	4.6	4.6
Min, Max	0.5, 25.3	0.3, 13.4	0.3, 25.3
BRAF STATUS			
MUTANT	11 (34.4)	4 (36.4)	15 (34.9)
WILD TYPE	21 (65.6)	7 (63.6)	28 (65.1)
PD-L1 status			
POSITIVE	15 (46.9)	5 (45.5)	20 (46.5)
NEGATIVE/INDETERMINATE	17 (53.1)	6 (54.5)	23 (53.5)
PRIOR NEO-ADJUVANT THERPY			
YES	0	0	0
NO	32 (100.0)	11 (100.0)	43 (100.0)

(A) Excluding immunotherapy and B-RAF inhibitor
(B) Excluding prior anti-CTLA4
(C) Subjects may have lesions at more than one site
(D) Includes both target and non-target lesions

PROGRAM SOURCE: /gbs/prod/clin/programs/ca/209/mma-nice/20150923/rpt/rt-dm-sumall037-v01.sas 29SEP15 11:25

Demographic and Baseline Characteristics Summary
All Randomized Subjects from United Kingdom

	NIVOLUMAB N = 32	INVESTIGATOR'S CHOICE N = 11	Total N = 43
PRIOR ADJUVANT THERAPY			
YES	2 (6.3)	1 (9.1)	3 (7.0)
NO	30 (93.8)	10 (90.9)	40 (93.0)
NUMBER OF PRIOR SYSTEMIC REGIMEN RECEIVED IN METASTATIC SETTING			
1	5 (15.6)	2 (18.2)	7 (16.3)
2	21 (65.6)	8 (72.7)	29 (67.4)
>2	6 (18.8)	1 (9.1)	7 (16.3)
PRIOR CHEMOTHERAPY IN METASTATIC SETTING (A)			
YES	22 (68.8)	6 (54.5)	28 (65.1)
NO	10 (31.3)	5 (45.5)	15 (34.9)
PRIOR IMMUNOTHERAPY IN METASTATIC SETTING (B)			
YES	1 (3.1)	0	1 (2.3)
NO	31 (96.9)	11 (100.0)	42 (97.7)
PRIOR SURGERY RELATED TO CANCER			
YES	32 (100.0)	11 (100.0)	43 (100.0)
NO	0	0	0

(A) Excluding immunotherapy and B-RAF inhibitor
(B) Excluding prior anti-CTLA4
(C) Subjects may have lesions at more than one site
(D) Includes both target and non-target lesions

PROGRAM SOURCE: /gbs/prod/clin/programs/ca/209/mma-nice/20150923/rpt/rt-dm-sumall037-v01.sas 29SEP15 11:25

Demographic and Baseline Characteristics Summary
All Randomized Subjects from United Kingdom

	NIVOLUMAB N = 32	INVESTIGATOR'S CHOICE N = 11	Total N = 43
PRIOR RADIOTHERAPY			
YES	11 (34.4)	6 (54.5)	17 (39.5)
NO	21 (65.6)	5 (45.5)	26 (60.5)
SUBJECTS WITH AT LEAST ONE LESION (%)	31 (96.9)	11 (100.0)	42 (97.7)
SITE OF LESION (C) (D) (%)			
BONE	6 (18.8)	2 (18.2)	8 (18.6)
INTESTINE	6 (18.8)	2 (18.2)	8 (18.6)
LIVER	13 (40.6)	3 (27.3)	16 (37.2)
LUNG	15 (46.9)	4 (36.4)	19 (44.2)
LYMPH NODE	15 (46.9)	6 (54.5)	21 (48.8)
OTHER	1 (3.1)	1 (9.1)	2 (4.7)
SKIN	4 (12.5)	2 (18.2)	6 (14.0)
SOFT TISSUE	7 (21.9)	4 (36.4)	11 (25.6)
VISCERAL, OTHER	17 (53.1)	3 (27.3)	20 (46.5)

(A) Excluding immunotherapy and B-RAF inhibitor
(B) Excluding prior anti-CTLA4
(C) Subjects may have lesions at more than one site
(D) Includes both target and non-target lesions
PROGRAM SOURCE: /gbs/prod/clin/programs/ca/209/mma-nice/20150923/rpt/rt-dm-sumall037-v01.sas 29SEP15 11:25

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:

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)

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 and Ipilimumab and standard chemotherapy (Dacarbazine).**

Is there significant geographical variation in current practice? **Variation occurs 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 and Ipilimumab 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. If Ipilimumab fails in wild type BRAF patients then chemotherapy is the only available treatment and is not very effective. The anti PD1 drugs give an alternative therapy for these patients.**

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.**

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.**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

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.**

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.**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

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.

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

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 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:

Name of your organisation: **NCRI/RCP/ACP**
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?

Advanced malignant melanoma is treated at tertiary care oncology centres by oncologists

Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be?

There is no significant geographical variation, or difference in opinion regarding the clinical management between treating health care professionals in the UK.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Choice of first-line treatment for patients with advanced malignant melanoma is dictated by whether the patient harbours an activating BRAF mutation or not, their performance score, anatomical sites of disease, bulk of disease, together with the speed of disease progression.

First-line treatment options presently include a BRAF inhibitor (vemurafenib or dabrafenib) for those with an activating BRAF mutation only, and CTLA4 inhibitors (ipilimumab) or cytotoxic chemotherapy (dacarbazine) for those who do not. Each of these classes of agent may be employed in sequence if appropriate for the clinical circumstances of the patient.

BRAF inhibitors have high response rate (approximately 70%), and moderate toxicity, and provide a moderate (approx. 7 month) progression free survival advantage. They are only suitable for patients whose tumour harbours an activating BRAF mutation.

The CTLA4 inhibitor ipilimumab has low response rate (approx. 14%) but for those who benefit there is a durable response lasting some years, which translates to an overall survival advantage. Toxicity is considerable however, with around 25% experiencing grade 3 or higher adverse events.

Cytotoxic chemotherapy with dacarbazine has a low response rate (approx. 10%), and short duration of response (approx. 3 months) but is associated with a relatively low rate and severity of toxicities.

*The comparators stated in **Appendix B** are therefore appropriate for this appraisal, as the marketing authorisation for nivolumab does not restrict its use based upon line of treatment.*

Nivolumab is a member of a new drug class of called PD-1 immune checkpoint inhibitors. These drugs act at a different point in the immune cycle and therefore

have a different mechanism of action, efficacy and toxicity profile compared to that of the CTLA4 inhibitor ipilimumab.

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?

Patients who harbour activating BRAF mutations represent a distinct subgroup as they have the additional treatment option of BRAF tyrosine kinase inhibitors. However the probability of response to PD-1 inhibitors such as nivolumab is not influenced by BRAF mutation status and BRAF positive patients are as likely to respond as BRAF negative patients.

It is currently uncertain whether PD-L1 expression status determines likelihood of response to PD-1 inhibitors. Nivolumab does not have marketing authorisation on the basis of selection by PD-L1 expression.

PD-1 inhibitors are however contraindicated in patients with a history of significant autoimmune disease, or autoimmune toxicity (grade $\geq$3) resulting from CTLA4 inhibitor use.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

Nivolumab will only be prescribed by oncologists specialising in the treatment of melanoma. In the UK, melanoma treatment is centralised at tertiary referral centres.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Nivolumab is an intravenous treatment and in the majority of cirucmstances will be administered on chemotherapy day units.

Autoimmune toxicities resulting from nivolumab use may occasionally necessitate the input of appropriate healthcare professionals (e.g. gastroenterologists, endocrinologists etc.).

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?

No PD-1 inhibitor is currently NICE approved for use within the NHS.

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

The use of PD-1 inhibitors is not covered in the NICE Guideline NG14 'Melanoma: assessment and Management' that was published in July 2015.

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?

Requirements for prescription and administration of nivolumab will be equivalent to that for ipilimumab. However, whereas ipilimumab is administed as 4 x 3 weekly infusions, nivolumab is licensed for continuous 2 weekly infusions until disease progression. Since the response/disease control rate is high, many patients will continue with treatment for 1-2 years or more. The sheer numbers of patients likely to be receiving treatment will mean chemotherapy units will come under significant capacity pressure. On the other hand, because of its significantly lower toxicity profile, use of nivolumab should require less additional in-patient resources to manage severe and life-threatening toxicities.

NICE is currently appraising Pembrolizumab, another anti-PD1 antibody. The 2 agents can be considered equivalent in terms of efficacy and toxicity. The major difference is that Pembrolizumab is administered every 3 weeks, while nivolumab is administered every 2 weeks.

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.

Patients will discontinue upon radiological disease progression. Repeat imaging will therefore be necessary throughout the duration of treatment, at clinically appropriate intervals.

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?

The trial data is appropriate and reflects anticipated UK clinical practice.

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?

Response rate

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

Nivolumab offered an objective response rate of 40%, in untreated BRAF negative patients when compared to dacarbazine (13.6%) in the CheckMate-066 study. Response rate is also superior to that for ipilimumab.

Overall survival
Survival in the CheckMate-066 study was improved compared to dacarbazine (1 year survivals 72.9% vs 42.1%). Direct comparison of overall survival is not possible for ipilimumab as the duration of follow-up in nivolumab in reported studies is currently too short. However clinicians anticipate from the early data that median survival will be at least equivalent.

Toxicity
The toxicity profile for nivolumab is considerably better than that of ipilimumab, and approximately equivalent to that for dacarbazine.

Comparison of with BRAF inhibitors is challenging, but of less relevance for the puposes of this appraisal, as it is anticipated by treating clinicians that for BRAF positive patients, a BRAF inhibitor and nivolumab will be offered sequentially. The order in which this occurs will vary for individual patients based upon clinical circumstances.

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 toxicity profile of nivolumab is well described, and includes a range of autoimmune side effects similar to that for CTLA4 inhibitor ipilimumab. The frequency of autoimmune side effects is however much lower for nivolumab than for 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.

In a recent report the combination of nivolumab and ipilimumab provided improved progression free survival (median 11.5 months vs 2.9 months) when compared to single agent ipilimumab. Comparison with nivolumab alone in a PD-L1 positive subgroup showed equivalent progression free survival (median 14.0 months), but the combination has significantly increased toxicity (55% vs 16.3% grade 3 or 4 toxicity). The combination of nivolumab and ipilimumab has yet to be evaluated by NICE, but is unlikely to be suitable for all patients considered for single agent nivolumab use. (Larkin J et al, NEJM, 2nd July 2015).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

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.

No known issues identified.

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)?

Implementation would add an additional line of treatment for those who had already received ipilimumab, but would be likely to supersede it for those who had not received it already.

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;

No comment

- 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;

No comment

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

No comment

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

No comment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

Thank you for agreeing to give us a statement on your 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 statement, 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? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **I see patients with any skin toxicity side effects as a result of the treatment.**
- 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.)? **YES, Consultant Dermatologist at the Royal Marsden Hospital**
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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? **Current treatment is with either BRAF inhibitors, ipilimumab and consideration or pembrolizumab after treatment with the aforementioned medications. Pembrolizumab is an antiPD1 inhibitor like nivolumab. Both can be used in BRAF mutant and wild type melanoma and are better tolerated than ipilimumab.**

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? **The advantage of nivolumab is that it can be given to both BRAF wild type and BRAF mutant patients. It is also better tolerated than ipilimumab.**

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)? **Secondary care, day care facilities are required as it is administered as an intravenous infusion.**

If the technology is already available, is there variation in how it is being used in the NHS? **No**

Is it always used within its licensed indications? **Yes**

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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?

It is an intravenous infusion given twice weekly (pembrolizumab is every 3 weeks). Ipilimumab is generally 4 infusions. BRAF inhibitors are oral medications.

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.

At the moment it is a continuous ongoing treatment until progression.

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 trials reflect how the treatment would be used. PFS and OS were measured.

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?

Side effects are as a consequence of the effect on the immune system but tend to be less than ipilimumab.

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Single Technology Appraisal (STA)

Equality and Diversity

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; **No**
- 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; **No**
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities **No**

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

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 and the Welsh Assembly Government 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 and the Welsh Assembly Government 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)?

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Single Technology Appraisal (STA)

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Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

Thank you for agreeing to give us a statement on your 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 statement, 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: Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology? yes
- 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.)? no
- other? (please specify)

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What is the expected place of the technology in current practice?

Nivolumab if approved will likely be used as another first line option for unresectable/metastatic melanoma in both mutant and BRAF melanoma cases, and as an option for patients pre-treated with anti-CTLA4. The response and side effect profile mean that in many cases clinicians may select nivolumab as a first treatment choice ahead of ipilimumab and BRAF inhibitors.

How is the conditions currently treated in the NHS?

Overview

Management of advanced (unresectable or metastatic melanoma) is managed with systemic therapy falling into 2 main categories (1) targeted agents and (2) immunotherapy treatments. Targeted agents available as first or subsequent treatment are the BRAF inhibitors vemurafenib and dabrafenib. Immunotherapy agents available are ipilimumab anti-CTLA4 agent as first or subsequent line treatments, and pembrolizumab and anti-PD1 agent following ipilimumab.

Prior to the development of these treatments, dacarbazine (DTIC) chemotherapy had been the standard of care though response rates are low, and survival benefit unproven. DTIC has served as the control arm for many phase III trials of newer agents. DTIC is still occasionally indicated in patients where immunotherapy or targeted treatments are not options.

An overview of current treatment algorithms is presented below:

Fig 1A. BRAF wild type current systemic treatment algorithm

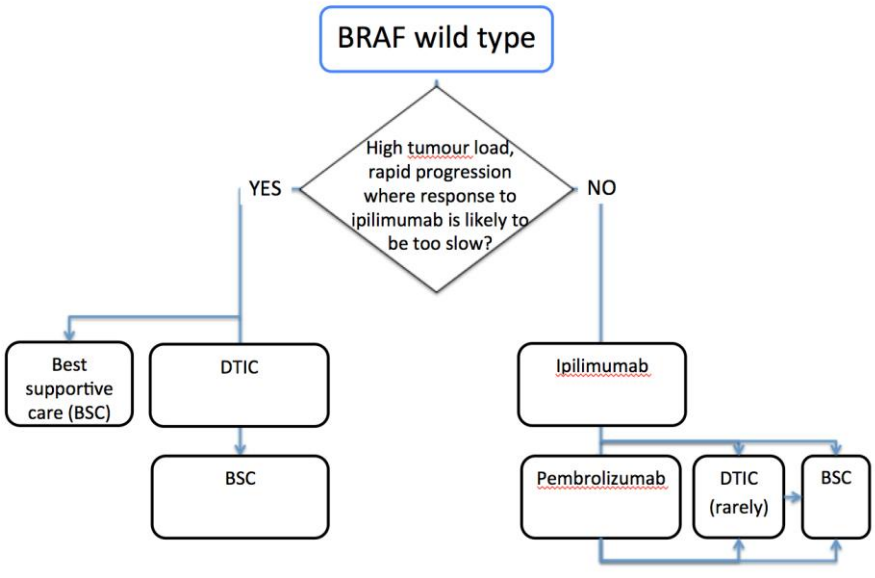

Fig 1B. BRAF V600 mutation current systemic treatment algorithm

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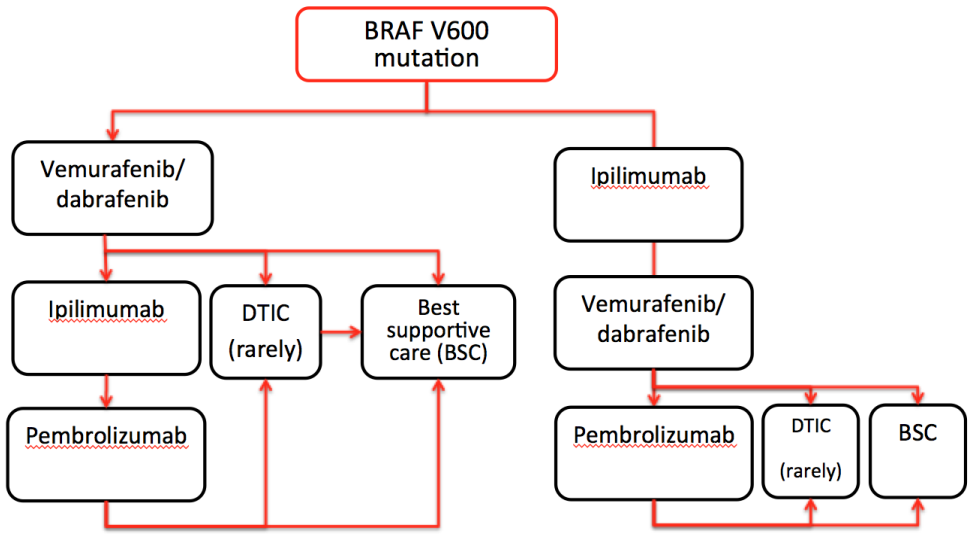

Targeted Treatment
Approximately 50% of patients will have mutation in the BRAF gene in their tumour, for which the BRAF inhibitors vemurafenib or dabrafenib are an option. Onset of action is rapid (days to weeks), with response rates of 50%, median progression free survival of around 7 months, and overall survival of 14 months compare with 10 months for DTIC (McArthur et al., 2014; Hauschild et a., 2014).

Immunotherapy - Ipilimumab
Ipilimumab is the only immunotherapy currently available as first line treatment. Onset of action is measured in months with the first assessment scan carried out after the course of 4 treatments at 3 months, response rates by conventional RECIST are is low at 15%. However, for those who respond to treatment, the response can be sustained. The CA284-24 phase III trial showed 3-year survival of 21% versus 12% for patients treated with ipilimumab and DTIC respectively (Roberts et al., 2011). This 10% difference in survival was maintained to 5 years with survival of 18% compared with 8% respectively (Maio et al., 2015). This and other combined analysis from phase II/III ipilimumab trials indicate there is a plateau of survival at 3 years, and that the 10% improvement survival is maintained to as far as the longest follow up point of 10-years (Schadendorf, 2015). Long term disease control, either as complete response or stable disease has been termed ‘clinical cure’.

Immunotherapy - Pembrolizumab
Pembrolizumab is available following progression on ipilimumab based on the KEYNOTE 002 phase II trial (Ribas et al., 2015) which showed RECIST response rates of 26% 2 mg/kg pembro compared with 4% for chemotherapy, and 6 month PFS of 34% versus 16% respectively.

Treatment Selection

First LineTreatment Selection
The selection of the most appropriate therapy depends on mutational status, tumour load, pace of disease, symptoms, co-morbidities and patient preference. For patients with a BRAF wild type melanoma, ipilimumab immunotherapy is the first line

treatment of choice unless there is a contra-indication, such as the patient not fit enough for treatment, or having rapidly progressive/symptomatic disease which would cause them to deteriorate too rapidly to gain a benefit from ipilimumab.

For patients with a melanoma with a BRAF mutation, immunotherapy tends to be selected as a first choice for those with low volume slowly progressive disease who are most likely to be able to complete the treatment and thus gain a benefit from treatment. For those who are symptomatic or have rapidly progressive disease, likely to cause clinical deterioration within 3 months, treatment with a BRAF inhibitor is indicated. Between these two end of the spectrum clinical judgement is need to select the correct treatment. Overall however, given that the long term sustained 'clinical cure' seen with ipilimumab has not been described for BRAF inhibitors, where there are no contraindications immunotherapy tends to be sequenced first, though there is not randomised control trial comparing the sequencing to guide practise.

Second Line Treatment Selection
For patients with BRAF wild type tumours progressing after ipilimumab, pembrolizumab would be the treatment of choice unless contra-indicated since it has been shown to be more effective than chemotherapy (see Fig 1A). For patients with melanoma with a BRAF mutation, if treated first with ipilimumab then treatment options include a vemurafenib or dabrafenib or pembrolizumab (Fig 1B). The best sequencing for these is not known. For patient with BRAF mutant tumours progressing following 1st line vemurafenib or dabrafenib, the options are ipilimumab, chemotherapy or best supportive care. And for those who have received both BRAF inhibitor and ipilimumab, if they are well enough and there are no contra-indications the treatment of choice is pembrolizumab. Chemotherapy is sometimes used where immunotherapy and targeted agents are not options.

Is there significant geographical variation in current practice?

Variation exists in access to drugs via clinical trials. Since cancer centres offer more trials than cancer units, and many of the drugs which have been shown to be effective are available at present on trial only. Nivolumab for example has recently been available in a limited number of centres on the phase II trial CA209-172. Therefore patients who live too far away to travel to a centre would not have access Similarly, access to combination targeted treatment with a BRAF and MEK inhibitor is currently restricted to within trials.

Are there differences of opinion between professionals as to what current practice should be?

For patients with BRAF mutation, the decision between ipilimumab and BRAF inhibitor first line may sometimes be 'grey' and the decision must be based on clinical experience, since there are no very accurate prognostic biomarkers or response biomarkers to immunotherapy, therefore there may be variation in practice because of lack of evidence. There is a similar lack of evidence for patients with a melanoma with BRAF mutation receiving ipilimumab first, for best sequencing of pembrolizumab versus BRAF inhibitor.

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Single Technology Appraisal (STA)

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Alternative classes of treatment and their characteristic properties of response and toxicity are shown in table 1.

Nivolumab shows has the advantage of high response rates similar to BRAF inhibitor, but with lower toxicity and better survival and higher 1 year overall survival. Compared with ipilimumab, nivolumab has much higher response rates, and higher PFS, 1-year survival and better toxicity profile. It is not yet known if 'clinical cure' is achievable with nivolumab as for ipilimumab.

Table 1 General properties of response and tolerability of nivolumab compared with current alternatives

	Response rate	Onset of action	Sustained long term disease control	PFS benefit	Survival benefit	Toxicity
Nivolumab	high	weeks/months	unknown - data immature	yes	yes	low
Ipilimumab	low	months	yes	yes	yes	medium
vemurafenib/ dabrafenib	high	days/weeks	no	yes	yes	low/medium
DTIC chemotherapy	low	weeks/months	no	not demonstrated	no	low/medium

Nivolumab is being assessed in two settings (1) previously untreated advanced/unresectable melanoma without a BRAF mutation (ID856) and with a BRAF mutation (ID847) (2) After progression with anti-CTLA4 therapy (ID845). Table 2A and 2B look in more details at the comparison of nivolumab with standard of care. The reasons for combining the untreated BRAF wild type and BRAF mutant melanoma patients are discussed below.

Nivolumab response and BRAF status

There is no evidence to date that BRAF mutations can affect response to immune checkpoint inhibitors. At the time of the original registration trials for ipilimumab were carried out, patients were not being routinely stratified by BRA. However, data from the ipilimumab Italian expanded access programme of 855 patients found no relationship between response and BRAF status (Ascierto et al., 2014).

The data is similar for nivolumab. Where it has been looked at, nivolumab is equally effective in BRAF mutant and wild type populations. Predefined subset analysis of the CHECKMATE 037, comparing nivolumab with DTIC in a ipilimumab pre-treated population (see Appendix 1 for summary of phase III trials) showed a response rate of 23% in patient with a mutation versus 34% in those with wild type. Recently, Larkin and colleagues carried out a pooled analysis of 4 trials with 440 patients in total, and found in this retrospective analysis that nivolumab has similar efficacy and safety outcomes in patients with wild type or mutant BRAF, regardless of previous

BRAF inhibitor or ipilimumab treatments (Larkin et al., 2015). There are no direct trial comparisons of sequencing of BRAF inhibitors with immunotherapy, and it seems that choices can be effective and are options, with the decision based on patient and tumour factors

(1) Nivolumab in previously untreated advanced unresectable melanoma

Table 2A. Summary of phase III trials of nivolumab effectiveness and tolerability in untreated unresectable/metastatic patients compared with standard of care

Agent	Response rate %	Median PFS (mo)	1-yr OS %	G3/4 treatment related toxicity	% discontinued due to toxicity
Nivolumab	40-44	5.1-5.9	73	12-16	7-8
Ipilimumab	15-19	2.9	47	27	15
vemurafenib/ dabrafenib	44-50	6.2-6.9	55	59	3-12
DTIC	5-14	1.6-2.7	36-43	18	2-12

Nivolumab data in Table 2A is from CHECKMATE 066 and CHECKMATE 067. Data for from comparator standard of care registration studies are from BRIM3 (Chapman et al, 2011), BREAK-3 (Hauschild et al., 2012), co-BRIM (Larkin et al.,2014). 1yr OS data for ipilimumab is taken from CA184-24 (Robert et al., 2011).

Nivolumab has the advantage of high response rates similar to BRAF inhibitor, but with lower toxicity and higher 1 year overall survival. Compared with ipilimumab, nivolumab has much higher response rates, and higher PFS, 1-year survival and better toxicity profile.

(2) Nivolumab in previously untreated advanced unresectable melanoma after progression with anti-CTLA4 therapy.

Table 2B. Summary of phase III trials of nivolumab effectiveness and tolerability for advanced unresectable melanoma after progression with anti-CTLA4 therapy compared with standard of care

Agent	Response rate %	Median PFS (mo)	6 month PFS %	1-yr OS %	G3/4 treatment related toxicity %	Discontinued due to toxicity %
Nivolumab	32	4.7	48	not mature	5	3
Pembrolizumab	21	2.9	34-38	not mature	11-14	3-7
Vemurafenib/ dabrafenib*	44-50	6.2-6.9	-	55	59	3-12
Chemo	4-11	2.7-4.2	16	matched data not mature	9-26	3-6

Nivolumab data from CHECKMATE 037 trial. Comparator trials are phase II KEYNOTE 002 (Robert et al., 2015) for pembrolizumab. Vemurafenib/dabrafenib data are taken from phase III untreated patients as for table 2A since there are no phase III ipi pretreated trials.

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Compared with pembrolizumab nivolumab shows marginally higher response rates and PFS, though this difference should be interpreted with caution since the pembrolizumab trial, KEYNOTE 002 was a smaller phase II trial compared with the nivolumab CHECKMATE 037 phase III trial, and there have been no head to head comparisons and therefore it is premature to judge whether one is superior. In every day practise they are regarded as showing having similar efficacy. Toxicity is the comparable for nivolumab and pembrolizumab. Comparison with BRAF inhibitors in table 2B is with untreated (rather than pre-treated) patients from phase III cohorts since there are no phase III trials for comparison in an ipilimumab treated population. In this context, response rates and 6 month PFS are comparable. Toxicity is less for pembrolizumab than BRAF inhibitors. Chemotherapy shows significantly lower response rates, median PFS and 6 month PFS, with higher toxicity.

Long term response nivolumab

Long term data similar to ipilimumab is not yet available for nivolumab (5 years plus survival). However, there is some evidence that efficacy is sustainable. Of 107 patients treated in a phase I trial with nivolumab, 3-year overall survival was 41% and of the 34 patients with objective response, median response duration was 22.9 months (Hodi et al., 2014; Topalian et al., 2014).

Summary of advantages of nivolumab

For melanoma patient with metastatic disease, from the time they are diagnosed the clock is ticking to the point where they become to unwell for treatment, unless an effective intervention is found. For this reason clinicians given the most effective treatments first rather than saving them, since waiting until the patient has failed a previous treatment, risks the patients becoming less well, and therefore not fit enough to for further treatment, or less able to tolerate treatment. The importance of early treatment with effective agents is illustrated by trials which allow crossover, such as the BREAK-3 trial comparing dabrafenib with DTIC chemotherapy (Hauschild 2013). The most common reason for stopping DTIC was progression rather than toxicity, and despite being permitted to change to a more effective treatment, only 60% did, and the survival for the DTIC population as whole never caught up with patients treated up front.

For this reason, the use of nivolumab which has higher response rates and PFS than ipilimumab available could make a large difference to outcomes. To date, response appears to be sustained, potentially similar to ipilimumab, though long term follow up data is awaited. Another factor to take into consideration is the high rate of auto-immune toxicity seen with ipilimumab when given first line which could potentially prevent 2nd line treatment with pembrolizumab. Therefor for this reason giving a less toxic regimen first is also an advantage.

Efficacy and tolerability of nivolumab post anti-CTLA at least as good a pembrolizumab, indicating a similar role potentially in routine treatment algorithms. In addition nivolumab could have a place in the BRAF mutant population who have not received a BRAF inhibitor, an indication that currently lies outside NICE guidance for pembrolizumab since the subset, and pooled trial analysis suggested that BRAF pre-treatment in the BRAF mutant population is not a necessary pre-requisite (Larkin et al., 2015).

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Single Technology Appraisal (STA)

It is likely that if nivolumab were available use of ipilimumab would reduce, saving morbidity from toxicity, and admission rates.

REFS

Ascierto PA, et al., J Transl Med. 2014 May 7;12:116
Chapman PB, et al. N Engl J Med. 2011 Jun 30;364(26):2507-16.
Hauschild A, et al. Lancet. 2012 Jul 28;380(9839):358-65.
Hodi FS, et al. 2010 Aug 19;363(8):711-23.
Hodi et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 9002).
Larkin J, et al. N Engl J Med. 2014 Nov 13;371(20):1867-76.
Larkin J, et al. JAMA Oncol.2015 Jul;1(4):433-40.
Larkin J, et al. N Engl J Med. 2015 Jul 2;373(1):23-34.
Maio M, et al. J Clin Oncol. 2015 Apr 1;33(10):1191-6.
Ribas A, et al. Lancet Oncol. 2015 Aug;16(8):908-18.
Robert C, et al. N Engl J Med. 2011 Jun 30;364(26):2517-26.
Robert C, et al. N Engl J Med. 2015 Jan 22;372(4):320-30.
Robert C, et al. N Engl J Med. 2015 Jun 25;372(26):2521-32.
Schadendorf D, et al. J Clin Oncol. 2015 Jun 10;33(17):1889-94.
Topalian SL, et al. J Clin Oncol. 2014 Apr 1;32(10):1020-30.
Weber JS, et al. Lancet Oncol. 2015 Apr;16(4):375-84.

Appendix – phase III nivolumab studies

Trial Name	no patients	Treatment	BRAF status	Publication
Phase III Nivolumab studies untreated				
CHECKMATE 066	418	nivolumab 3 mg/kg DTIC 1000 mg/m2	wild type	Robert et al., 2015
CHECKMATE 067	945	nivo 1 mg/kg + ipi 3 mg/kg nivo 3 mg/kg ipi 3 mg/kg	mutant and wild type	Larkin et al., 2015
Phase III nivolumab studies after progression with anti-CTLA-4 therapy				
CHECKMATE 037	405	nivolumab 3 mg/kg DTIC/carbo-taxol	mutant and wild type	Weber et al., 2015

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

There are generally poorer prognosis patients, with more advanced stage, increased LDH, and higher volume of disease, and brain metastases, but there is no evidence that these benefit differentially from nivolumab.

The biomarker PDL1 has been looked at in a number of trials, notably the phase III CHECKMATE 067 study. However, the positive and negative predictive values are not sufficient to be used as a biomarker in mainstream practise. The cut-off level for considering a patient PDL1 positive is not clearly determined and there is no standard antibody for determining PDL1 status.

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Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Particular subgroups who would benefit potentially are BRAF wild type patient with rapidly progressive disease and who are therefore unsuitable for ipilimumab in whom without nivolumab their only option would be chemotherapy. Nivolumab has very low toxicity and there are therefore not subgroups that would be put at risk from the technology.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

Specialist clinics

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Since toxicities for nivolumab are lower than for ipilimumab or BRAF inhibitors, it may be that there is less professional input required overall to manage toxicities, and less inpatient admissions. There is likely to be potentially a reduction in the use of ipilimumab and BRAF inhibitors, since patients who response will not need second line treatment. I think clinicians are likely to choose nivolumab as a first choice of treatment rather than ipilimumab or BRAF inhibitors in many (but not all) patients.

If the technology is already available, is there variation in how it is being used in the NHS?

Not yet available

Is it always used within its licensed indications?

NA

If not, under what circumstances does this occur?

Within trials

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 incorporate approved drugs on a ‘static’ list into the NICE melanoma guidelines. However, these guidelines refer to NICE STAs for the use of these drugs and do not provide guidance for example on which or the options available are preferable, or which sequence they should be used in. The only treatment NICE melanoma guidelines specifically offer guidance on is DTIC, in which the guidance is ‘consider dacarbazine for patients with stage IV melanoma if immunotherapy or targeted therapy are not suitable.’

The advantages and disadvantages of the technology

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Single Technology Appraisal (STA)

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?

Answer: the treatment is likely to be easier to use than ipilimumab and potentially BRAF inhibitors since the toxicities are less. For patients who are responding the quality of their life will be better. Compared with ipilimumab treatment will continue for a longer time, rather than being a course of 4, however their use will be comparable with BRAF inhibitors, being ongoing until patient stop deriving clinical benefit.

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.

Answer: As for other targeted treatments, patients will continue whilst they continue to get clinical benefit past progression. Unlike chemotherapy, where a new lesions tends to herald general progression and treatment resistance, response to targeted agents show more heterogeneity of response with non-progressing lesions remaining stable or sometimes responding. The benefit of continuing past progression is illustrated in the phase III CHECKMATE 037 study (Weber et al. 2015; Appendix). Patients continued past first RECIST progression continued to benefit (Figure 4). On this study, 31% of the patient on trial continued past progression, of these 8% subsequently had a greater than 30% reduction in the sum of the longest diameters of target lesions, consistent with immune-related response.

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?

Answer: I am familiar with nivolumab and the clinical condition used in trials reflects that observed in clinical practise, and the trials were conducted in circumstances that reflect UK practise in which they would be used. The most important outcomes are progression free survival, response rate and overall survival.

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?

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Single Technology Appraisal (STA)

Introduction of nivolumab is likely to reduce treatment related toxicity in the metastatic melanoma population since has half the rate of serious toxicity of ipilimumab, and will be selected instead of ipilimumab as a first treatment of choice. There are no toxicities which have come to light and which were not apparent in the clinical trials.

Equality and Diversity

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

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.

Evidence that BRAF status does not affect nivolumab response:

Larkin J, et al. Efficacy and Safety of Nivolumab in Patients With BRAF V600 Mutant and BRAF Wild-Type Advanced Melanoma: A Pooled Analysis of 4 Clinical Trials. JAMA Oncol.2015 Jul;1(4):433-40.

Evidence for long term survival following nivolumab treatment:

Hodi et al. Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial.J Clin Oncol 32:5s, 2014 (suppl; abstr 9002).

Implementation issues

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The NHS is required by the Department of Health and the Welsh Assembly Government 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 and the Welsh Assembly Government 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)?

Answer: Nurses and medical staff in site specific teams are familiar with managing toxicities of nivolumab and therefore there would not be any extra education and training needed. The side effects profiles are similar for nivolumab to ipilimumab but less common, and treatment of toxicity is the same, based around steroids.

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Patient/carer organisation submission (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

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, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

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 length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Melanoma UK

Your position in the organisation: Founder

Brief description of the organisation: Registered charity and support group to advanced melanoma patients and families. The organisation has a board of trustees and a panel of medical experts.

2. Living the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Melanoma is a very serious disease and is becoming increasingly more common in the UK. Advances in treatments mean that some patients are now able to live longer with this disease, whereas previously, their future was certainly premature death. The disease is very worrying for patients and families, particularly for those patients who are young and have young families. The disease affects different people in different ways and of course, the severity of symptoms depends on the spread of the disease.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Patients and carers are anxious to see as many new treatments made available as is practically possible. A number of treatment options have become available for melanoma patients in recent years and it is important that patients access to different treatment options.

 Current NICE-recommended treatment options for metastatic melanoma include:

- ✓ Ipilimumab for previously untreated unresectable or metastatic melanoma.
- ✓ Vemurafenib for previously untreated, locally advanced or metastatic melanoma which is BRAF V600 mutation-positive.
- ✓ Dabrafenib for unresectable or metastatic BRAF V600 mutation-positive melanoma.

 Whilst other forms of treatment, such as chemotherapy, work by targeting the tumour itself, immuno-oncology can harness the power of the immune system to fight back against the cancer. Immuno-oncology treatments have the potential to significantly boost one year cancer patient survival.

 In September 2015, pembrolizumab (brand name Keytruda) was recommended by NICE as a second line treatment either:

- after the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor (such as dabrafenib or vemurafenib [BRAF inhibitors] or trametinib or cobimetinib [MEK inhibitors]), and

- when the company provides pembrolizumab with the discount agreed in the patient access scheme.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The patients we represent are not in positions to say what treatments they prefer, as this can often be dictated by where the disease has spread and what prior treatments they have received. The patients that have been fortunate enough to have had access to some of the new treatments since Ipilumumab first became available and are still alive, report their relief at being given such hope.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Patients are encouraged by the results shown in clinical trials and again, are anticipating being able to return to their normal lives which they cannot hope for whilst not on treatment.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Patients understand that the side effects of this treatment are likely to be more tolerable than other treatments. This is very important to patients

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do patients and/or carers 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 patients or carers have about current NHS treatments in England.

Melanoma patients' main concerns are about NOT getting access to treatments, not the treatments themselves.

Please list any concerns patients or carers have about the treatment being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Patients who have managed to stay reasonably "well" are likely to tolerate treatments more easily than a patient group who are struggling with the disease.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Patients who are quite poorly and therefore not in a good starting position.

7. Research evidence on patient or carer views of the treatment

Is your organisation 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 patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

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?

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 (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

☐ **Yes**

If yes, please explain what makes it significantly different from other treatments for the condition

Nivolumab has shown 1 year survival rates in advanced or metastatic melanoma of 73% compared to ipilimumab that doubled one and two year survival rates for patients with advanced and metastatic melanoma, achieving a 1 year survival rate of 46%.

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Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- For patients with certain types of melanoma, progression-free survival could be as long as 14 months – a considerable advance in outcomes.

 The treatment-related adverse event rate for nivolumab was 82.1% compared to 86.2% for ipilimumab The most common adverse reactions (≥20%) reported with nivolumab in Trial 1 were rash (21%) and in Trial 3 were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%).

 There is evidence that combinations of immuno-oncology treatments (such as ipilimumab and nivolumab) will be able to boost one year survival rates for melanoma patients further still.

 Although this combination is not yet licensed for use in the UK, it is likely that it will be the future 'gold standard' of advanced melanoma treatment in the future. The combination therapy improved progression-free survival by a median of 11.5 months compared to 6.9 months for nivolumab on its own, with just 2.9 months for ipilimumab monotherapy. It is vital that clinicians have access to nivolumab ahead of the combination becoming available, in order for them to gain clinical experience using the drug and managing the side effects.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Nivolumab for treating advanced (unresectable or metastatic) melanoma

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Date completed 28th October 2015

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/06/11.

Declared competing interests of the authors

None

Acknowledgements

We would like to thank Dr Pippa Corrie (Consultant and Associate Lecturer in Medical Oncology, Addenbrooke's Hospital, Cambridge, UK) for providing clinical advice during the production of this report, and for commenting on a draft of the report.

We also thank: Karen Welch, Information Scientist, SHTAC, for appraising the literature search strategies in the company's submission, running an update of the company's searches and searching for ongoing studies; Dr Jo Picot, Senior Research Fellow, SHTAC, for assistance with appraising the company submission; Professor Joanne Lord, Director, SHTAC, for acting as internal editor for the draft report; and Dr Vicky Copley, independent statistical adviser, for providing statistical advice to the team.

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.

This report should be referenced as follows:

Cooper K, Kalita N, Streit E, Shepherd J, Chorozoglou M, Frampton G. Nivolumab for treating advanced (unresectable or metastatic) melanoma: A Single Technology Appraisal. Southampton Health Technology Assessments Centre (SHTAC), 2015.

Contributions of authors

Keith Cooper (Senior Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. Neelam Kalita (Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. Elke Streit (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report. Jonathan Shepherd (Principal Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor. Maria Chorozoglou (Senior Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the

report. Geoff Frampton (Senior Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report.

Word count:

38,822

[redacted]

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AE	Adverse events
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
AUC	Area under the curve
BIC	Bayesian information criterion
CHMP	Committee for Medical Products for Human Use
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CS	Company's submission
CSR	Clinical study report
DC	Discontinuation
DIC	Deviance Information Criterion
DTIC	Dacarbazine
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
EQ-5D	EuroQoL five dimension questionnaire
ERG	Evidence Review Group
HRQoL	Health-related quality of life
HR	Hazard ratio
ICC	Investigator's choice of chemotherapy
ICER	Incremental cost-effectiveness ratio
IRRC	Independent radiological review committee
ITT	Intention-to-treat
LDH	Lactate dehydrogenase
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD-L1	Programmed death receptor ligand 1
PFS	Progression-free survival
PP	Per protocol
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
STA	Single Technology Appraisal
SmPC	Summary of product characteristics

TA	Technology Appraisal
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event

SUMMARY

Scope of the company submission

The company's submission (CS) reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). The submission assesses the clinical effectiveness and cost effectiveness of nivolumab monotherapy compared to BRAF inhibitors (dabrafenib and vemurafenib for BRAF V600 mutation-positive melanoma), ipilimumab, dacarbazine (DTIC), and to best supportive care for the treatment of adults with advanced (unresectable or metastatic) melanoma.

Summary of submitted clinical effectiveness evidence

The company's systematic review of clinical effectiveness identified three relevant phase III RCTs of nivolumab monotherapy. In these, nivolumab was administered by intravenous infusion at a dosage of 3mg/kg every two weeks.

- The CheckMate 066 trial compared nivolumab with 1000mg/m^2 DTIC, administered every three weeks by intravenous infusion. Participants were treatment-naïve patients who did not have a BRAF mutation.
- The CheckMate 067 trial compared nivolumab with 3mg/kg ipilimumab, administered every three weeks by intravenous infusion. Participants were treatment-naïve patients, and BRAF mutation-negative as well as BRAF mutation-positive patients were enrolled in this trial. Nivolumab in combination with ipilimumab was also investigated in this study, but is outside the NICE scope and therefore not included in the CS.
- The CheckMate 037 trial was an open-label study that compared nivolumab with the investigator's choice of chemotherapy (ICC), either 1000mg/m^2 DTIC every three weeks or paclitaxel 175mg/m^2 combined with carboplatin area under the curve 6 every three weeks. Participants were patients who progressed on or after prior ipilimumab, or ipilimumab and a BRAF inhibitor if they were BRAF mutation-positive.

The primary outcome in all three studies was overall survival (OS). Additional primary outcomes were progression-free survival (CheckMate 067) and objective response rate (CheckMate 037). The trials were judged by the Evidence Review Group (ERG) to be of generally good methodological quality. The ERG believes that it is likely that the company has identified all relevant RCTs.

The CS reports the effects of nivolumab across a range of outcomes relevant to the NICE scope and decision problem, summarised below. All CheckMate trials are still ongoing for extended follow-up in order to generate evidence on longer-term outcomes, including OS, PFS, and health-related quality of life (HRQoL).

OS data are available for the CheckMate 066 trial. There was a significant reduction in all-cause mortality with nivolumab when compared to DTIC. At the time of database lock (August 2014), the median OS had not been reached, i.e. more than half of the nivolumab-treated patients were still alive, whereas most of the patients treated with DTIC had already died (median OS = 10.84 months).

Significant PFS benefit was observed when nivolumab was compared with DTIC (CheckMate 066) or ipilimumab (CheckMate 067), but no difference in PFS was detected between nivolumab and ICC in CheckMate 037, presumably due to the immaturity of the PFS data in the latter trial.

In terms of ORR, there was significant benefit of nivolumab over comparator drugs in all three CheckMate trials. More patients treated with nivolumab experienced complete response than those treated with alternative drugs, although the total number of patients with complete response was low in all study groups (<10%). Furthermore, treatment response was found to be more durable in nivolumab-treated patients compared to patients treated with DTIC, ipilimumab, or ICC, with the longest duration of response observed in the CheckMate 067 nivolumab group exceeding 12 months at the time of reporting.

There was also a significant change in tumour burden in nivolumab-treated patients. More patients in the nivolumab groups of the CheckMate trials experienced reductions in tumour size and achieved at least a partial response, compared with patients treated with DTIC, ipilimumab, or ICC.

In all three CheckMate trials, patients were able to continue treatment beyond progression if experiencing clinical benefit, and a proportion of those treated with nivolumab continued to respond to the drug (ORR up to 27.0% in CheckMate 037).

Interim analyses of health-related quality of life (HRQoL) were available only for the CheckMate 066 trial. Patients receiving nivolumab tended to have higher HRQoL scores at baseline than those receiving DTIC but the statistical significance of the difference is questionable. Although nivolumab appeared to improve some aspects of HRQoL relative to

baseline scores when assessed on the EQ-5D and different subscales of the EORTC-QLQ-C30 questionnaire (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 questionnaire), there is no consistent evidence that nivolumab had a sustained effect on HRQoL. The company concluded that nivolumab does not impair HRQoL (relative to baseline), and the ERG agrees that this is a reasonable conclusion based on the interim data that are available.

Pre-defined subgroup analyses were undertaken for most baseline characteristics, and outcomes were in favour of nivolumab for most subgroups. Nivolumab-treated patients experienced benefit regardless of programmed death receptor ligand 1 (PD-L1) status compared to patients treated with the comparator drugs, although benefit was highest in PD-L1-positive patients, with lower mortality rates and longer PFS compared to patients with PD-L1-negative status. Subgroup analyses by BRAF mutation demonstrated a benefit for nivolumab compared to ipilimumab in terms of PFS and ORR in CheckMate 067, regardless of BRAF mutation status, but patients in the BRAF mutation-negative group experienced higher benefit than those with BRAF positive status.

The proportion of patients who experienced adverse events (AEs) was generally similar between nivolumab and the comparator drugs. Nearly all patients experienced at least one AE of any grade, regardless of treatment allocation, and the majority of AEs were treatment-related. Higher grade and serious AEs occurred less frequently in nivolumab-treated patients, and a smaller proportion of patients discontinued nivolumab treatment due to treatment-related AEs (TRAEs) compared to patients treated with any of the comparator drugs. The most frequently reported TRAEs among nivolumab-treated patients were fatigue, pruritus, rash, diarrhoea, and nausea. Treatment-related serious AEs (TRSAEs) included hyperglycaemia, vomiting, pyrexia, and pneumonitis. These were not reported by more than two patients in any CheckMate trial, and most were resolved. One death due related to nivolumab treatment was reported.

Indirect comparisons were conducted using selected RCTs from the company's systematic review of clinical effectiveness. Two separate evidence networks were created, for the comparison with ipilimumab and palliative chemotherapy (BRAF mutation-negative patients), and for the comparison with BRAF inhibitors (vemurafenib and dabrafenib, BRAF mutation-positive patients). The networks used patient-level data / 'pseudo' patient-level data (BRAF mutation-negative / mutation-positive patients, respectively) from the trials to inform covariate-adjusted parametric survival models used directly in the economic model.

Summary of submitted cost effectiveness evidence

The CS includes:

i) A review of published economic evaluations of nivolumab for advanced melanoma

ii) An economic evaluation undertaken for the NICE STA process. The cost effectiveness of nivolumab is compared to that ipilimumab and DTIC for BRAF mutation-negative patients and compared to ipilimumab, dabrafenib and vemurafenib for BRAF mutation-positive patients.

A systematic search of the literature was conducted by the company to identify economic evaluations of nivolumab for advanced melanoma. The review did not identify any relevant studies.

The cost effectiveness analysis (CEA) uses a semi-Markov model to estimate the cost-effectiveness of nivolumab compared with DTIC and ipilimumab for BRAF mutation-negative patients and with dabrafenib, ipilimumab and vemurafenib for BRAF-mutation-positive patients with advance melanoma. The model adopted a lifetime horizon of 40 years and a cycle length of one week. The model consisted of three health states: pre-progression, progression and death.

The economic evaluation used data from the CheckMate 066 trial. The company conducted covariate-adjusted indirect comparisons between comparators using patient-level data. These data were used to estimate time to progression (TTP), post-progression survival (PPS) and pre-progression survival (PrePS), which were used to derive the transition probabilities between health states.

Results of the economic model were presented as incremental cost per quality-adjusted life years (QALY) and incremental cost per life years gained. Three of the comparators (ipilimumab, dabrafenib and vemurafenib) have a confidential patient access (PAS) scheme. Results were presented at the list price and at the estimated PAS prices. The results of the cost effectiveness analysis for BRAF mutation-negative patients at the list price showed that nivolumab is cost effective compared to ipilimumab and DTIC and for BRAF mutation-positive patients nivolumab is cost effective compared to dabrafenib, vemurafenib and ipilimumab at a willingness to pay threshold of £30,000 per QALY.

The company performed a range of deterministic and probabilistic sensitivity analyses to assess model uncertainty. The base case results were robust to uncertainties in the key model parameters and assumptions, except for changes in the maximum treatment duration for nivolumab. The PSA showed that there is 87% and 99% probability of nivolumab being cost-effective for BRAF-mutation-negative patients at a willingness to pay threshold of £30,000 and £50,000 per QALY gained, and a 100% probability of nivolumab being cost effective for BRAF-mutation-positive patients for both thresholds.

Commentary on the robustness of submitted evidence

Strengths

The decision problem in the company submission generally accords with the NICE scope. However, the ERG notes that the economic analysis includes DTIC as a comparator in the BRAF mutation-negative analysis, but not in the BRAF mutation-positive analysis, with no apparent justification.

The company's systematic review of clinical-effectiveness followed standard procedures and is of good quality. The ERG is not aware of any additional relevant published trials that could be included.

The three key CheckMate RCTs were well-designed and well-conducted and provide an appropriate evidence base to inform the assessment of clinical-effectiveness and cost-effectiveness of nivolumab.

The structure of the economic model was appropriate, comprehensive and reflected the clinical pathway for patients with advanced melanoma. The model was well-structured and provided the relevant data sources in a transparent way.

The methods chosen for the analysis were generally appropriate and conformed to NICE methodological guidelines.

The company performed a wide range of sensitivity analyses including one-way, probabilistic and scenario analyses to assess model uncertainty.

Weaknesses and areas of uncertainty

All three of the key RCTs included by the company in their systematic review of clinical-effectiveness are ongoing with further follow-up results expected to be published in the next year. Consequently, some of the results reported in the CS are from interim time points, in some cases based on relatively small numbers of patients or events, and are considered to be relatively immature due to lack of follow-up. This is notably for overall survival, one of the key outcomes that informs the assessment of cost-effectiveness in the CS.

The comparative efficacy of nivolumab with the comparator treatments in the NICE scope is uncertain due to a lack of available head-to-head data from clinical trials. The company's indirect comparison is complex and is based upon a number of assumptions and survival data extrapolations. Some of these assumptions appear reasonable and are noted by the CS to have been accepted in previous NICE appraisals of treatments for advanced melanoma. However, there is some uncertainty regarding the assumption and that there is no difference in treatment effects for nivolumab by BRAF mutation status. This is of significance as evidence from the CheckMate 066 trial, which included BRAF mutation-negative patients, was indirectly compared with evidence from a BRAF inhibitor trial, by definition including BRAF mutation-positive patients, and informed cost-effectiveness estimates for the BRAF mutation-positive patient group.

There is some uncertainty about the survival curves that best represent long-term overall survival and progression free survival, due to the short follow-up data currently available for the CheckMate trials.

The time spent on treatment is a key factor influencing cost effectiveness results but the maximum duration of treatment likely in practice is unclear.

DTIC has not been included as a comparator in BRAF mutation-positive patients.

Summary of additional work undertaken by the ERG

The ERG conducted the following additional scenario analyses:

- A series of one-way analyses choosing different types of survival models for treatment efficacy. This includes:

    - using the Weibull, lognormal, log-logistic and generalised gamma distributions to model TTP for nivolumab and the Gompertz distribution for DTIC and ipilimumab
    - using the exponential, Gompertz, log-logistic, lognormal and Weibull distributions to model PFS for BRAF inhibitors (vemurafenib assumed to be equivalent to dabrafenib)
- Using the data extrapolation method to model long-term survival for nivolumab
- Including DTIC as a comparator in BRAF mutation-positive patients
- A scenario that combines the following assumptions:
    - using the Weibull distribution to model TTP for nivolumab patients
    - modelling PFS using the lognormal distribution for BRAF inhibitors
    - using the data extrapolation method to model long-term survival for nivolumab
    - between two years and no maximum treatment duration for nivolumab

Generally, the individual scenario analyses had a small impact on the base case model results, with changes to the method for estimating long-term overall survival for nivolumab (using data extrapolation) having the largest impact. This increased the ICER for nivolumab compared to ipilimumab in BRAF mutation-negative patients to £36,072 per QALY and in mutation-positive patients to £27,171 per QALY. The results of the combination scenarios had a much greater impact on the model results which showed nivolumab was dominated by ipilimumab in both the BRAF mutation-negative and BRAF mutation-positive patient groups.

The ERG repeated all the above analyses with the confidential PAS discounts for the comparator drugs in a separate confidential appendix for the NICE Appraisal Committee.

1 Introduction to the ERG Report

This report is a critique of the company's submission (CS) to NICE from Bristol Myers Squibb Pharmaceuticals Ltd on the clinical effectiveness and cost effectiveness of nivolumab for advanced (unresectable or metastatic) melanoma. It identifies the strengths and weaknesses of the CS. Expert clinical advice was sought by the ERG to inform this report.

Clarification on some aspects of the CS was requested from the manufacturer by the ERG via NICE on 17th September 2015. A response from the company via NICE was received by the ERG on 2nd October 2015 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of the company's description of the underlying health proble

The CS generally provides a clear and accurate overview of the condition in sections 3.1 (CS p. 28) and 3.3 (CS p.33). However, the ERG notes that no reference is made to the genetic mutation BRAF (V600) that is prevalent in around 50% of people with melanoma. The presence of a BRAF mutation influences treatment choices.

Melanoma is described as an aggressive type of skin cancer which represents only 4% of all skin cancers, but accounts for 90% of skin-cancer related deaths. It mainly affects people of working age, with a mean age at diagnosis of 50 years. Incidence rates have been increasing over the past 50 years and the CS states that they are expected to continue rising by around 3.5% annually.

The CS estimates that 11,763 new cases were expected in England in 2013. Up to 10% of people diagnosed with melanoma present with advanced disease (unresectable or metastatic melanoma), and this is the patient group defined in the NICE final scope. The CS estimates there will be 1,304 new cases of advanced (unresectable or metastatic) melanoma in England during 2016. The company explains that the prognosis in advanced melanoma is generally poor and that life expectancy is commonly estimated at less than one year from diagnosis, but may have improved recently due to the availability of new treatments.

The CS lists a number of factors that can increase the risk of developing melanoma, and also lists prognostic factors (CS section 3.1 p 28).

2.2 Critique of company's overview of current service provision

The CS generally provides a clear and accurate overview of current pharmaceutical treatment options available to people with advanced melanoma in section 3.2 (CS p. 30). A list of relevant NICE guidance and other clinical guidelines is provided in Section 3.4 (CS p. 34). The company accurately describes current first-line treatments in advanced melanoma that have been recommended by NICE, with ipilimumab being the drug of choice for BRAF negative patients, and either ipilimumab or a BRAF inhibitor (either vemurafenib or dabrafenib) for those who have BRAF mutation. In this latter patient group, both drugs also represent second line treatment options for patients who did not receive them as their first-line therapy. For patients for whom ipilimumab or a BRAF inhibitor are not suitable, dacarbazine (DTIC) chemotherapy is the most common treatment in England. Last line systemic treatment is described as "palliative chemotherapy" regardless of BRAF mutation status. The ERG notes that this information is in line with current NICE guidlines[1], although the CS makes no mention of non-pharmacological options and service provisions described in the NICE Guideline NG14.

The CS does not explicitly describe which factors might make ipilimumab or a BRAF inhibitor unsuitable, or the proportion of patients this might apply to. After a clarification question from the ERG (clarification question A4) the company stated that eligibility for ipilimumab is determined according to the patient's overall fitness and the speed and extent of the disease. It is stated that patients should be fit enough to receive all four cycles of ipilimumab over a 12 week period. Expert clinical advice to the ERG also suggested that patients with immune toxicity (e.g. affecting people with rheumatoid arthritis) would be unlikely to be able to tolerate ipilimumab. The company did not state what factors might make treatment with a BRAF inhibitor unsuitable (other than BRAF mutation-negative status). However, expert clinical advice to the ERG suggested that there would be very few BRAF mutation-positive patients unable to take a BRAF inhibitor. The company also stated that of the BRAF mutation-negative population (who comprise 50% of the advanced melanoma population) up to 20% would not be suitable for ipilimumab and therefore may receive palliative chemotherapy, based on advice from UK clinicians participating in a BMS advisory board meeting. In summary, this appears to suggest there would be a minority of patients in whom ipilimumab or BRAF inhibitors would be unsuitable, and who, based on current management, would receive palliative chemotherapy or best supportive care (a comparator to nivolumab – see below).

The CS provides an overview of the limitations of current pharmacological treatment options in CS Table 7 (p. 35), stating that no long-term survival benefit has been demonstrated for BRAF inhibitor therapy or for chemotherapy (including DTIC chemotherapy). It is stated that the long-term survival benefit from ipilimumab treatment is observed in only 20% of patients. The CS suggests that the role of nivolumab in the clinical pathway will be to provide additional first and subsequent line treatment options that can be used regardless of BRAF status, and that are expected to provide longer-term survival benefits than currently available drugs (CS p. 32). Expert clinical advice to the ERG suggests that nivolumab could be potential a first-line treatment, in place of ipilimumab.

2.3 Critique of company's definition of decision problem

Population

The population is defined in the company's description of the decision problem as adults with advanced (unresectable or metastatic) melanoma. This is the population specified in the final scope issued by NICE and the ERG believes that this population is appropriate for the potential use of nivolumab in the NHS.

Intervention

The intervention described in the company's decision problem is nivolumab (brand name: Opdivo), and this is in line with the final scope issued by NICE. Nivolumab received marketing authorisation for advanced melanoma in June 2015. It is an immuno-oncology treatment that, according to the company, "stimulates the patient's own immune system to directly fight cancer cells" (CS p. 22).

As outlined in the CS (Table 2 p. 16, and chapter 2 p. 21 - 27), the summary of product characteristics (SmPC)[2] states that nivolumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults at a dosage of 3mg/kg every two weeks by intravenous infusion over 60 minutes. The treatment duration should be as long as there is clinical benefit or until treatment is no longer tolerated. The maximum duration is anticipated to be two years (CS Table 5, p. 25). Dose escalation or reduction is not recommended in the SmPC, and the company's European Public Assessment Report (EPAR) summary states that "dosing delay or discontinuation may be required based on individual safety and tolerability." Guidelines for treatment modifications and discontinuation are provided (CS Appendices Table 1 p. 4).

The CS states that the only contraindication is hypersensitivity to the active substance or to any listed excipients. However, the ERG notes that the CHMP has requested the

implementation of special warnings and precautions for the minimisation of immune-related adverse reactions that are associated with nivolumab treatment. The company describes these safety-related conditions of marketing authorisation on CS p. 25 and in Appendix 1, and these are specified in educational materials for professionals, patients and carers, including a "patient alert card" and a physician "adverse reaction management guide."

Overall, the intervention described in the decision problem reflects its use in the UK and is appropriate for the NHS. The impact on NHS service provision is described in CS section 2.4 (p. 26). The company points out that adequate infrastructure is already in place in the UK in the form of hospital oncology units, but adds that the nivolumab two-weekly dosing requirement represents a more frequent administration regimen than current therapies. The ERG notes that, in addition to the more frequent dosing of nivolumab as compared to current therapies, the continuous treatment of up to two years' duration may also impact on NHS service provision.

Comparators

The comparators of interest listed by the company are

- BRAF inhibitors (dabrafenib and vemurafenib – for people with BRAF V600 mutation-positive melanoma who have not previously received a BRAF inhibitor),
- Ipilimumab (for people who have not previously received ipilimumab),
- DTIC (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is/are unsuitable), and
- Best supportive care (for people who have received both a BRAF inhibitor and ipilimumab, or for whom either or both of these is/are unsuitable).

Referring to previous submissions to NICE, the company states that it considers DTIC to be a palliative chemotherapy, which forms part of best supportive care (CS Table 1, p. 14-15). Expert clinical advice to the ERG agrees with this and points out that the drug is rarely used in practice. However, the ERG notes that NICE Guideline NG14[1] recommends DTIC as a "systemic cancer treatment" for people with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable. The NICE guideline adds in a footnote that "this use is common in UK clinical practice" but states that DTIC did not have a UK marketing authorisation for this indication at the time of guideline publication (July 2015).

The final scope specified DTIC as a comparator drug for patients who have previously received "both a BRAF inhibitor and ipilimumab, or for whom either or both of these is/are

unsuitable." The ERG notes that the economic analysis includes DTIC as a comparator for BRAF mutation-negative patients, but not for BRAF mutation-positive patients.

The CS does not refer to pembrolizumab (brand name: Keytruda) for the treatment of advanced melanoma in adults. NICE has recently recommended the use of pembrolizumab in advanced melanoma after disease progression with ipilimumab (NICE TA357),[3] and in patients not previously treated with ipilimumab (this recommendation is based on the final appraisal determination issued in October 2015. Final guidance is due in November 2015). The ERG notes that although pembrolizumab is a potential comparator to nivolumab it was not included in the final scope issued by NICE and the ERG therefore considers the company's choice of comparators to be appropriate.

Outcomes

The outcomes stated in the company's decision problem are all those specified to be of interest in the final scope:

- Overall survival,
- Progression-free survival,
- Response rate,
- Adverse effects of treatment,
- Health-related quality of life.

Economic analysis

The approach to the economic analysis proposed in the decision problem matches the final scope issued by NICE and is appropriate for the NHS. The company states that costs are considered from a National Health Service and Personal Social Services perspective, and that the availability of patient access schemes for the comparator technologies has been taken into account.

Other relevant factors

- Subgroups

The final scope does not specify any subgroups and the CS has not specified any subgroups in the decision problem. The ERG notes that the CS reports the results of various pre-defined subgroup analyses for the overall survival outcome from the CheckMate 066[4] trial in the main body of the CS (CS section 4.8 p. 89-91) and for CheckMate 067[5] in CS Appendix 7. The economic analysis presents results by BRAF mutation status. The ERG considers

this approach to be adequate although the usual caveats regarding subgroup analyses apply (e.g. small sample size, need for appropriate analysis, caution in interpretation).

- Equity or equality

No equity or equality issues were specified in the final scope, and the company did not identify any in their decision problem. The ERG is also not aware of any specific issues related to equity or equality in the use of nivolumab in patients with advanced melanoma, and expert clinical advice to the ERG confirmed that the more frequent dosing regimen required in nivolumab treatment compared to alternative treatments was unlikely to put patients at a disadvantage.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's approach to systematic review

3.1.1 Description of the company's search strategy

The searches are generally fit for purpose, with the strategies well-constructed and with relevant search filters applied. An appropriate range of databases, including those recommended by NICE (Medline, Embase, Medline In-Process and Other Non-Indexed Citations, and The Cochrane Library), have been used, and tabulated, with only one minor transcription error. The search terms representing the indication were left broad (i.e. "melanoma") to maximise the number of references identified , rather than having been restricting to advanced, unresectable or metastatic disease.

The clinical-effectiveness searches, although deemed thorough with adequate documentation, contain three different searches:

(i) a search designed to identify RCTs of nivolumab and comparator therapies used in the first-line treatment of advanced melanoma, originally conducted in October 2014 and updated in May 2015;

(ii) a search to identify RCTs of nivolumab and comparator therapies in the subsequent-line setting, originally conducted in July 2014 and updated in May 2015.

(iii) a search aligned to the current decision problem, conducted in May 2015

This sequence of searches is assumed to be explained by the fact that originally there were three separate planned NICE single technology appraisals of nivolumab monotherapy for advanced melanoma, which were subsequently combined into the current appraisal.

The search strategies did not document the number of hits attained (returned) for each line of the strategy, which lessens immediate transparency and renders comparison of hits in replication of the searches more difficult.

The ERG replicated the Medline and Cochrane searches from the clinical-effectiveness search strategies as they were four months out of date (conducted on 7th/8th May 2015). No additional studies relevant to the systematic review of clinical-effectiveness inclusion criteria in the CS were identified from this search (CS Table 8, p. 38).

The ERG re-ran the searches for cost effectiveness, cost and resource identification and quality of life studies, since all three (dated 25th November 2015) were nine months out of date. No additional relevant studies were identified from this search, however, through *ad hoc* searching the ERG found identified a potentially relevant cost-effectiveness study reported in a 2015 conference abstract (see Section 4.1 of this report).[6] The School of Health and Related Research Health Utilities Database (ScHARRHUD) was additionally searched by the ERG, for utility papers on melanoma; however, the only reference found was already in the CS reference list.

Although the CS stated that annual proceedings of the conferences were hand searched in order to identify any relevant ongoing research (e.g. the American Society of Clinical Oncology), there were no specific details recorded of an ongoing trials search having been conducted on clinical trials databases. The ERG searched UKCRN, WHOICTRP, ISRCTN databases. One additional on-going trial was identified by the ERG (see Table 3 of this report)

Separate searches were undertaken for non-randomised studies of nivolumab (CS p. 121, CS Appendix 2.2.2). The CS states that these used similar methodologies and search strategies as those described for the systematic review of RCTs. The searches were conducted up to December 2014 for studies of nivolumab as first line treatment, and August 2014 for studies of subsequent line treatment. Given that these searches were for non-randomised studies the ERG has not updated them to the present time.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The inclusion and exclusion criteria are clearly stated in CS Table 8 (p. 38). The inclusion criteria reflect the nature of the decision problem stated in the CS, the licensed indication,

and the current NHS position. Only randomised controlled trials (of any design type) were eligible for inclusion in the company's systematic review, and only those RCTs that investigated the clinical efficacy and/or safety of stated interventions were included (NB. The inclusion criteria included as ‘interventions’ all of the treatments listed in the decision problem, whether they were listed there as an intervention or a comparator, to permit an indirect comparison to be conducted – see Section 3.1.7 of this report). Systematic reviews and meta-analyses were included as a source of references. Inclusion criteria for outcomes were in line with the decision problem, but no exclusion criteria for outcomes were defined. The company explained that trials were not excluded on the basis of outcomes alone.

No limits were placed on inclusion relating to the quality of the RCTs, and setting was not used as an inclusion criterion.

A PRISMA flow diagram was provided showing the numbers of records included and excluded at each stage (CS Figure 6, p. 40). The diagram contains the numbers of records identified during the three database searches described above, as well as conference abstracts, three clinical study reports (CSR) and unspecified "other" eligible records.

The ERG notes that there is an unexplained discrepancy between the number of full-text articles assessed during the three database searches (n=240) and the number of unique full-text articles assessed for eligibility (n=204), possibly due to the removal of duplicates, for which no data were reported. All other sums are correct and a summary of the reasons for article exclusion was reported.

In total, 90 records of 44 studies were included and data sources for these were presented in CS table 9 (p. 41). A reference list of excluded reports (without reasons for exclusion) was provided in CS Appendix 5 (CS Appendices p. 64).

For non-randomised studies, a table of eligibility criteria is provided in CS Appendix 2.2 (CS Appendices p. 43). Only studies investigating nivolumab 3mg/kg monotherapy were eligible for inclusion, and other agents (e.g. the comparator drugs named in the decision problem) were excluded.

A PRISMA diagram for non-RCT evidence is also included (CS Appendices p. 45). All sums in the "first-line setting" searches are correct, but the ERG notes that there appears to be an error in the "subsequent-line setting" part of the diagram, where the number of records screened for eligibility (n=327) is smaller than the number of records subsequently excluded

(n=335). Seven records of two studies were included in the review of non-RCT evidence, but only the CheckMate 003 study[7] was subsequently discussed in the CS (CS p. 121). The other study was a phase I study[8] that did not provide additional data so this is not further discussed in the CS.

The company does not explicitly discuss bias, but states that the non-randomised CheckMate 003 study[7] was considered relevant to the decision problem because of its long-term survival data that support the company's position on nivolumab treatment duration and discontinuation. The ERG appreciates that long-term survival data from randomised studies of nivolumab are not yet available and considers the company's approach to providing supporting evidence from non-randomised studies to be reasonable. The ERG has not, however, reported the results of this study in detail in this report.

The ERG concludes that in general, inclusion and exclusion criteria for non-RCT studies are in line with the decision problem, the licensed indication and the NICE scope.

3.1.3 Identified studies

The CS identified and included three pivotal phase III RCTs of nivolumab monotherapy at the licensed dose in patients with advanced melanoma as specified in the NICE final scope. The trials (CheckMate 066[4], CheckMate 067[5] and CheckMate 037[9]) are reported in three journal articles and in six conference abstracts. All are international multi-centre studies, initiated in December 2012, (CheckMate 037[9]) January 2013 (CheckMate 066[4]) and June 2013 (CheckMate 067[5]). All are currently ongoing for extended follow-up. The company states that the CS used data from the CSR in addition to the published study results (CS p. 46).

The trials differ in their populations and comparators, as shown in CS Table 10 (p. 45):

- CheckMate 066[4] recruited treatment naïve, BRAF mutation-negative (wild-type) patients. The comparator in this trial was DTIC 1000mg/m2 administered every three weeks. The company explains that DTIC was the most common first-line therapy for BRAF mutation-negative patients prior to the approval of ipilimumab, and that this was the reason to include it in this trial as the comparator drug. In total, 418 patients were randomised (210 to nivolumab and 208 to DTIC as shown in CS Figure 7, p. 61).
- CheckMate 067[5] recruited treatment naïve patients with any BRAF mutation status. This was a three arm trial and the two comparator treatments were ipilimumab 3mg/kg administered every three weeks, and a combination of Nivolumab at a dose of 1mg/kg and ipilimumab 3mg/kg, administered every three weeks. The combination therapy

arm is outside of the NICE final scope and thus is not reported on in detail in the CS. The ipilimumab 3mg/kg arm of this trial allows a direct comparison between nivolumab and ipilimumab. A total of 945 patients were randomised, 316 to nivolumab and 315 to ipilimumab, as shown in CS Figure 8, p. 62. The remaining 314 patients were randomised to the combination therapy.

- CheckMate 037[9] recruited patients who progressed on or after prior anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy (ipilimumab) and (if BRAF mutation-positive) BRAF inhibitor therapy. This was an open-label study with the comparator the investigator's choice of one of two chemotherapy options, either DTIC 1000mg/m2 or carboplatin area under the curve 6 + paclitaxel 175mg/m^2. Both comparators were administered every three weeks. In total 405 patients were randomised (272 to nivolumab and 133 to ICC (CS Figure 9, p. 63).

The ERG presents a summary of trial characteristics in Table 1.

Table 1 - Summary of characteristics of the included trials

	CheckMate 066 (n=418)	**CheckMate 067 (n=631)[a]**	**CheckMate 037 (n=405)**
Phase	Phase III	Phase III	Phase III
Blinding	Double blind	Double blind	Open label
Population	Previously untreated patients with advanced melanoma	Previously untreated patients with advanced melanoma	Previously treated patients with advanced melanoma
BRAF mutation status	Without BRAF mutation	With or without BRAF mutation	With or without BRAF mutation
PD-L1 status	PD-L1-positive, negative or intermediate classification	PD-L1-positive, negative or intermediate classification	PD-L1-positive, negative or intermediate classification
Comparator	DTIC	Ipilimumab	ICC
Primary outcome(s)	OS	OS, PFS	ORR, OS
Start date	January 2013	June 2013	December 2012
Status	Terminated[b]	Ongoing	Ongoing
Cut-off (database lock)	5 August 2014	17 February 2015	30 April 2014 (clinical database lock) 20 May 2014 (IRRC database lock)
Currently available primary/survival outcomes	1 year OS PFS	PFS	ORR PFS
Expected availability of further data	18 month OS: November 2015; 2 year OS: Q4 2016	OS and PFS: Q4 2016	OS and PFS: November 2015; OS extended follow/up: June 2016

DTIC = dacarbazine; ICC = investigator's choice chemotherapy (dacarbazine or carboplatin plus paclitaxel; IRRC = independent radiology review committee; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q4 = quarter 4.

[a] Nivolumab monotherapy and ipilimumab monotherapy arms. The trial included a third arm of combined nivolumab and ipilimumab treatment, which not included in this ERG report.

[b] Recommendation by the data management committee to allow cross-over from DTIC to nivolumab treatment.

Reporting of study characteristics in the CS

The company submitted generally adequate summary details of the RCTs:

- Trial design, population (eligibility criteria), trial drugs (and permitted concomitant medications), outcomes (primary, secondary, and key exploratory outcomes), and pre-planned subgroups are described for all trials (CS Table 11, p. 49-55). Locations and settings are also included in this table.
- Patient numbers are shown in CS Figure 7 for CheckMate 066[4], Figure 8 for CheckMate 067[5] and Figure 9 for CheckMate 037[9] in the form of CONSORT diagrams (CS p. 61-63). Numbers of patients enrolled, randomised, and treated are provided, but the ERG notes that the numbers of patients screened for eligibility are not reported for any of the trials and no reasons are provided for loss of patients or exclusion of patients between enrolment and randomisation. All trials lost a small number of patients between randomisation and treatment and reasons for these withdrawals and exclusions are briefly discussed in the narrative summary of participant flow (CS p. 60).

  The numbers of patients who discontinued the trial medication during the course of the trial are reported in the CONSORT diagrams, and reasons are provided for discontinuations. All of these sums appear to be correct.

  The numbers of participants who continued to receive the study drug are reported for all included trials. The numbers of those who continued to participate in the study and are still being followed up for survival analysis are also reported. However, the ERG notes a possible error in the footnote attached to the CONSORT diagrams stating that "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." In all CONSORT diagrams, the sum of patients continuing treatment and patients continuing study in the nivolumab group is larger than the number of patients treated with nivolumab. The ERG believes that the number of patients "continuing study" includes not only those who have discontinued the study drug, but also those who are continuing treatment.

  No numbers are reported for patients who crossed over between study drugs. The CS states (p. 46) that the option of crossing-over from DTIC to nivolumab for those who were not benefiting from treatment was permitted in the CheckMate 066[4] trial, after a study protocol amendment in June 2014 (approximately 18 months after trial initiation) was made in response to a recommendation by the data monitoring

committee. The company states that the data presented in the CS are based on a database lock dated 5th August 2014. At this time point no data on patients randomised to DTIC and subsequently treated with nivolumab post DTIC discontinuation were available (CS p. 46). The ERG supports the company's view that the results of the DTIC arm reported in the CS are unlikely to be confounded by un-blinding of treatment allocation or by subsequent nivolumab use.

- The methods of the statistical analyses of the nivolumab trials are summarised in CS Table 12 (p. 57-59). The table describes for each of the included trials the hypothesis objective, the statistical analysis, and the sample size and power calculations. Intention-to-treat (ITT) analyses were undertaken in all three trials for primary outcomes, and censoring methods were used to take account of missing data. The company's selection of outcomes is described in section 3.1.5 of this report.

The CS did not identify any specific patient groups in the decision problem for whom subgroup analyses were required. However, as stated earlier in this report, the comparative summary of RCT methodology (CS Table 11, p. 49-55) specified a range of pre-planned subgroup analyses for each trial, to assess the impact of participant characteristics (including demographic data and a range of disease-related baseline characteristics), and the geographic regions of the trials.

CSRs were supplied to the ERG by the company for information, though the ERG has not performed an analysis of these in the preparation of this report. All of the included studies of nivolumab were sponsored by the company.

Characteristics of study participants

Baseline characteristics of participants in the included RCTs are presented in CS Table 13 (p. 65-68). The company states that baseline characteristics of CheckMate 066[4] and CheckMate 067[5] are "well balanced with no key differences between treatment groups." Overall, the ERG agrees with the company's assessment, but notes that participants from both trials appear to be somewhat older in the comparator arms. The ERG also notes that patients randomised to DTIC in CheckMate 066[4] appear to have poorer Eastern Cooperative Oncology Group (ECOG) performance status as compared to those in the nivolumab group. However, expert clinical advice to the ERG suggested that the observed differences in ECOG performance status are unlikely to be clinically significant.

For the CheckMate 037 trial[9] the CS describes baseline characteristics as "generally well balanced." The company points out that higher proportions of patients with a history of brain metastases or with higher LDH were observed in the nivolumab group, suggesting that patients randomised to nivolumab had a poorer prognosis than those in the comparator group (CS p.64). The ERG also observed that the ECOG performance scores appeared to be somewhat lower in the nivolumab group. Overall, the ERG agrees with the company's assessment, but again, the significance of these observations remains unclear.

The ERG also agrees with the CS that differences between trials in patients' baseline characteristics are attributable to the individual trial eligibility criteria. The company points out that participants in CheckMate 037[9] were previously treated, and therefore had a longer time from diagnosis than those in CheckMate 066[4] and CheckMate 067.[5] They were also on average younger than those in CheckMate 066[4] and CheckMate 067,[5] and the company believes that this may reflect younger patients' ability to withstand multiple lines of therapy. The ERG notes that a higher proportion of CheckMate 037[9] participants (>75%) appeared to have metastasis stage M1c (the most severe M category) as compared to 61% in CheckMate 066[4] and 58% in CheckMate 067.[5] Expert clinical advice to the ERG points out that the CheckMate 037 participants are noteworthy as they have been able to receive several lines of treatment, but have other poor prognostic features such as higher M1c compared with the other trial populations.

Overall, the ERG agrees with the company that there are no noteworthy differences in patient characteristics between CheckMate 066[4] and CheckMate 067[5],and that differences in patient characteristics between these trials and CheckMate 037[9] are reflective of the fact that failure of previous treatments was an eligibility criterion for this trial.

In order to assess the applicability of the CheckMate trials to the UK patient population The ERG asked the company to confirm the number of UK participants in each trial and provide their baseline characteristics (clarification questions A1 and A2). In CheckMate 037[9] there were five UK trial centres and 43 UK patients were randomised to treatment. Seven UK trial centres participated in the CheckMate 067[5] study, with 93 UK patients randomised to treatment (27 to nivolumab, 36 to ipilimumab, and 30 to nivolumab in combination with ipilimumab). No UK patients were enrolled in CheckMate 066.[4] The baseline characteristics of UK participants were presented in appendices 1 and 2 of the company's response to the clarification questions (1st October 2015). There were some differences between UK patients and the total CheckMate 067 and CheckMate 037 trial populations, although most were small. Of note are differences in PD-L1 status and BRAF mutation status, presented in

Table 2. The proportion of participants with positive PD-L1 status in CheckMate 067 appeared to be higher in the UK group compared to the total trial population, and in CheckMate 037 BRAF mutation-positive status was found to be more prevalent in UK patients. The ERG is uncertain whether these differences are significant, given the small size of the UK patient group.

Table 2 – Differences in PD-L1 and BRAF status between UK participants and trial populations

	CheckMate 067		**CheckMate 037**		
	UK participants (n=93)	Total trial population (n=945)[a]	UK participants (N=43)	Total trial population (n=405)	
				Nivolumab	ICC
PD-L1 positive, %	49.5	23.6	46.5	49	50
BRAF mutation-positive %	36.6	31.5	34.9	22	22

[a] The company provided UK participant data across all three arms of the CheckMate 067 trial.

Ongoing trials

The CS identified five ongoing studies. Three of these (CheckMate 066, CheckMate 067, CheckMate 037) are the trials included in the CS[4;5;9]. These are currently ongoing or in extended follow-up in order to generate evidence on long-term outcomes, including overall survival, progression-free survival, and HRQoL (CS Table 53, p. 150). Two further studies mentioned in the CS are CheckMate 069, a phase II RCT of nivolumab in combination with ipilimumab compared to ipilimumab alone, and CheckMate 064, a phase II study that investigates the sequential administration of nivolumab and ipilimumab. Both trials are outside the NICE scope and decision problem defined for this CS.

The ERG notes that the company only listed ongoing trials that are expected to report data within the next 12 months. A search for ongoing trials undertaken by the ERG identified just one additional relevant study – a single-arm study of nivolumab in patients progressing after previous anti-CTLA-4 treatment (Table 3).

Table 3 - Ongoing trials

Trial identifier, sponsor	**Design, Country**	**Intervention, comparator, patient group**	**Expected end date**
NCT02156804 Bristol-Myers Squibb	Single-Arm, Open-Label, Multicentre Clinical Trial. International (168 sites, incl. 15 UK sites)	Nivolumab 3 mg/kg every two weeks. No comparator. Subjects with histologically confirmed stage III (unresectable) or stage IV melanoma and progression post prior treatment containing an anti-Cytotoxic T Lymphocyte Antigen (CTLA-4) monoclonal antibody (N=800)	October 2017 (Final data collection date for primary outcome measure).

In summary, all three the RCTs included in the systematic review of clinical effectiveness meet the inclusion criteria, and the ERG believes that it is likely that the CS has identified all relevant RCTs. The CS provides generally adequate details of the characteristics of the RCTs.

3.1.4 Description and critique of the approach to validity assessment

The company critically appraised the included nivolumab trials using the NICE-recommended criteria and presents a summary of findings on CS p. 69 and in CS Table 14 (p. 70). The complete quality assessments of each of the RCTs are included in CS Appendix 3 (CS Appendices p. 55, Tables 10-12). The ERG agrees with the company assessment for most criteria (Table 4).

The ERG assessment differs for question 1 (randomisation) because the sequence generation process is not described. The ERG notes that stratified allocation methods were applied in the randomisation procedures for all three trials. In CheckMate 066[4], randomisation was stratified by PD-L1 status and metastasis stage via permuted blocks within each stratum. In CheckMate 067[5] randomisation was also performed by permuted bocks within strata, and stratification was defined by PD-L1 status, BRAF mutation status and metastasis stage (as per American Joint Committee on Cancer definition). In CheckMate 037[9] randomisation was stratified by PD-L1 status, BRAF mutation status and prior anti-CTLA-4 best response.

For question 3 (balance in prognostic factors) the ERG notes small imbalances between groups in CheckMate 066[4] (relating to age and ECOG PS scores 0 and 1) and CheckMate 067[5] (relating to age) as described above (section 3.1.3 of this report and CS Table 13 p. 65-68). The potential impact of these small imbalances on trial outcomes is not clear; however, age and ECOG PS score are two of the baseline characteristics with known prognostic effects on outcomes (presented in CS Table 26 p. 101).

Table 4 - Company and ERG assessment of trial quality

		CheckMate 066[4]	**CheckMate 067[5]**	**CheckMate 037[9]**
1. Was randomisation carried out appropriately?	CS:	Yes	Yes	Yes
	ERG:	Not clear	Not clear	Not clear
Comment: Randomisation was stratified in all of the trials. In CheckMate 066 and 067 randomisation was performed by permuted blocks within each stratum, as described in the study				

		CheckMate 066[4]	CheckMate 067[5]	CheckMate 037[9]
protocols (supplementary material published online). The ERG notes that the sequence generation process (e.g. use of a random number table or random number generator) is not described.				
2. Was concealment of treatment allocation adequate?	CS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
Comment: Randomisation was performed by interactive voice response system.				
3. Were groups similar at outset in terms of prognostic factors?	CS:	Yes	Yes	No
	ERG:	Not clear	Not clear	No
Comment: The ERG notes small imbalances between groups in CheckMate 066 (relating to age and ECOG PS scores 0 and 1) and CheckMate 067 (relating to age).				
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS:	Yes	Yes	Outcome assessors only
	ERG:	Yes	Yes	Outcome assessors only
Comment: Use of matched placebos in CheckMate 066 and 067. CheckMate 037 is an open-label study, where patients and care providers were not blind to treatment allocation. Primary efficacy assessment of ORR was conducted by an independent radiological review committee, and committee members were blind to treatment allocation.				
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	No	No	Yes
	ERG:	No	No	Yes
Comment: Although higher proportions of patients discontinued the study treatment in the comparator groups of CheckMate 066 and 067 this was due to greater proportions discontinuing due to disease progression. Discontinuations for other reasons were similar between groups. In CheckMate 037 a number of patients randomised to ICC withdrew consent, resulting in an imbalance in numbers of patients withdrawing between groups prior to treatment initiation. The company explains that withdrawals included patients who went on to receive other PD-1 therapies outside of the trial, and this would have had an impact on the outcome of OS of the ITT population.				
6. Is there any evidence that authors measured more outcomes than reported?	CS:	No	No	No
	ERG:	No	No	No
Comment: In CheckMate 067 OS data were not yet available when the CS was produced.				
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
Comment: ITT analyses were performed for the primary outcomes in all of the trials and outcomes were censored on the last date the subject was known to be alive (for OS) or on the date of the last tumour assessment (for PFS). The ERG considers this approach to be appropriate. In CheckMate 037 the approach to censoring only appeared to be reported for the time to response outcome rather than other time to event outcomes.				

3.1.5 Description and critique of company's outcome selection

The outcomes selected in the decision problem match the NICE scope and are appropriate for the assessment of cancer drugs.

Overall survival (OS) and progression free survival (PFS) were defined consistently between the three key RCTs included in the CS. Response is defined as 'objective response rate' (ORR) in all three trials, consisting of the 'best overall response' (BOR) of complete or partial response (CR or PR) divided by the number of randomised patients. (IRRC as well as investigator assessed in CheckMate 037, where it was the primary outcome measure).

Response was measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria[10] (version 1.1) in all three trials. Time to treatment response (TTR) was reported in all three trials and defined consistently (IRRC as well as investigator assessed in CheckMate 037). Duration of response (DOR) is also reported for all three trials, and defined consistently between them (IRRC as well as investigator assessed in CheckMate 037).

HRQoL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) scale, as a secondary outcome in the three trials. In addition the EQ-5D, and the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) were used to measure HRQoL as exploratory outcomes in the trials (WPAI:GH was not measured in CheckMate 037).

Adverse events were measured in all three trials, including deaths and laboratory abnormalities. Severity was measured using the National Cancer Institute Common Terminology Criteria for Adverse Events.

In terms of instrument validation, the EQ-5D has been validated and used in a number of economic evaluations. However, the CS does not mention the EQ-5D value set used in the trials and it is therefore unclear how applicable the preference weighting is to the UK general population. The CS does not state whether the EORTC-QLQ-C30 scale is validated (CS Appendix 6 provides limited further information on this instrument). The EORTC website reports that it is has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide, though this does not necessarily imply scientific validation (http://groups.eortc.be/qol/eortc-qlq-c30). The website also mentions that a melanoma module is under development – called QLQ-MEL38.[11] (not mentioned in the CS).

There are no additional outcomes reported in the clinical trial publications that are not included in the CS. However, the ERG notes that TTP, PrePS and PPS outcomes are not reported in the trial journal publications, but are presented in the CS specifically to inform the transitions in the economic model (see Section 3.1.7 and Section 4.2.4 of this report).

3.1.6 Description and critique of the company's approach to trial statistics

The CS reports all relevant outcomes for the three included primary RCTs, apart from overall survival and HRQoL which are only reported for CheckMate 066. The CS states this is because OS data for the other two RCTs are currently immature due to insufficient follow-up,

whilst HRQoL data for CheckMate 067 and 037 are likely to become available in the next 12 months.

The outcomes are classed as primary, secondary and exploratory (CS Table 11, p.54). Primary outcomes are those for which the trials are powered statistically (the meaning of secondary and exploratory outcomes is not defined in the CS). Primary outcomes are OS in all three RCTs, plus the co-primary outcomes of PFS in CheckMate 067 and ORR in CheckMate 037. Secondary outcomes vary across the three RCTs and include: PFS and ORR (CheckMate 066, 067), TTR, DOR and PFS (CheckMate 037 only) and HRQoL (measured in all three RCTs, but reported in the CS for CheckMate 066 only). Secondary outcomes also include OS for specified subgroups, which in all RCTs include presence or absence of PD-L1 expression. The exploratory outcomes are adverse events in all three RCTs and, in CheckMate 067, also the time to TTR and DOR.

Two RCTs tested hypotheses of superiority of nivolumab against dacarbazine (CheckMate 066) or ipilimumab monotherapy (CheckMate 067) whilst CheckMate 037 also appears to have tested a superiority hypothesis although this was phrased as “nivolumab will provide meaningful activity” compared to ICC (CS Table 12, p. 57-59).

All three RCTs randomised a larger number of participants than their intended sample sizes (CS Table 12, p. 57-59). However, due to the interim nature of the reported analyses, which is acknowledged in the CS, the number of events (death or progression) which had occurred by the time of analysis of primary outcomes were fewer than the number required to achieve the statistical power specified in the CS for detecting pre-specified HRs for overall survival or for progression-free survival (CS Table 12, p. 57-59). For example, CheckMate 066 required ≥312 deaths to detect a pre-specified HR for overall survival of 0.69 at 90% power (2-sided α=0.05) but at the time of analysis only 146 deaths in total across both trial arms had occurred (CS Table 15, p.72). Sources of some assumptions in the power calculations are not explained in the CS (CheckMate 066 assumed median OS of 10 months for DTIC and 14.49 months for nivolumab; CheckMate 067 assumed median OS of 14 months for ipilimumab and 19.4 months for the comparator arms). However, on balance, given that the analyses in these RCTs are testing superiority rather than equivalence, the ERG believes that the under-powering of these interim primary outcome analyses would not influence interpretation of the reported analyses. As stated in the CS, further follow-up data for these analyses will be reported during 2015-2016.

The statistical analyses for determining time-to-event measures (OS, PFS, ORR, DOR, and TTR) in each of the RCTs are based on standard Kaplan-Meier survival analysis methods (CS Table 12, p. 57-59). Outcomes are reported as event rates and as median values with 95% CIs (several approaches for calculating the 95% CIs are reported in the CS based on published methods).

In CheckMate 066 and 067, comparisons of survival across treatment arms are based on Cox proportional hazards models to give hazard ratios for death or disease with 95% CI, median OS with 95% CI, and median PFS with 95% CI (CS p. 73-76). Comparisons of ORR across trial arms were estimated using Cochran-Mantel-Haenszel tests to calculate odds ratios with 95% CI in CheckMate 066 (CS Table 17, p. 77) and CheckMate 067 (Table 18, p. 81). In CheckMate 037 ORR are compared across trial arms as differences in rates with two-sided 95% CI (Newcombe approach) (CS Table 19, p. 84).The CS states that analyses were stratified by prognostic variables: metastasis stage and PD-L1 status in CheckMate 066 for analyses of OS, PFS and ORR; and metastasis stage, PD-L1 status and BRAF status in CheckMate 067 for analyses of PFS and ORR (CS Table 12, p. 58). Subgroup analyses are also reported for these prognostic variables as well as for a range of other prognostic and demographic variables for OS in CheckMate 066 (CS Figure 22), for PFS in CheckMate 067 (CS Appendix 7) and for ORR in CheckMate 037 (CS Appendix 7).

Secondary outcomes derived from the Kaplan-Meier analyses and reported in all 3 RCTs are the median TTR plus range (CS Tables 17-19, p. 77-84) and the median duration of response plus range (CS Tables 17-19, p. 77-84) (also reported with 95% CI for CheckMate 066: CS Figure 14, p. 78).

All three RCTs employed an ITT analysis approach (Table 4). The method of data censoring was reported for progression-free survival in CheckMate 066 and 067, for overall survival in CheckMate 066, and for time to response in CheckMate 037 (CS Table 12, p. 57-59) but not for the other time-to-event outcomes reported in these trials.

Analysis of HRQoL in CheckMate 066 was based on the EORTC QLQ-C30 instrument and EQ-5D using a Cox proportional hazards regression model to determine time to first deterioration and first improvement (as defined by the minimal important difference for each scale applied at individual patient-level). Results are presented as hazard ratios for nivolumab versus DTIC with 95% CI (CS Table 20, p. 88-89).

Adverse events in all 3 RCTs are reported as numbers (%) of events, numbers (%) of discontinuations, and the median times (without variance measures) to onset and to resolution of events. For CheckMate 067 the median number of adverse events with 95% CI was estimated from Kaplan-Meier survival analysis for time on treatment (CS Figure 46, p. 139) whilst for CheckMate 037 a Kaplan-Meier survival curve for time on treatment is presented but without accompanying statistics (CS Figure 47, p. 142).

Overall, the ERG believes that the statistical analysis approaches employed in the 3 RCTs are generally appropriate. Where survival analyses were employed, the resulting curves are clearly reported in Figures together, in most cases, with the derived statistical parameters. However, the method of data censoring was not reported for the primary outcomes in CheckMate 037 and the ERG noted that this trial also had unexpected unbalanced attrition (see Table 4).

Company's approach to trial statistics in non-randomised studies

The single non-randomised study included in the CS, CheckMate 003, was a phase I study of nivolumab safety in treating solid tumours, including melanoma (CS Table 42, p. 123-124). Participants with melanoma were assigned across five dose cohorts (0.1, 0.3, 1.0, 3.0 and 10.0 mg/kg nivolumab every 2 weeks). Initially, small numbers of patients were allocated to the dose cohorts but maximum tolerated dose was not reached and "expansion cohorts" of further patients were allocated to the 3.0 and 10.0 mg/kg cohorts, as well as further patients randomly allocated to the 0.1, 0.3 and 1.0 mg/kg groups. Overall sample size at analysis was N=107 melanoma patients in total across all dose cohorts, of which n=17 were in the licensed dose cohort (3.0 mg/kg). Although described as a dose escalation study, dose changes were not permitted for individual patients unless allocated to the 0.1 or 0.3 mg/kg expansion cohorts who could escalate to 1.0 mg/kg if disease progressed within the first two treatment cycles. The flow of participants in this study from enrolment to analysis is not explicitly reported and as such is difficult to follow – the CS refers to "participant flow" when citing Table 43 (CS p. 126) but this merely presents a cross-sectional overview of patient status at analysis.

Safety and tolerability were specified as the primary outcomes in CheckMate 003. Secondary outcomes are listed in the CS as immunogenicity, pharmacokinetics, "preliminary efficacy", and characterisation of the dose-response relationship in melanoma (and non-small-cell lung cancer). The specified secondary efficacy outcomes included objective response rate, progression-free survival, duration of response and time to response, while overall survival was specified as being an exploratory outcome. The CS does not define

what are meant by primary, secondary or exploratory outcomes, and no mention is made in the CS of the statistical power of the study to detect effects on any outcomes.

The ORR and stable disease rates in CheckMate 003 were estimated together with 95% CI by using the Clopper–Pearson method. Time-to-event end points, including progression-free survival, overall survival, and duration of response were estimated by using Kaplan-Meier survival analysis methods, with 95% CI based on Greenwood's formula. Survival data were collected retrospectively. The CS states only that efficacy analysis was based on all treated patients with standard censoring methods to account for missing data, without providing details (CS, p. 125). Analyses are reported for different database lock times for each outcome, although it is unclear how the data availability at each analysis time relate to the cross-sectional overview of patient status at analysis as reported in CS Table 43 (p. 126).

Outcomes are reported in CheckMate 003 as ORR without variance measures or survival curves for the overall population and the licensed dose cohort (CS p. 128-130); median PFS with 95% CI for all five dose cohorts combined (CS Fig 43, p. 132); and median OS with 95% CI (CS Fig. 44, p. 133) for all five dose cohorts combined and for the licensed (3mg/kg) dose cohort alone.

Overall, the ERG believes that the results of CheckMate 003 should be interpreted with caution, due to the small sample size in the relevant dose cohort (n=17 only), uncertainty about relevance of the analyses on the overall study population (since these included non-licensed nivolumab doses); and lack of clarity regarding participant flow in relation to analysis timing and data censoring.

3.1.7 Description and critique of the company's approach to the evidence synthesis

Narrative synthesis

A narrative review of the nivolumab RCTs is provided. Each outcome measure is taken in turn (e.g. survival analysis, response analysis) with tabulated data and Kaplan-Meier survival curves and other figures provided for each of the three key trials respectively. A narrative description accompanies the tables and figures. The ERG has cross-checked the outcome data in the CS, where available, with that provided in the trial journal publications, and these are consistent, with only one identified exception – target lesion reduction in the CheckMate 066 trial. The CS (p. 80) reports that of the 103 patients treated beyond Response Evaluation Criteria in Solid Tumors (RECIST)[10] defined progression (54 nivolumab; 49 DTIC), 12 (22.2%) treated with nivolumab and 2 (4.1%) treated with DTIC developed or

maintained a target lesion reduction of >30% compared to baseline. In the trial journal paper[4] the corresponding figures are 17 (31%) and 8 (16%). Note that the journal paper states 'a reduction of 30% or more' in the target lesion whereas the CS just says '>30%', which may explain the discrepancy.

A meta-analysis was not conducted, as the CS states that the clinical trials are too clinically diverse to be combined (CS section 4.9, p. 92). The key reasons include differences in control arms (DTIC, ICC and ipilimumab) and differences in patient populations enrolled (e.g. previous treatment experience; BRAF mutation status - though the ERG notes that much of the CS analysis assumes no independent effect of these patient variables anyway). The ERG agrees with the rationale for not meta-analysing, primarily due to differences between the trials in the comparator drug.

Indirect comparison overview

It is stated (CS Section 4.10, p.97) that a mixed treatment comparison of all the treatments within the scope of the appraisal was not possible for a number of reasons, including non-proportional hazards between the different drugs due to their differing mechanisms of action; cross-over of patients in some but not all of the trials; and heterogeneity in the trial designs (e.g. in terms of previous treatment experience, and BRAF mutation status). The ERG agrees that a mixed treatment comparison would be difficult to construct and interpret due to these reasons. However, the ERG notes that the company have made an apparent contradiction in their subsequent indirect comparison by assuming that previous treatment status and BRAF mutation status do not independently influence treatment effects (CS p. 100; see below for more detail).

The company reports an indirect comparison of nivolumab with its comparators (CS section 4.10). A 'broad evidence' network diagram is presented (CS Figure 23) showing the treatment comparisons possible from the trials of DTIC, dabrafenib, vemurafenib, ipilimumab and nivolumab that met the inclusion criteria for the company's systematic review of clinical effectiveness (n=44) (CS section 4.1). It is stated that only trials that reported OS were eligible for inclusion in the indirect comparison as this is considered to be the most important outcome in patients with advanced melanoma. The ERG agrees with this assertion but also notes that PFS is also a clinically relevant outcome measure.

It is not stated in the CS how many trials were ineligible on this criterion but it does apply to the pivotal CheckMate 067 RCT for which the OS data are stated to be currently unavailable as the required minimum follow-up has not yet been reached. The ERG considers this to be

a significant omission as it would obviate the need for an indirect comparison of nivolumab and ipilimumab since they were compared head-to-head in this trial.

A network diagram is presented showing the comparisons between the trials eligible for the indirect comparison (CS Figure 24). There were five such trials included:

- CheckMate 066 (nivolumab vs DTIC)[4],
- BRIM-3 (vemurafenib vs DTIC)[12],
- BREAK-3 (dabrafenib vs DTIC)[13],
- CA184-024 (ipilimumab 10mg/kg + DTIC vs DTIC)[14], and
- MDX010-20 (ipilimumab vs ipilimumab 3mg/kg + gp-100 vs gp-100)[15].

As described below, three of these trials are subsequently used to inform the analysis (CheckMate 066[4], BRIM-3[12] and MDX010-20[15]).

Two indirect comparison networks were analysed, differing according to the type of comparators used:
(i) comparison with ipilimumab and palliative chemotherapy;
(ii) comparison with BRAF inhibitors.
Each of these is described and appraised in turn below, in terms of the identification of the clinical trial evidence used to conduct the indirect comparisons and the statistical procedures used (e.g. covariate adjustment to account for differences between trial arms). Section 4.2.4 of this report describes and critiques the statistical procedures used to fit and extrapolate parametric survival curves from the trials to inform the comparisons made within the economic model. As described in the following sub-sections, the indirect comparison used an approach whereby selected trial arms were compared using a covariate-adjusted survival model approach. This nomenclature is used in the CS and in this report to distinguish it from an adjusted indirect comparison that the company also reported, for purposes of comparison (described below).

(i) Indirect comparison of nivolumab to ipilimumab and palliative chemotherapy
This comparison informed the cost-effectiveness analysis for BRAF mutation-negative patients and comprises comparisons of treatments from trials using a common comparator. CS Table 25 describes the comparisons made. For nivolumab compared to ipilimumab, patient-level data from the CheckMate 066 trial[4] (nivolumab arm) were compared to patient-level data from the MDX010-20 trial[15] (ipilimumab arm) linked together by DTIC (CheckMate 066) and by gp100 melanoma peptide vaccine (MDX010-20) (NB. gp100 is assumed to be equivalent to DTIC in efficacy and therefore is used as a proxy for DTIC for purposes of

comparison – see below). Figure 1 illustrates the evidence network used (replicated from CS Figure 26). The CA184-024 trial[14], which used a higher dose of ipilimumab (10mg/kg) was only used in a scenario analysis as the CS states that 3mg/kg of ipilimumab and 10 mg/kg cannot be assumed to be equivalent (as noted in NICE TA319[16]). Nivolumab was compared directly to DTIC using patient-level head-to-head data from the CheckMate 066 trial.[4]

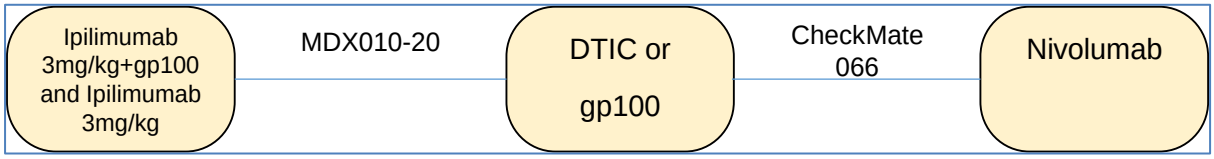

Figure 1 - Network diagram for the comparison of nivolumab with ipilimumab

The company makes the following assumptions for the indirect comparison:

1. *The line of treatment does not independently predict treatment effectiveness*. CheckMate 066 only included previously untreated patients, whilst MDX010-20 included patients who had been previously treated. The CS cites studies of ipilimumab and nivolumab that support this assumption and reports that this assumption was accepted in the NICE TA319 of ipilimumab.[16] Clinical advice to the ERG agreed with this assumption.
2. *There is no difference in treatment effect by BRAF mutation status.* This assumption was necessary because CheckMate 066 included only BRAF mutation-negative patients, MDX010-20 did not report the BRAF mutation status of patients. To support this assumption the CS cites a published retrospective pooled analysis of four on-going nivolumab studies by Larkin and colleagues (2015)[17], sponsored by the company. The ERG has done a brief assessment of this study and notes that three were phase I studies of nivolumab (respective sample sizes <100 patients), and the fourth was the phase III CheckMate 037 RCT[9], described earlier in this report. Of the 440 patients analysed, 334 were BRAF mutation-negative and 106 were BRAF mutation-positive, and 83% of the patients received nivolumab at the licensed 3mg/kg dose. The outcome measure used in the analysis by Larkin and colleagues[17] was treatment response though the CS uses survival in the indirect comparison, and it is not clear whether the assumption made on the basis of response analysis is necessarily applicable to survival. Limited details are provided of the included studies or the analysis methods to pool the studies and due to its retrospective nature the ERG urges caution in the interpretation of its results, and therefore its use to support the assumption.
3. *Gp100 is equivalent to DTIC in terms of OS and PFS outcomes*. The CS provides a rationale for this assumption that citing published meta-analyses[18;19] (both of which appear to be sponsored by BMS) of gp100 and existing treatments, including palliative

chemotherapy, showing them to be similar for OS. The CS also states that this assumption had been discussed and accepted in NICE appraisals of ipilimumab (NICE TA268[20] and TA319[16]). Expert clinical advice to the ERG agreed that these drugs can be considered generally equivalent and also that DTIC can be considered as palliative chemotherapy. However, the ERG notes that the CS does not report any evidence for the equivalence of gp100 and DTIC (or other palliative chemotherapy) for alternative cancer outcomes, including those used to inform transition probabilities in the economic model: time to progression (TTP), post-progression survival (PPS) and pre-progression survival (PrePS) (see below for discussion of these outcomes). The ERG notes that the Kaplan-Meier curves for TTP (measured from day 100) for gp100 and for DTIC do not appear to be similar (though this comparison is unadjusted and is based on small numbers of patients remaining in the trial arms). It is therefore unclear whether the equivalence of DTIC and gp100 can also be demonstrated for these outcomes.

4. *Ipilimumab 3mg/kg + gp100 and ipilimumab 3mg/kg are equivalent based on the MDX010-20 results.* The CS notes that this was an accepted assumption in the NICE TA268 of ipilimumab in previously treated patients, and this therefore allowed the pooling of these two trial arms to provide a larger dataset for analysis than if only the ipilimumab 3mg/kg monotherapy arm of MDX010-20 had been used.

Alternative outcomes

The CS states that the OS data for CheckMate 066 are relatively immature (i.e. they do not reach median survival) and long-term survival extrapolations of OS will therefore be subject to uncertainty (CS p. 101). The CS used the following alternative outcomes to inform long-term extrapolations. These were:

- Time to progression (TTP) – similar definition to PFS, however patients classified as progressors in PFS due to death are censored at death.
- Pre-progression survival (PrePS) – the same definition as OS except patients that progress are censored at time of progression.
- Post-progression survival (PPS) – only included patients that have progressed and follows time to death, or censoring, from the point of progression.

TTP and PrePS were used to inform long-term extrapolations of PFS. TTP, PrePS and PPS were used to inform long-term extrapolations of OS.

The ERG notes that these outcomes were not pre-specified as primary or secondary outcome measures for the CheckMate RCTs and data for them were not provided in the

main clinical effectiveness results section of the CS (CS Section 4.7, p. 71) or in the trial journal publications. (NB. The data are given in CS Section 4.10 'Indirect and mixed treatment comparisons'). They therefore appear to have been used retrospectively for the purposes of informing the economic model for this appraisal.

The TTP survival data are also split into two time periods (pre-and post-100 days) which use different modelling methods. This was done to allow a more clinically and statistically plausible shape and continuous flow to the occurrence of progression from day 100 onwards (CS p. 104; for a more detailed description and critique of this please refer to Section 4.2.4 of this report).

The CS argues that, due to the immaturity of OS survival data for nivolumab, use of the alternative outcomes allowed a more robust estimation of long-term survival extrapolations in (CS p. 101). This ERG acknowledges that this approach does avoid using immature OS data, but by using three endpoints rather than two, and splitting one of these (TTP) into two time periods, the sample sizes become smaller and the attendant survival curves are based on smaller samples and will have fewer observed events. To this extent they will also be less robust. For example, the Kaplan-Meier curves for PrePS (CS Figure 34) shows a population at risk in the nivolumab arm of 210 at outset, but of only seven at approximately 12 months, with apparently no observed events between six months and 12 months (as the curve for nivolumab is flat between these time points). Furthermore, median survival for PrePS is not reached for nivolumab or DTIC suggesting data immaturity for this outcome (CS Figure 34).

Covariate adjustments for the parametric survival model indirect comparison

To account for potential differences in patient characteristics between the CheckMate 066[4] and MDX010-20[15] trials the CS identified factors shown by a meta-analysis of trials by Korn and colleagues[21] to affect prognosis (in terms of OS and PFS) in patients with advanced melanoma treated with palliative chemotherapy. The CS applied the prognostic factors from the Korn and colleagues[21] meta-analysis to the TTP, PrePS and PPS outcomes which inform the economic model (see below). These factors are reported to be consistent with prognostic factors used in NICE TA319 of ipilimumab in previously untreated advanced melanoma.[16]

CS table 26 illustrates the comparability of the CheckMate 066[4] and MDX010-20[15] trials in terms of seven prognostic factors (six of which were baseline patient characteristics). The list of factors was reported to have been validated with UK clinicians during an advisory board

meeting in March 2015. Clinical advice to the ERG indicated that there were no key prognostic factors absent from those chosen.

There were differences between the trials in certain factors:

- Eastern Cooperative Oncology Group (ECOG) performance status zero (higher CheckMate 066)
- M stage disease (extent of metastatic melanoma) = M1c (higher in the MDX010-20 trial indicating more visceral disease)
- History of brain metastases (higher in the MDX010-20 trial)
- Age (higher in the MDX010-20 trial)
- Subsequent ipilimumab use (occurred only in CheckMate 066).

Patients in the MDX010-20 trial could therefore be considered to have a poorer prognosis based on some of these factors.

The prognostic factors were included in the covariate-adjusted analysis, thus attempting to control for differences between the trials (CS Table 27). The proportion of patients with complete covariate data was high (e.g. 199 of 210 (95%) nivolumab-treated patients in CheckMate 066, CS Table 28), lessening any bias due to missing data.

The ERG considers the approach used to adjust for covariates to be generally reasonable. However, the following issues may cause uncertainty in the estimates obtained:

- The ERG notes that the Korn and colleagues[21] meta-analysis identified four significant covariates for OS, and three for PFS. The CS included a greater number (nine; see CS Table 27). It is not clear from the Korn and colleagues[21] study which prognostic factors could be applicable specifically to the outcomes analysed to inform the cost-effectiveness analysis (i.e. TTP; PrePS; PPS). Furthermore, Korn and colleagues[21] state that controlling for these prognostic variables eliminated the between-trial variability in one-year OS rates, but not in six-month PFS rates (where there was residual between-trial variation). This raises the question of whether the between-trial differences in prognostic factors were adequately adjusted for, and whether the covariates identified by Korn and colleagues[21] are applicable to the analyses of the alternative outcomes in the CS, such as TTP.
- The survival models adjusted for covariates had relatively small sample sizes for some of the time periods and outcomes considered and in many cases the prognostic factors were not significant at the 95% level (e.g. CS Table 30 and CS Table 32). In some cases treatment effects were also non-significant (e.g. ipilimumab - CS Table 32). The

non-significance of the prognostic factors may arise because of the small sample sizes, and/or the fact that they are not prognostic for the outcomes considered such as TTP (as discussed above). The ERG notes that TTP (post 100 days) was one of the most influential parameters in the CS deterministic sensitivity analysis (CS section 5.4.2).

- The CS notes (p. 113) that non-significant prognostic factors were retained in the various models in order to fully adjust for them, and to allow more flexibility within the economic model for different patient populations. This is a reasonable approach to take in this context, although many prognostic factors were adjusted for, and it is possible that they were not evenly distributed in the sample patient population – some subgroups may contain more patients than others. For example, CS Table 26 shows that there were differences between the trials for some of the prognostic characteristics (as described above), particularly for history of brain metastases. The extent to which this between-trial imbalance in prognostic factors biases the estimates is hard to gauge without access to the data used.
- The CS examined the validity of the covariate-adjusted survival models by comparing their relative treatment effect estimates with relative treatment effect of nivolumab and ipilimumab obtained an adjusted indirect comparison (CS Table 36 p. 115, and see below). Similar results were obtained, lending support to the approach used.

Adjusted indirect comparison of nivolumab and ipilimumab

The CS also reported an adjusted indirect comparison of nivolumab and ipilimumab using what it describes as a traditional approach (CS p. 115), citing the method described by Bucher and colleagues.[22] CS Table 36 reports the results of the adjusted indirect comparison for the outcomes TTP post 100 days, PPS, OS and PFS, alongside the results for these outcomes from a Weibull parametric model. A Cox proportional hazards regression was performed for the CheckMate 066 trial and for the MDX010-20 trial to obtain HRs for nivolumab versus DTIC and for ipilimumab versus gp100 (as a proxy for DTIC), respectively. The HRs were adjusted for the same covariates as used to inform the parametric survival models (described above). The primary purpose of CS Table 36 is to compare the results of two methods of indirect comparison: the adjusted approach based on the Bucher and colleagues method;[22] and the covariate adjusted parametric survival model method (used to inform the economic model). The two methods showed similar results for nivolumab and ipilimumab. The ERG notes that the Bucher and colleagues[22] method for adjusted indirect comparisons has been widely used in the health literature,[23] and in this method the comparison of the interventions of interest is adjusted by preserving the strength of randomisation. The parametric survival model-based indirect comparison appears to

preserve randomisation through inclusion of the trial as a covariate in the analyses. Both methods are therefore appropriate in this respect.

The ERG also notes that no justification is given for use of the Weibull parametric model in CS Table 36 for comparison with the adjusted indirect comparison. Use of the Gompertz model for TTP post 100 days (as used in the economic model) would have produced an HR of 0.35 compared to the HR of 0.38 for the Weibull model, which was slightly less comparable to the 0.37 HR in the adjusted indirect comparison. Likewise, use of the log-logistic HR for PPS (used in the economic model) of 0.98 instead of the HR of 0.95 from the Weibull model would have been less comparable to the HR of 0.92 in the adjusted indirect comparison. Gompertz model-based HRs might have been used throughout Table 36 instead, for example, and might not have given such a favourable comparison to the adjusted indirect figures as the Weibull model. Therefore, a justification for use of this model in the CS would have been informative.

(ii) Indirect comparison of nivolumab to BRAF inhibitors

This comparison informed the cost-effectiveness analysis for BRAF mutation-positive patients, and also comprises comparisons of treatments from trials using a common comparator. CS Table 25 describes the comparisons made and CS Figure 35 illustrates the network diagram, replicated in Figure 2 in this report. For nivolumab compared to vemurafenib, patient-level data from CheckMate 066[4] (nivolumab arm) was compared to aggregate data from the BRIM-3 trial[12] (vemurafenib arm) linked together by DTIC, which was a comparator in both trials. The ERG assumes that patient-level data from the BRIM-3 trial were not available to the company, whereas patient-level data were available for both nivolumab and ipilimumab in the BRAF mutation-negative network, since the company markets both drugs. However, the CS goes on to describe a process to create pseudo patient-level data for vemurafenib from Kaplan-Meier curves (CS P. 118, and see below).

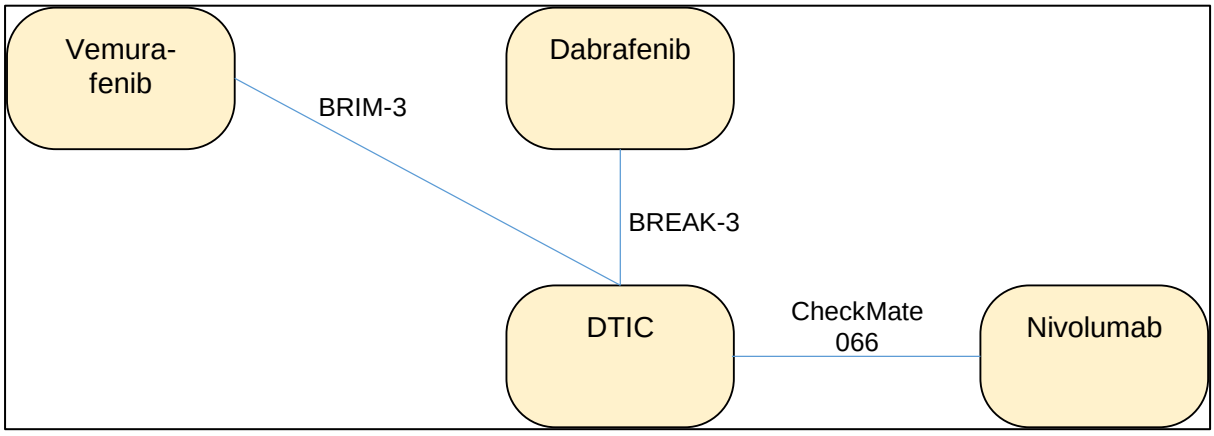

Figure 2 - Network diagram for nivolumab and BRAF inhibitor

For nivolumab compared to dabrafenib, patient-level data from CheckMate 066[4] (nivolumab arm) potentially could have been compared to aggregate data from the BREAK-3[13] trial (dabrafenib arm) linked together by DTIC (a comparator in both trials). However, the indirect comparison and survival curve fitting was subsequently restricted to nivolumab compared to vemurafenib, on the assumption that vemurafenib and dabrafenib are generally equivalent in efficacy, based on a meta-analysis used in the NICE TA321[24] of dabrafenib. (The ERG notes that the indirect comparison in the dabrafenib appraisal was not considered robust by the ERG who appraised that company submission, but that the Appraisal Committee concluded that it would not be unreasonable to assume that vemurafenib and dabrafenib have similar effect.[24])

The BRIM-3 trial[12] (vemurafenib versus DTIC) was used for the indirect comparison and survival curve fitting in preference to the BREAK-3 trial[13] (dabrafenib versus DTIC), on the basis that this was a larger trial (n=675 patients, n=250 patients, respectively) and the judgement that it was more reflective of UK patients receiving BRAF inhibitors (The journal publication for this trial[12] does not explicitly identify whether any UK patients were included, though just under two-thirds of the patients were classified as being in Western Europe, and two of the authors are affiliated with British university/hospital institutions, suggesting that there were UK centres). The CS identifies the higher lactate dehydrogenase (LDH) levels in the BRIM-3 trial[12] than the BREAK-3 trial[13] as being one factor that increased its applicability to the UK patient population, though the ERG notes that this was also higher than in the CheckMate 066[4] trial that it was indirectly compared to (CS Table 37), decreasing the similarity between these two trials. The CheckMate 066[4] trial also had a higher patient median age than the BRIM-3[12] and BREAK-3[13] trials, which potentially could confound the indirect comparison given that age is stated to be a known prognostic factor affecting treatment outcome. However, this would be accounted for in the covariate-adjusted analysis of the CheckMate 066 and BRIM-3 trials (see below).

The CS mentions a further RCT, Combi-V[25], which was included in the company's systematic review of clinical effectiveness, but subsequently not included in the indirect comparison alongside the BRIM-3 trial, as this would have necessitated multiple comparisons (stated to be necessary due to the strategy used for forming the indirect comparisons, but no further detail given, including whether it could have been used in a scenario analysis). The Combi-V trial compared vemurafenib against dabrafenib + trametinib combination therapy and does not include a DTIC arm. It is therefore not clear to the ERG

how this could have been linked to the evidence network to form a comparison with nivolumab.

Estimation of survival data and covariate-adjustment

The CS describes the process for estimating survival data from the BRIM-3 trial (CS P. 118)

- Kaplan-Meier data were estimated from the Kaplan-Meier curves for OS and PFS for vemurafenib using digitisation software.
- Using the estimated Kaplan-Meier data, pseudo patient-level data were created for vemurafenib using the Guyot 2012 method.[26] The ERG considers that this is a robust method of reconstructing survival data based upon limited published information, and it has been used in a previous technology assessment report used in a NICE appraisal.[27]
- Parametric survival curves for OS and PFS were fitted to the single-arm pseudo patient-level data – used directly in the economic model.
- The nivolumab estimates of OS and PFS (as constructed in the economic model from TTP, PrePS and PPS) were re-estimated adjusted for the observed patient characteristics from the BRIM-3 trial (CS p. 118). It is not explicitly stated which patient characteristics were included in this analysis. However, the ERG assumes it was the same covariates as used in the nivolumab versus ipilimumab comparison, based on the Korn and colleagues study[21] (CS Table 60).

Section 4.2.4 of this report describes and critiques the statistical procedures used to fit and extrapolate parametric survival curves from the trials to inform the comparisons made within the economic model.

Critical appraisal of trials included in the indirect comparison

The CS provides critical appraisal summaries for the MDX010-20 and BRIM-3 RCTs based on the Cochrane Collaboration's Risk of Bias criteria for RCTs in CS Appendix 3 (CS Appendices: Table 13 and Table 16, p. 58 and p. 61).

For MDX010-20 the ERG agrees broadly with the company's critical appraisal, with the RCT being considered at low risk of bias overall (CS Appendices Table 13, p. 58).

For BRIM-3, the ERG disagrees with the company's critical appraisal in the following aspects:

- The company concluded that randomisation was adequate. However, the ERG considers that the randomisation process (described as a minimisation procedure in

the study protocol) is unclear, and hence the risk of selection bias due to this methodological aspect is unclear.

- The company concluded that allocation concealment was adequate. However, no allocation concealment was reported for BRIM-3. The ERG therefore considers that there is a high risk of selection bias due to lack of adequate allocation concealment.
- The company concluded that although the RCT was open-label, the risk of bias would be low since there were no patient-reported outcomes specifically considered. The ERG cannot discount the possibility that outcome assessors might have introduced bias by being aware of patient allocations, e.g. when assessing and documenting disease progression, although this is unclear. The ERG therefore considers there to be an unclear risk of detection bias.

The company's overall opinion is that BRIM-3 was generally at low risk of bias except that unexpected drop-outs between groups and applicability of ITT analysis were both unclear due to the high rates of crossover permitted from DTIC to vemurafenib (i.e. unclear attrition bias risk) (CS Appendices Table 16, p. 61). The ERG concurs that risk of attrition bias is unclear, but as noted above considers that, additionally, BRIM-3 is at high risk of selection bias and unclear risk of detection bias.

Despite the above discrepancies in judgement the ERG considers that, overall, the MDX010-20 and BRIM-3 trials are appropriate for inclusion in the indirect comparison. Both trials were included as evidence considered in previous NICE melanoma appraisals.

Summary of indirect comparisons

Head-to-head comparisons of all the treatments within the scope of the STA were not conducted within the RCTs, necessitating indirect comparison. The company did not conduct a mixed treatment comparison to compare all treatments simultaneously due to clinical and methodological heterogeneity in the available evidence. As an alternative, indirect comparisons were conducted using selected RCTs from the company's systematic review of clinical effectiveness. Two separate evidence networks were created, for the comparison with ipilimumab and palliative chemotherapy (to inform the estimation of cost-effectiveness for BRAF mutation-negative patients), and for the comparison with BRAF inhibitors (for the estimation of cost-effectiveness for BRAF mutation-positive patients). Both networks used patient-level data / 'psuedo' patient-level data (BRAF mutation-negative / mutation-positive patients, respectively) from the trials to inform covariate-adjusted parametric survival models used directly in the economic model. Due to the immaturity of OS data alternative outcomes

were used: TTP and PrePS (to inform long-term extrapolations of PFS); and TTP, PrePS and PPS (to inform long-term extrapolations of OS).

The CS presents a pragmatic approach to indirectly comparing nivolumab with other treatments given the evidence limitations. The ERG considers that, overall, the approach taken is reasonable with some of the assumptions used having been accepted in previous NICE appraisals of treatments for advanced melanoma. The ERG is not aware of any relevant trials that were not included in the systematic review of clinical effectiveness, and thus absent from the indirect comparison. The trials that have been used were all multi-centre international RCTs judged to be of good methodological quality.

Trials which did not report OS were not eligible for the indirect comparison but it is not clear how many of the 44 trials identified in the systematic review would have been excluded on this criterion, and therefore how many could have provided estimates for other cancer outcomes such as PFS for potential inclusion in the analysis (though, according to the company it would not have been possible to include them unless OS events were also available – see next point).

A significant limitation is that the pivotal CheckMate 067 trial,[5] which directly compares nivolumab with ipilimumab, was not included in the indirect comparison, due to lack of available OS data. The CS does not state whether it would have been possible to have used data from the alternative outcomes (i.e. TTP, PrePS and PPS) from this trial as was done for the CheckMate 066 trial. The company clarified to the ERG that this was not possible as it requires both PFS and OS events to be available. The ERG agrees with this statement.

3.2 Summary statement of company's approach

The ERG's quality assessment of the company's systematic review of clinical effectiveness is summarised in Table 5. The processes for inclusion or exclusion of studies are described in the CS (CS p. 37-39), but the ERG notes that processes for data extraction are not described for the systematic review or the indirect comparison. Included studies were subject to critical appraisal using standard criteria recommended for use in company submissions by NICE. Overall, the ERG considers the study selection and critical appraisal processes are adequate and they appear to follow standard accepted systematic review methodology.

The ERG concludes that the submitted evidence generally reflects the decision problem defined in the CS and considers the overall risk of systematic error in the review to be low.

Table 5 - Quality assessment (Centre for Reviews and Dissemination criteria) of CS review

Quality Item: Yes/ No/ Uncertain	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes, inclusion and exclusion criteria are clearly stated.
2. Is there evidence of a substantial effort to search for all relevant research? I.e. all studies identified	Uncertain. There was substantial effort to search for all relevant published studies, and the ERG believes that all of these were identified. Ongoing trials were also searched, but these results are not provided in the CS. Only those trials are included that are expected to report data within the next 12 months.
3. Is the validity of included studies adequately assessed?	Yes. The validity of the studies is assessed in the CS using NICE-recommended criteria. However, the ERG assessment differed from the CS assessment in two criteria.
4. Is sufficient detail of the individual studies presented?	Yes, overall methodology, patient characteristics and outcomes are described in sufficient detail.
5. Are the primary studies summarised appropriately?	Yes, the primary studies are summarised appropriately, and details are presented in tables and figures. Meta-analysis was not considered possible due to heterogeneity in trials, and the ERG agrees with this.

3.3 Summary of submitted evidence

3.3.1 Summary of results for survival analysis

CheckMate 066[4], CheckMate 067[5] and CheckMate 037[9] all measure both overall survival (OS) and progression-free survival (PFS), as reported in CS Table 11 (p.49-59). The trials are still ongoing or in extended follow up, and to date OS data are only available for the CheckMate 066[4] trial. In response to the ERG's clarification question A8 the company indicated that OS data from CheckMate 067 will not be available until the number of pre-specified events (deaths) has been reached. The company does not expect this to be the case until the fourth quarter of 2016. PFS data are reported for all three trials.

The analyses demonstrate significant differences in both OS and PFS in favour of nivolumab.

Overall survival

Table 6 provides a summary of OS data from the CheckMate 066 trial (CS Table 15, p. 72).

Table 6 - Overall survival

	CheckMate 066	
	Nivolumab (n=210)	**DTIC (n=208)**
Events, n (%)	50 (23.8)	96 (46.2)
Hazard ratio (95% CI) p-value	0.42 (0.30, 0.60) <0.001	
Median OS (95% CI), months	Not reached	10.84 (9.33, 12.09)
OS rate at 6 months, % (95% CI)	84.1 (78.3, 88.5)	71.8 (64.9, 77.6)
OS rate at 12 months, % (95% CI)	72.9 (65.5, 78.9)	42.1 (33.0, 50.9)

CI = confidence interval; DTIC = dacarbazine; OS = overall survival

In this trial, OS was analysed by ITT and was based on a database lock date of 5 August 2014 (approximately 18 months after trial initiation). It contains data obtained prior to the implementation of the study protocol amendment that was made in response to a recommendation by the data monitoring committee, allowing patients who did not benefit from DTIC to cross over to nivolumab (see ERG report section 3.1.3). 'Event' is defined as death.

The OS analysis demonstrates a significant difference in deaths in favour of nivolumab. At a median follow-up of 8.9 months, a higher proportion of patients in the DTIC group had died, as compared to the nivolumab group. The corresponding hazard ratio confirms that these differences are statistically significant.

The median OS (when half of the patients have died) had not been reached in the nivolumab group at the time of the analyses, while the DTIC group had already reached a confirmed median OS, i.e. half of the patients in the DTIC group had died. The 75% OS (when a quarter of the patients have died) was reached in both the nivolumab group (10.3 months) and in the DTIC group (5.2 months) and shows an additional survival of 5.1 months in favour of nivolumab (CS narrative p. 72).

Survival rates at six months and at one year were also higher in patients randomised to nivolumab, i.e. after six months, and after one year, more patients were alive in the nivolumab group than in the DTIC group. The company comments that the one-year survival rates in the DTIC group are unusually high, potentially as a result of subsequent treatment with ipilimumab after disease progression within the first year (38% of DTIC patients).

Progression-free survival

Progression-free survival (PFS) is reported in CS Table 16 for CheckMate 066[4] (CS p. 72), and in the CS narrative for CheckMate 067[5] and CheckMate 037[9] (CS p. 75-76). Table 7 summarises PFS for these trials.

Table 7 - Progression-free survival

	CheckMate 066		**CheckMate 067**		**CheckMate 037**	
	Nivolumab (n=210)	**DTIC (n=208)**	**Nivolumab (n= 316)**	**Ipilimumab (n= 315)**	**Nivolumab (n= 122)**	**ICC (n= 60)**
Events, n (%)	108 (51.4)	163 (78.4)	174 (55.1)[b]	234 (74.3)[b]	71 (58.2)[b]	26 (43.3)[b]
Hazard ratio (95% CI) p-value	0.43 (0.34, 0.56) <0.001		0.57 (0.43, 0.76) <0.001		0.82[d]	
Median PFS (95% CI), months	5.06 (3.48, 10.81)	2.17 (2.10, 2.40)	6.9 (4.3, 9.5)[c]	2.9 (2.8, 3.4)[c]	4.67 (2.33, 6.51)	4.24 (2.14, 6.34)
PFS rate at 6 months (95% CI)	48.0 (40.8, 54.9)	18.5 (13.1, 24.6)	Not reported	Not reported	48 (38, 56)[e]	34 (18, 51)[e]
PFS rate at 12 months (95% CI)	41.8 (34.0, 49.3)	Not produced[a]	Not reported	Not reported	Not reported	Not reported

CI = confidence interval; DTIC = dacarbazine; ICC = investigator's choice chemotherapy, PFS = progression-free survival
[a] all PFS times were less than 12 months for the DTIC group.
[b] % calculated by ERG
[c] 95% CI were not reported in the CS but were taken from the trial publication[5]
[d] 95% CI and p-value are not reported. 99.99% CI is reported as 0.32-2.05.
[e] 95% CI were not reported in the CS but were taken from the trial publication[9]

In all of the trials, PFS was analysed by ITT, and 'event' was defined as death or progression. Data from all randomised patients were included in the PFS analyses for CheckMate 066[4] and CheckMate 067.[5] The PFS analysis for CheckMate 037[9] was undertaken at an interim time point, when the first 120 patients treated with nivolumab had a minimum follow-up of 6 months (median follow-up was 8.4 months). Hence, this analysis does only include a proportion of the 405 trial participants.

The PFS analyses for CheckMate 066[4] and CheckMate 067[5] demonstrate significant differences in disease progression or death between patient groups. A smaller proportion of patients in the nivolumab groups had died or experienced disease progression, as compared

to the comparator groups (DTIC or ipilimumab). The corresponding hazard ratios confirm that these differences are statistically significant.

In CheckMate 037[9] differences in PFS between patients treated with nivolumab and those treated with ICC were small. In their narrative (CS p.76), the company points out that the immaturity of the data analysed from the CheckMate 037[9] trial was primarily responsible for the uncertainty of these results, along with imbalances in prognostic factors between trial groups in favour of ICC, and high withdrawal rates in the ICC arm. The ERG agrees with the company that the observed imbalances between patient groups are likely to introduce bias. The company also states that the use of the RECIST criteria[10] for progression resulted in false-positive progression assessments in the nivolumab arm. However, the ERG notes that the RECIST criteria were also used in the assessment of patients in CheckMate 066[4] and CheckMate 067,[5] where hazard ratios for death or progression were found to be statistically significant.

3.3.2 Summary of results for response analysis

Measures of treatment response were analysed in CheckMate 066[4], CheckMate 067[5] and CheckMate 037[9] and were summarised in CS tables 17 (CS p. 77), 18 (CS p. 81), and 19 (CS p. 84). Table 8 presents a synopsis of the results from the individual analyses.

Table 8 - Response analysis

	CheckMate 066		CheckMate 067		CheckMate 037	
	Nivolumab (n=210)	**DTIC (n=208)**	**Nivolumab (n= 316)**	**Ipilimumab (n= 315)**	**Nivolumab[a] (*PP*: n= 120) (*ITT*: n=122)**	**ICC (*PP*: n= 47) (*ITT*: n=60)**
Objective response rate (ORR)						
Responders, n (%) (95% CI)	84 (40.0)[b] (33.3, 47.0)	29 (13.9)[b] (9.5, 19.4)	138 (43.7)[b] (38.1, 49.3)	60 (19.0)[b] (14.9, 23.8)	*PP*: 38 (31.7)[c] (23.5, 40.8)	5 (10.6)[c] (3.5, 23.1)
					ITT: 38 (31.1)[c] (23.1, 40.2)	5 (8.3)[c] (2.8, 18.4)
Best overall response CR, n (%) PR, n (%)	16 (7.6) 68 (32.4)	2 (1.0) 27 (13.0)	28 (8.9) 110 (34.8)	7 (2.2) 53 (16.8)	*PP*: 4 (3.3) 34 (28.3)	0 5 (10.6)
					ITT: 4 (3.3) 34 (27.9)	0 5 (8.3)
Unweighted ORR difference, % (95% CI)	26.1 (18.0, 34.1)		24.7[c]		*PP*: 21.0 (6.8, 31.7)	
					ITT: 22.8 (10.5, 32.7)	
Estimated odds ratio (95% CI) p-value	4.06 (2.52, 6.54) <0.0001		3.40 (2.02, 5.72) <0.0001		Not reported	
Duration of response						
Median (range), months	Not reached (0.0, 12.5)	5.98 (1.1, 10.0)	Not reached	Not reached	*PP*: Not reached (1.4+, 10.0+)	3.5 (1.3+, 3.5)
Time to treatment response						
Median (range), months	2.10 (1.2, 7.6)	2.10 (1.8, 3.6)	2.8 (2.3, 12.5)	2.8 (2.5, 12.4)	*PP*: 2.1 (1.6, 7.4)	3.5 (2.1, 6.1)

CI = confidence interval; CR = complete response; DTIC = dacarbazine; ITT = intention-to-treat; ORR = Objective response rate; PP = per-protocol; PR = partial response rate.
[a] CheckMate 037[9] reports both ITT and PP analyses for tumour response. [b] Confirmed response (CR+PR) as per RECIST v1.1 criteria, investigator-assessed.
[c] Confirmed response (CR+PR) as per RECIST v1.1 criteria, assessed by independent radiological review committee. [d] 95% CI not reported in the CS or in the trial publication.[5]

In CheckMate 066[4] and CheckMate 067[5], response analyses were undertaken by ITT, and data from all randomised patients were included. Tumour response was assessed by the investigators.

In CheckMate 037,[9] treatment response was assessed separately by IRRC and by investigators. IRRC-assessed response was analysed by both PP and ITT, and the ERG included these data in Table 8. PP investigator assessment is also available in the CS (CS Table 19, p. 84), but the ERG has not reported these outcomes. The ERG notes that outcome analyses in CheckMate 037 did not include all trial participants, and that analyses were undertaken at an interim time point, as described above in section *Progression-free survival*.

Overall, the analyses demonstrate significant benefit of nivolumab over comparator drugs. More patients treated with nivolumab experienced complete response (i.e. when the cancer completely disappears for a time) than those treated with alternative drugs, although the total number of patients with complete response was low in all study groups (<10%). The corresponding estimated odds ratios confirm that these differences are statistically significant.

Time to treatment response was similar between nivolumab and ipilimumab / DTIC, but appeared to be longer in the ICC group (CheckMate 037). However, the ERG notes that overall differences in time to treatment response are small.

Investigators also measured the duration of response, and treatment with nivolumab was found to be more durable than treatment with alternative drugs. The DTIC and the ICC study groups had already reached a confirmed median duration of response, i.e. half of the patients treated with DTIC or ICC were no longer experiencing benefit from treatment. In contrast, this end point was not reached in any of the nivolumab study groups and in the ipilimumab group of the CheckMate 067 trial, indicating that most patients were still experiencing treatment response at the time of analysis. The CS states that the longest duration of response observed in the nivolumab group was over 12 months at the time of analysis. A high proportion of patients continue to experience treatment response in all of the nivolumab trials and the company expects further increase in treatment duration to be found at the next data analysis (CS p. 77, p. 81, and 84).

The CS also comments on tumour burden, and changes in tumour burden are presented as waterfall plots in CS figures 15 for CheckMate 066[4] (CS p. 79), 17 for CheckMate 067,[5] and 20 for CheckMate 037[9] (CS p. 86). In all of the trials, more patients in the nivolumab groups experienced a reduction in tumour size, and achieved at least a partial response, compared with patients in the comparator groups. A best reduction in tumour size of at least 50% was reported in the majority of responding patients in the nivolumab groups of CheckMate 066[4] and CheckMate 037[9] CS p. 78 and p. 85). The median change in tumour size reported in CheckMate 067[5] was -34.5% (i.e. reduction in tumour size by more than one third) in the nivolumab group, compared to +5.9% (i.e. increase in tumour size) in the ipilimumab group (CS p. 81). Median change in tumour burden was not reported for CheckMate 066[4] and CheckMate 037.[9]

Post-RECIST criteria progression response

Continued treatment after disease progression was permitted in CheckMate 066[4] and CheckMate 067[5] for patients who experienced clinical benefit and who were tolerating the treatment. Patients in the nivolumab group of CheckMate 037[9] were also offered treatment after progression. In all three trials progression was defined by RECIST criteria (version 1.1)[10] and suitability for treatment continuation was determined by the investigators. Post-RECIST progression treatment response was reported in the CS narrative for each of the trials (CS p. 80 for CheckMate 066; CS p. 83 for CheckMate 067; CS p. 87 for CheckMate 037). In addition, the CS presents graphic representations of response patterns in Figure 16 (CS p. 80) for CheckMate 066, Figure 18 (CS p. 83) for CheckMate 067, and Figure 21 (CS p. 87) for CheckMate 037. The ERG presents a summary of these outcomes in Table 9.

Table 9 - Post RECIST progression response

	CheckMate 066[a]		**CheckMate 067[b]**		**CheckMate 037[c]**
	Nivolumab	**DTIC**	**Nivolumab**	**Ipilimumab**	**Nivolumab**
Patients treated post-progression, n	54	49	86	99	37
Responders, n (%)[d]	12 (22.2)[e]	2 (4.1)[e]	Not reported	Not reported	10 (27.0)

[a] Population described in the CS as "all treated patients" (CS p. 80).
[b] Population described in the CS as "patients with a best ORR of progressive disease" (CS p. 83).
[c] Population described in the CS as "all treated nivolumab patients at the time of interim analysis" (CS p. 87).
[d] Described in the CS as having developed or maintained a target lesion reduction of >30% compared to baseline after initial RECIST defined progression.
[e] The ERG notes that in the trial journal paper[4] the corresponding figures are 17 (31%) and 8 (16%), as discussed in section 3.1.7 of this report.

Of all patients treated with nivolumab beyond RECIST-defined progression, 22.2% in CheckMate 066 and 27.0% CheckMate 037 developed or maintained a target lesion reduction of >30% compared to baseline after progression. In comparison, only 4.1% of DTIC-treated patients experienced benefit from treatment beyond progression. As described

in Section 3.1.7 of this report, the ERG notes that the CheckMate 066 journal paper[4] reports post-progression treatment response in 17 (31%) nivolumab-treated patients and in 8 (16%) patients treated with DTIC, at odds with the figures given in the CS (and reproduced in this report in Table 9). The reason for this discrepancy is not clear. Post-progression response data were not reported for CheckMate 067, but the company states in their narrative that "many" nivolumab-treated patients experienced treatment response (CS p. 83).

The ERG concludes that a proportion of patients appear to benefit from continued nivolumab treatment beyond disease progression and the ERG would support the company's statement that treatment to progression may not always be reasonable in clinical practice (CS p.18). However, the duration of post progression treatment benefits remains unknown, as the trials are still ongoing or in extended follow-up.

3.3.3 Summary of health related quality of life

The CS provides an overview of results from CheckMate 066 for the EORTC-QLQ-C30 (which has 15 subscales), the EQ-5D utility index and the EQ-5D VAS, summarising narratively the differences in scores between the nivolumab and DTIC groups and describing changes in scores over time and in relation to baseline values (CS p. 87-89). No results for the WPAI:GH instrument are reported in the CS. Clinically meaningful differences in scores are defined in the CS by minimally important differences cited in the literature (EORTC-QLQ-C30 ≥10 points; EQ-5D utility index ≥0.08 points; EQ-5D VAS ≥7 points). The CS also presents hazard ratios (nivolumab versus DTIC; Cox proportional hazards regression models) for the time from randomisation to first decline in HRQoL and also for the time to first improvement in HRQoL, which is defined as the minimally important difference for the instrument as applied at the patient-level (CS Table 20). Due to the interim nature of the analyses, no HRQoL results from CheckMate 037 or CheckMate 067 are presented in the CS. Upon request of the ERG (clarification question A6), the company provided additional (interim) HRQoL data for CheckMate 066 (see below) and confirmed that no further data are currently available for CheckMate 037 or CheckMate 067, although partial HRQoL results from CheckMate 067 are expected in the second half of November 2015.

Initial EQ-5D and EORTC-QLQ-C30 scores as reported in the CS

The initial HRQoL results presented in the CS (p. 87-89) are from the CSR for CheckMate 066 and an abstract by Long and colleagues.[28] The CS states that the completion rates at baseline for EORTC-QLQ-C30 were 79% for the nivolumab group and 78% for the DTIC

group and adjusted completion rates (i.e. based on the numbers of patients remaining in the study) remained ≥70% up to visit week 73. Adjusted completion rates for the EQ-5D utilities index were 70% in the nivolumab group and 69% in the DTIC group and the CS states they remained similar throughout the study. However, the CS points out that due to a high attrition rate in the DTIC arm from week 13 there is high uncertainty with the HRQoL analysis after this time. No completion rates for the EQ-5D VAS are reported in the CS and the reasons for non-completion of the EORTC-QLQ-C30 and EQ-5D utility index are not specified.

The CS concludes that nivolumab does not impair HRQoL and in some cases HRQoL improved relative to baseline. However, the CS (p. 87-88) does not report individual scores for all analysis time points and it is therefore difficult to get a clear picture from the CS of whether there are any overall patterns in scores for the EORTC-QLQ-C30 and EQ-5D instruments.

Additional HRQoL data provided in the company's clarification response

The additional HRQoL data provided by the company for CheckMate 066 at the request of the ERG include graphs which clarify the time course of changes in the HRQoL measures. These graphical presentations demonstrate that EQ-5D utility index scores and EORTC QLQ-C30 global health status subscale scores were consistently higher for nivolumab than DTIC at baseline and this difference persisted throughout the study (Figures 3 and 5 in the company's clarification response). The graph for EQ-5D (Figure 3 in the company's clarification document) is reproduced in Figure 3 below.

In the clarification document the company points out that improvement in the EQ-5D utility score for nivolumab at week 37 was greater than the minimal important difference (0.08), indicating clinically meaningful improvement. However, the company does not clarify whether this difference was statistically significant. The ERG notes that uncertainty in Figures 3 to 6 in the company's clarification response (and as reproduced in Figure 3 below) is represented by standard errors rather than 95% confidence intervals; if presented instead as 95% confidence intervals there would be substantial overlap of the intervals for nivolumab and DTIC, which would indicate no statistically significant differences between the drugs for many of the time points analysed.

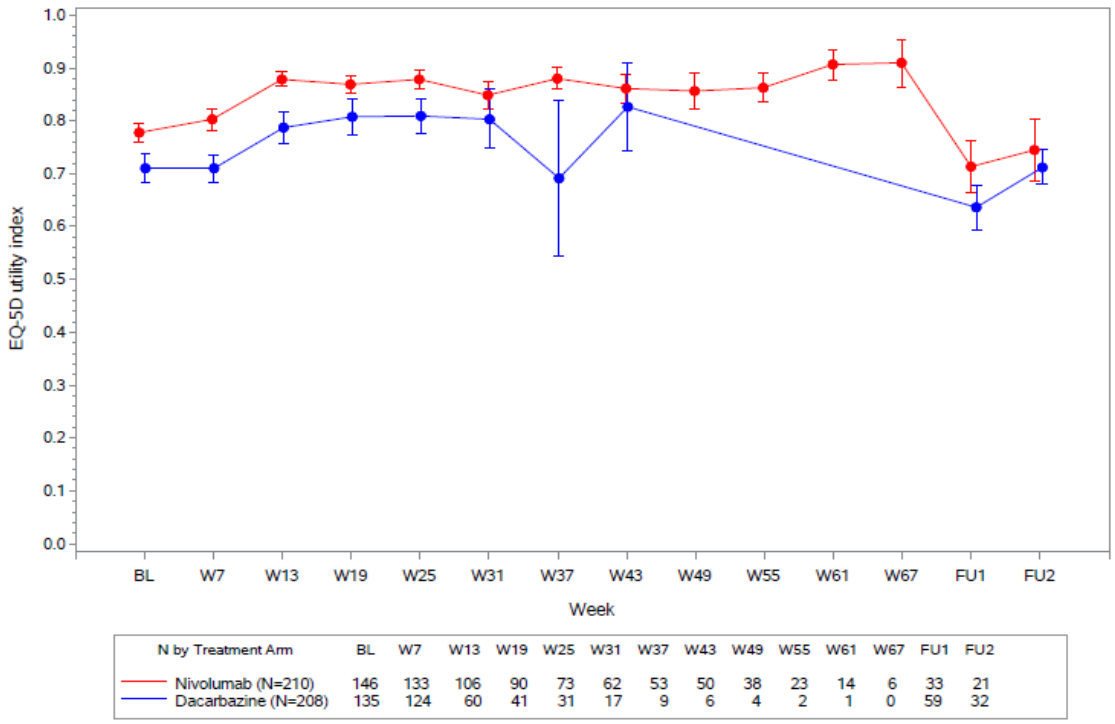

Figure 3 - Mean (±SE) EQ-5D utility index scores in the nivolumab and DTIC arms of CheckMate 066

The additional HRQoL data provided by the company also include graphs which show the change from baseline in EQ-5D utility index and EORTC QLQ-C30 global health status subscale scores (Figures 4 and 6 in the company's clarification response). These show that, when the baseline scores are taken into account, there are no consistent differences between nivolumab and DTIC and there is also no discernible improvement relative to baseline for the nivolumab arm. The graph for change from baseline in the EQ-5D utility index (Figure 4 in the company's clarification document) is reproduced in Figure 4 below. Given that the error bars presented in the graph are standard errors and error bars based on 95% confidence intervals would be wider, it appears unlikely that any of the differences between nivolumab and DTIC in Figure 4 could be considered statistically significant.

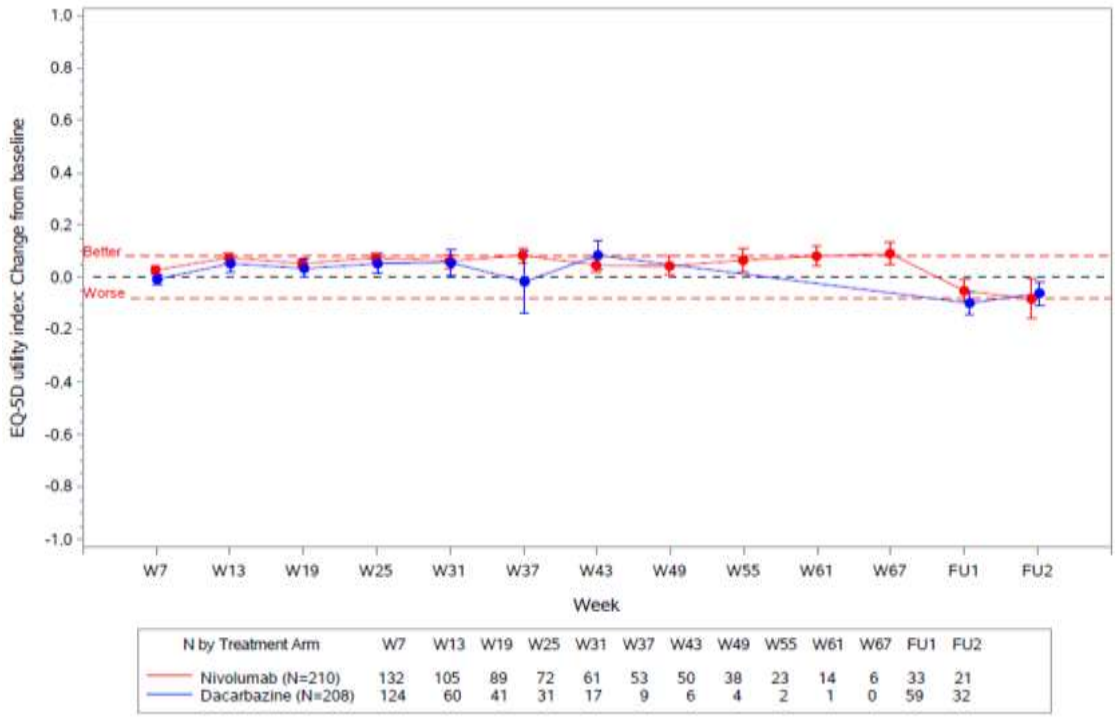

Figure 4 - Mean (±SE) changes from baseline in the EQ-5D utility index scores for the nivolumab and DTIC arms of CheckMate 066

In their clarification response, the company presents an analysis of statistically significant and/or clinically meaningful changes from baseline for nine of the EORTC QLQ-C30 subscales (Table 5 in the company's clarification response). This analysis includes 72 pairwise statistical comparisons between nivolumab and DTIC. The ERG considers that such a large number of multiple comparisons would inflate the rate of type I statistical error, potentially resulting in spurious conclusions about differences in HRQoL scores between the nivolumab and DTIC arms. Overall, the ERG's interpretation is that whilst there may be positive impacts of nivolumab on EORTC-QLQ-C30 scores relative to the baseline scores these appear to be transient and uncertain, with no clear indication of a consistent long-term improvement for any of the instrument's subscales.

Time to first decline or improvement in HRQoL as reported in the CS

The CS reports that regression analysis of time to first decline in HRQoL (CS Table 20) suggests that nivolumab had a favourable effect (HR <1.0) compared to DTIC for most of the 15 subscales of the EORTC-QLQ-C30, as well as for the EQ-5D utility index (but not for the EQ-5D VAS). Statistical significance of HR is indicated where 95% CI for the HR do not include 1.0. The largest differences in time to first decline in EORTC-QLQ-C30 subscales were for nausea and vomiting (HR=0.43 [95% CI 0.28 to 0.67]; p<0.001), dyspnoea (HR=0.50 [95% CI 0.33 to 0.75]; p<0.001), appetite loss (HR=0.43 [95% CI 0.29 to 0.65];

p<0.001), and constipation (HR=0.51 [95% CI 0.34 to 0.76]; p<0.001). Subscales of the EORTC QLQ-C30 that demonstrated no significant difference in time to first decline between nivolumab and DTIC were fatigue (HR=0.74 [95% CI 0.55 to 1.00]), diarrhoea (HR=0.87 [95% CI 0.53 to 1.43]), and financial difficulties (HR=0.66 [95% CI 0.41 to 1.05]). The time to first decline in the EQ-5D utility index favoured nivolumab (HR=0.55 [95% CI 0.38 to 0.80]; p=0.002) whereas there was no difference between nivolumab and DTIC for the time to first decline of EQ-5D VAS scores (HR=0.82 [95% CI 0.59 to 1.14]).

In contrast to the time to first decline in HRQoL, the CS provides only a brief summary of the Cox proportional hazards regression analysis results for time to first improvement in HRQoL (CS p. 88). The CS reports that time to first improvement favoured nivolumab over DTIC (i.e. HR > 1.0) for four of the 15 subscales of the EORTC-QLQ-C30. These were: global health (HR=1.52; p=0.043); physical functioning (HR=1.92; p=0.027); fatigue (HR=1.69; p=0.008); and dyspnoea (HR=2.20; p=0.013) (no 95% CI for the HR were reported). The CS also reports that time to first improvement in the EQ-5D utility index favoured nivolumab (HR=1.86; p=0.002).

Although time to first decline appears to favour nivolumab for most of the HRQoL scales assessed, including the EQ-5D utility index, the ERG notes that the method of analysis is not clearly explained in the CS, particularly with regard to whether unbalanced attrition between the trials arms after week 13 could have influenced the reported outcomes (the CS does not explicitly state which time periods are covered by the regression analyses). The ERG also notes that any initial improvements in HRQoL suggested by these Cox proportional hazards regression analyses did not appear to translate into longer-term HRQoL benefits to patients. For these reasons, and given the interim nature of the analyses, the ERG suggests that these findings should be interpreted with caution.

In summary, based on the interim HRQoL evidence presented in the CS and in the company's clarification response, the ERG agrees with the company's conclusion that nivolumab does not impair HRQoL (relative to baseline), but the ERG notes that there is no current evidence that nivolumab leads to a consistent and sustained improvement in HRQoL. Although the company's analyses suggest that nivolumab has a favourable time to first decline in HRQoL and, to a lesser extent, favourable time to first improvement in HRQoL when compared to DTIC, the best available evidence from the initial analyses does not currently suggest that this translates into longer-term HRQoL benefits.

3.3.4 Summary of results for sub-group analysis

The company undertook pre-defined subgroup analyses for most baseline characteristics (e.g. age, M stage, ECOG performance status, history of brain metastases, etc), and these are reported in the CS (p. 89-91) for CheckMate 066 (OS and response),[4] and in CS Appendix 7 for CheckMate 067(PFS; response)[5] and CheckMate 037 (response)[9] (CS Appendices p. 77-80). Forest plots are provided for all CheckMate trials.

In most subgroup analyses, outcomes were found to be in favour of nivolumab, indicating that nivolumab-treated patients benefited more compared to those treated with alternative drugs. In CheckMate 037,[9] several CIs crossed zero, indicating that nivolumab may not be effective for certain subgroups in terms of ORR (e.g. patients with BRAF mutation, ECOG PS 1, LDH above upper limit of normal, or negative PD-L1 status, among others). Subgroup analyses for CheckMate 066[4] and CheckMate 067[5] also indicated that some subgroups may not experience survival benefit from nivolumab (e.g. patients aged ≥75). However, some of these subgroups are very small and the ERG believes that the analyses should be interpreted with caution.

The ERG presents a summary of the findings from subgroup analyses by PD-L1 expression status and by BRAF mutation status below.

Subgroup analysis by PD-L1 expression status

A subgroup analysis of overall survival (OS) by PD-L1 expression status is presented for the CheckMate 066[4] trial in CS Table 21 (CS p. 90), replicated here in Table 10.

Table 10 - Overall survival by PD-L1 expression status (CheckMate 066)

	Nivolumab (n=210)	**DTIC (n=208)**
PD-L1-positive patients, n (%)	74 (35.2)	74 (35.6)
Events, n (%)	11 (14.9)	29 (39.2)
Median OS (95% CI), months	Not reached	12.39 (9.17, not reached)
Unstratified hazard ratio (95% CI)	0.30 (0.15, 0.60)	
PD-L1-negative/indeterminate patients, n (%)	136 (64.8)	134 (64.4)
Events, n (%)	39 (28.7)	67 (50.0)
Median OS (95% CI), months	Not reached	10.22 (7.59, 11.83)
Unstratified hazard ratio (95% CI)	0.48 (0.32, 0.71)	

CI = confidence interval; DTIC = dacarbazine; OS = overall survival; PD-L1 = programmed death-ligand-1.

The ERG notes that both PD-L1-positive and PD-L1-negative patients benefited from nivolumab treatment, although the proportion of patients who died was almost twice as high in the PD-L1-negative group (28.7%) than in the PD-L1-positive group (14.9%). For both PD-L1-subgroups the median OS was not reached in the nivolumab arm, i.e. more than half of these patients were still alive at the time of analyses, whereas more than half of the patients treated with DTIC had died.

A brief narrative of progression-free survival (PFS) by PD-L1 status was supplied for CheckMate 067[5] (CS Appendices p. 77). Again, patients benefited from nivolumab treatment irrespective of PD-L1 status, although median PFS in the PD-L1 positive group was longer than in the PD-L1 negative group (14.0 months compared to 5.3 months). Median PFS in PD-L1 positive ipilimumab-treated patients was 3.9 months, and 2.8 months in PD-L1 negative patients.

Objective response rates were reported by PD-L1 expression status for CheckMate 066[4] (CS Table 22, p. 90) and CheckMate 037[9] (Table 20, CS Appendices p. 79). A brief narrative ORR was also supplied for CheckMate 067[5] (described as a post-hoc analysis, CS Appendices p. 77). The results are summarised in Table 11.

Table 11 - Objective response rate by PD-L1 expression status

	CheckMate 066 ITT analysis		**CheckMate 067** Post-hoc ITT analysis		**CheckMate 037** PP objective response set IRRC assessment	
	Nivolumab n=(210)	**DTIC n=208)**	**Nivolumab (n=316)**	**Ipilimumab (n=315)**	**Nivolumab (n=120)**	**ICC (n=47)**
PD-L1-positive patients, n (%)	74 (35.2)	74 (35.6)	80 (25.3)	(75 (24)	55 (45.8)	22 (46.8)
Responders, n (%)(95% CI)	39 (52.7) (40.8, 64.3)	8 (10.8) (4.8, 20.2)	-	-	24 (43.6) (30.3, 57.7)	2 (9.1) (1.1, 29.2)
Unweighted ORR difference, % (95% CI)	-		-		34.5 (12.2, 49.2)	
ORR %	-	-	57.5	21.3	-	-
Odds ratio (59% CI)	-	-	5.03 (2.44, 10.37)		-	-
PD-L1-negative/in-determinate patients, n (%)	136 (64.8)	134 (64.4)	Not reported	Not reported	64 (53.3)	23 (48.9)
Responders, n (%)(95% CI)	45 (33.1) (25.2, 41.7)	21 (15.7) (10.0, 23.0)			13 (20.3) (11.3, 32.2)	3 (13.0) (2.8, 33.6)
Unweighted ORR difference, % (95% CI)	-		-		7.3 (-13.4, 21.5)	
ORR %	-	-	41.3%	17.8%	-	-
Odds ratio (59% CI)	-		3.25 (2.05, 5.13)		-	

CI = confidence interval; DTIC = dacarbazine; ICC = investigators choice chemotherapy; IRCC = independent radiological review committee; ORR = objective response rate; PD-L1 = programmed death-ligand-1.

In all of the trials, objective response rates were higher in nivolumab-treated patients with positive PD-L1 status than in nivolumab-treated patients with PD-L1 negative status. Both groups experienced higher response rates than patients treated with alternative drugs. However, the ERG notes that the lower bound of the 95% CI around the unweighted ORR difference between treatments in the PD-L1-negative subgroup fell below zero, indicating a potential better response for ICC treated patients in this subgroup. The trial journal publication[9] notes that these analyses, although pre-defined, were 'exploratory' and 'descriptive in nature' (p. 381) and that the patient sample sizes in some of the subgroups

were small. The ERG agrees that caution is required in the interpretation of these results for this reason.

Subgroup analysis by BRAF mutation status

Subgroup analyses by BRAF mutation status are included in the forest plots presented in CS appendix 7 (CS appendices p. 77-80). Median progression-free survival is reported for CheckMate 067[5] (CS Appendices Figure 3, p. 78), and objective response rate is reported for CheckMate 037[9] (CS Appendices Figure 4, p. 80). The ERG summarised the results in Table 12 and Table 13. No subgroup analyses by BRAF mutation status were undertaken for CheckMate 066[4] as this trial only included BRAF mutation-negative patients.

Table 12 - Progression-free survival by BRAF mutation status (CheckMate 067)

	Nivolumab (n= 316)	**Ipilimumab (n= 315)**
BRAF mutation-positive n (%)	98 (31.0)[a]	100 (31.7)[a]
Number of events n (%)	57 (58.2)[a]	66 (66.0)[a]
Median PFS (95% CI), months	5.62 (2.79, 9.46)	4.04 (2.79, 5.52)
Unstratified hazard ratio (95% CI)	0.77 (0.54, 1.09)	
BRAF mutation-negative n (%)	218 (69.0)[a]	215 (68.3)[a]
Number of events n	117 (53.7)[a]	168 (78.1)[a]
Median PFS (95% CI), months	7.98 (4.68, 12.68)	2.83 (2.76, 3.09)
Unstratified hazard ratio (95% CI)	0.50 (0.39, 0.63)	

CI = confidence interval; PFS = progression-free survival.
[a] % calculated by ERG.

The highest benefit in terms of PFS was observed in nivolumab-treated patients without BRAF mutation (BRAF wild-type), with median PFS of 7.98 months. All nivolumab-treated patients experienced longer PFS than those treated with ipilimumab, irrespective of BRAF mutation status. However, the 95% CI around the unstratified HR for BRAF mutation-positive patients crossed one, indicating no statistically significant difference between nivolumab and ipilimumab in this sub-group of patients.

Table 13 - Objective response rate by BRAF mutation status (CheckMate 037)

	Nivolumab (n=120)	ICC (n=47)
BRAF mutation-positive n (%)	26 (21.7)[a]	11 (23.4)[a]
Responders n (%)	6 (23.1)	1 (9.1)
ORR % (95% Exact CI)	23.1 (9.0, 43.06)	9.1 (0.2 41.3)
Unweighted ORR difference % (95% CI)	14.0 (-17.1, 34.4)	
BRAF mutation-negative n (%)	94 (78.3)[a]	36 (76.6)[a]
Responders n (%)	32 (34.0)[a]	4 (11.1)[a]
ORR % (95% Exact CI)	34.0 (24.6, 44.5)	11.1 (3.1, 26.1)
Unweighted ORR difference % (95% CI)	22.9 (6.2, 35.0)	

CI = confidence interval; ICC = investigator choice of chemotherapy; ORR = objective response rate.
[a] % calculated by ERG.

Nivolumab-treated patients experienced higher response rates than those treated with ICC, irrespective of BRAF mutation status. However, response rates were highest in patients with BRAF mutation-negative status. Furthermore, the lower bound of the 95% CI around the unweighted ORR difference between treatments in the BRAF mutation-positive subgroup fell below zero, indicating a potential better response for ICC treated patients in this subgroup. As described above, these subgroup analyses should be interpreted with caution due to the small sample size within each stratum.

3.3.5 Summary of adverse events

Adverse events (AE) are reported in CS section 4.2 (p. 134-145), and summaries of overall rates of AE and discontinuations due to AE are presented in CS Table 46 (CS p. 136) for CheckMate 066,[4] Table 48 (CS p. 140) for CheckMate 067[5], and Table 50 (CS p. 143) for CheckMate 037.[9] These data from the CS are replicated here in Table 14.

Table 14 - Adverse events

	CheckMate 066				CheckMate 067				CheckMate 037			
	Nivolumab (n=206)[a]		DTIC (n=205)[a]		Nivolumab (n= 313)[a]		Ipilimumab (n= 311)[a]		Nivolumab (n=268)[a]		ICC (n=102)[a]	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
All AEs, n (%)	192 (93.2)	70 (34.0)	194 (94.6)	78 (38.0)	311 (99.4)	136 (43.5)	308 (99.0)	173 (55.6)	255 (95.1)	92 (34.3)	95 (93.1)	44 (43.1)
TRAEs, n (%)	153 (74.3)	24 (11.7)	155 (75.6)	36 (17.6)	257 (82.1)	51 (16.3)	268 (86.2)	85 (27.3)	181 (67.5)	24 (9.0)	81 (79.4)	32 (31.4)
All SAEs, n (%)	64 (31.1)	43 (20.9)	78 (38.0)	54 (26.3)	113 (36.1)	88 (28.1)	162 (52.1)	119 (38.3)	118 (44.0)	78 (29.1)	22 (21.6)	16 (15.7)
TRSAEs, n (%)	19 (9.2)	12 (5.8)	18 (8.8)	12 (5.9)	25 (8.0)	18 (5.8)	69 (22.2)	51 (16.4)	17 (6.3)	12 (4.5)	10 (9.8)	9 (8.8)
DC due to AEs, n (%)	14 (6.8)	12 (5.8)	24 (11.7)	19 (9.3)	43 (13.7)	27 (8.6)	70 (22.5)	62 (19.9)	25 (9.3)	19 (7.1)	12 (11.8)	5 (4.9)
DC due to TRAEs, n (%)	5 (2.4)	4 (1.9)	7 (3.4)	5 (2.4)	24 (7.7)	16 (5.1)	46 (14.8)	41 (13.2)	6 (2.2)	6 (2.2)	8 (7.8)	3 (2.9)
Deaths relating to study drug, n (%)	0		0		1		1		0		0	

AEs = adverse events; DC = discontinuation; DTIC, dacarbazine; ICC = investigator's choice chemotherapy SAEs, serious adverse events; TRAEs, treatment-related adverse events; TRSAEs, treatment related serious adverse events.

[a] Patients who received at least one infusion of nivolumab or comparator drug (DTIC / ipilimumab / ICC).

Nearly all patients in these trials (>93%) experienced at least one AE of any grade, regardless of the study drug administered, with very little difference between nivolumab-treated patients and those treated with comparator drugs. In the majority of cases, AEs were treatment-related, and the proportion of nivolumab-treated patients experiencing treatment-related AEs (TRAEs) of any grade ranged from 67.5% in CheckMate 037[9] to 82.1% in CheckMate 067.[5] No major differences in the rate of TRAEs were observed between nivolumab and the comparator treatments.

Grade 3-4 AEs, TRAEs, and serious AEs (SAEs) appeared to occur less frequently in nivolumab-treated patients compared to alternative treatments, with the exception of CheckMate 037,[9] where a higher proportion of nivolumab-treated patients experienced grade 3-4 SAEs (29.1% vs. 15.7% in the ICC group) or discontinued nivolumab treatment due to grade 3-4 AEs (7.1% vs. 4.9% in the ICC group).

In all of the CheckMate trials, the proportion of patients who discontinued the study drug due to TRAEs was lower in the nivolumab groups than in the comparator groups. The ERG notes that in Checkmate 067[5] a higher proportion of patients discontinued treatment due to AEs of any grade (nivolumab: 13.7%; ipilimumab: 22.5) compared to CheckMate 066[4] (nivolumab: 6.8%; DTIC: 11.7%) and CheckMate 037[9] (nivolumab: 9.3; ICC: 11.8). In addition, discontinuation of treatment due to TRAEs occurred more frequently in Checkmate 067,[5] irrespective of treatment. The CS does not discuss between-trial differences in safety outcomes.

The most frequently reported TRAEs (reported in ≥15% of patients) in the nivolumab groups of the CheckMate trials were fatigue, pruritus, rash, diarrhoea, and nausea, as summarised in Table 15.

Table 15 - Most frequently reported TRAEs in nivolumab-treated patients[a]

	CheckMate 066 Nivolumab (n=206)	**CheckMate 067 Nivolumab (n= 313)**	**CheckMate 037 Nivolumab (n=268)**
Fatigue	19.9%	34.2%	25.0%
Pruritus	17.0%	18.8%	16.0%
Rash	15.0%	25.9%	
Diarrhoea	16.0%	19.2%	
Nausea	16.5%		

[a] Empty cells indicate that TRAE was reported in less than 15% of patients.

Hyperglycaemia, vomiting, pyrexia, pneumonitis, and infusion-related reaction were the only TRSAEs reported in more than one nivolumab-treated patient in CheckMate 066,[4] and each occurred in two patients. Hyperglycaemia was the only TRSAE reported in more than one patient in CheckMate 037,[9] and occurred in two patients. No TRSAEs were reported in more than 2% of patients in CheckMate 067.[5] None of the CheckMate trials reported TRSAEs leading to the discontinuation of nivolumab treatment in more than 1 patient (CheckMate 066, 037) or in more than 2% of patients (CheckMate 067).

One patient died from toxic effects of nivolumab (neutropenia) in CheckMate 067,[5] and there was also one treatment-related death in the ipilimumab group of this trial (cardiac arrest). CheckMate 066[4] and CheckMate 037[9] did not report any treatment-related deaths.

The CS also reports details of select AEs, which are defined as AEs "with a potential immunological cause that need frequent monitoring and potential intervention." These are categorised by organ system (endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin) and are presented in CS Table 47 (CS p. 137-138) for CheckMate 066,[4] Table 49 (CS p. 140-141) for CheckMate 067,[5] and Table 51 (CS p. 144-145) for CheckMate 037.[9]

In nivolumab-treated patients, the most frequently reported select AE occurred in the skin (between 35.8% in CheckMate 037[9] and 53.4% in CheckMate 067[5]) and in the gastrointestinal categories (between 20.5% in CheckMate 037[9] and 31.6% in CheckMate 067[5]), and the least frequent categories were pulmonary and renal select AEs and hypersensitivity reactions (pulmonary: between 1.5% in CheckMate 066[4] and 3.0% in CheckMate 037;[9] renal: between 3.2% in CheckMate 067[5] and 6.7% in CheckMate 037;[9] hypersensitivity reactions between 3.0% in CheckMate 037 and 7.8% in CheckMate 066). Select AEs occurred more frequently in the nivolumab groups of CheckMate 066[4] and CheckMate 037,[9] with the exception of hypersensitivity reactions, which were more common in patients treated with ICC (CheckMate 037). In CheckMate 067,[5] select AEs were reported more frequently in ipilimumab-treated patients, and only select AEs in the endocrine, hepatic, and hypersensitivity reaction categories were reported more frequently in patients treated with nivolumab. Differences in rates of select AEs between nivolumab and ipilimumab were generally smaller than those observed between nivolumab and DTIC or ICC (apart from hypersensitivity reactions in CheckMate 066), and the ERG assumes that this is due to the fact that both nivolumab and ipilimumab belong to the

group of immune-therapies, while CheckMate 066[4] and CheckMate 037[9] compare nivolumab to chemotherapies.

The majority of select AEs were low-grade. Most were resolved with corticosteroids or other immunosuppressant medication, although median time to resolution was up to 18.4 weeks in the skin category, and up to 8 weeks in the hepatic category for nivolumab-treated patients. In CheckMate 066[4] and CheckMate 067,[5] some events of endocrine select AEs in nivolumab-, DTIC-, and ipilimumab-treated patients were controlled, but not resolved at the time of reporting (i.e. the median time to resolution had not been reached).

The ERG notes that nivolumab-treated patients had higher drug exposure than those receiving alternative treatments, as summarised in Table 16. Relative dose intensity of ≥90% was achieved by the majority of patients (84.0% to 91.3%) treated with nivolumab (33.3 to 88% in the comparator groups). This, together with the relatively low rates of treatment discontinuation due to TRAEs, indicates that nivolumab is generally better tolerated than the comparator drugs.

Table 16 - Treatment exposure

	CheckMate 066		**CheckMate 067**		**CheckMate 037**	
	Nivolumab (n=206)	**DTIC (n=205)**	**Nivolumab (n= 313)**	**Ipilimumab (n= 311)**	**Nivolumab (n=268)**	**ICC (n=102)**
Median number of doses	12	4	15	4	8	DTIC: 3 carboplatin + paclitaxel: 5
Median duration of therapy - months	6.5	2.1	6.6	3.0	5.3	2.0
% patients who received relative dose intensity ≥90%	91.3	52.2	~88	~88	84.0	DTIC: 71 carboplatin: 33.3 paclitaxel: 54.4

In summary, there was a lower incidence of high grade and serious AEs in nivolumab-treated patients compared to those treated with ipilimumab or chemotherapy, although nearly all trial participants experienced AEs (of any grade or category). AEs were typically those with potential immunological cause. Discontinuation rates due to AEs were also lower in the nivolumab

groups. Most of these were reported less often in nivolumab-treated patients than in patients treated with ipilimumab, and were generally resolved or controlled. The ERG's interpretation is that overall, nivolumab appeared to be better tolerated than the comparator drugs.

3.4 Summary

The ERG considers that the CS presents a generally unbiased estimate of the treatment effect of nivolumab for adults with advanced melanoma within the stated scope of the decision problem, although there are some exceptions and uncertainties as described below. The company's systematic review of clinical effectiveness followed standard procedures and is of good quality. The ERG is not aware of any additional relevant published trials that could be included. The three key CheckMate RCTs are well-designed and well-conducted and provide an appropriate evidence base to inform the assessment of clinical and cost-effectiveness of nivolumab. The trials show statistically significant differences in favour of nivolumab relative to alternative treatments in terms of measures of survival and treatment response, with a generally favourable safety profile.

The key uncertainties identified include:

1. All three of the key RCTs included by the company in their systematic review of clinical effectiveness are on-going with further follow-up results expected to be published in the next year. Consequently, some of the results reported in the CS are from interim time points, in some cases based on relatively small patient numbers/events, and are considered to be relatively immature due to lack of follow-up, notably for OS, one of the key outcomes that informs the assessment of cost-effectiveness in the CS. Although the duration of follow-up reported to date can be considered informative for a disease with relatively short survival time, the long-term survival benefit and benefits in terms of other relevant outcomes such as tumour response claimed by the company (CS section 4.13) cannot yet be fully substantiated.
2. The comparative efficacy of nivolumab with the comparator treatments in the scope and the decision problem is uncertain due to a lack of head-to-head data from clinical trials. Notably the CheckMate 067 trial directly compared nivolumab with ipilimumab but the results are not used to inform the company's economic model as OS data are not yet available due to insufficient follow-up, and the company stated in their response to a clarification question from the ERG that PFS data from this trial was not able to be used

to inform the model without OS events also being available (clarification question A9). This is a significant limitation of the analysis and the company has therefore made an indirect comparison of nivolumab with ipilimumab and nivolumab with the other comparators in the decision problem.

3. The indirect comparison is based upon a number of assumptions and covariate-adjusted survival data extrapolations. Some of these assumptions appear reasonable and are noted by the CS to have been accepted in previous NICE appraisals of treatments for advanced melanoma. Two of the key assumptions that influence the assessment of clinical effectiveness, and the modelling of cost effectiveness, are that previous melanoma treatment experience does not have an independent impact on treatment effect in advanced melanoma, and that there is no difference between treatment effects by BRAF mutation status. The ERG notes that there are potential limitations in the cited published pooled analysis of nivolumab studies[17] that has been used to support the assumption that BRAF mutation status does not affect outcomes in nivolumab-treated patients. Furthermore, pre-planned sub-group analyses in the CheckMate 067 and CheckMate 037 trials showed that BRAF mutation-negative patients had better outcomes (PFS and ORR, respectively) relative to comparators than BRAF mutation-positive patients, though caution is advised due to small patient sample sizes in some cases (NB. neither of these two trials directly inform the economic model).

4 ECONOMIC EVALUATION

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

i) a review of published economic evaluations of nivolumab for patients with advanced melanoma.

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of nivolumab was compared with DTIC and ipilimumab for BRAF-mutation-negative patients and with dabrafenib, ipilimumab and vemurafenib for BRAF-mutation-positive patients with advanced melanoma.

In this section, an overview is presented of the company's submission. Further details and critique are provided in Section 4.2.

Company's review of published economic evaluations

A systematic search of the literature was conducted to identify economic evaluations of nivolumab for the treatment of melanoma. The company's search strategy for economic evaluations was adequate, though the ERG ran an update of the search to cover the nine months since the search was conducted. (See Section 3.1 of this report for the ERG critique of the search strategy).

The inclusion and exclusion criteria for the systematic review are listed in section 5.1.1 of the CS, p. 152. The inclusion criteria state that full economic evaluations of nivolumab or nivolumab in combination with ipilimumab in adults with advanced (unresectable or metastatic) melanoma would be included. The exclusion criteria state that studies before 1970 or not published in English would be excluded. One study was identified from screening 140 titles and abstracts, but was excluded during full paper screening as it was not a full economic evaluation.
No further cost effectiveness studies were identified through the ERG's update search but the ERG identified a conference abstract[6] through ad hoc searching that described a cost effectiveness analysis of nivolumab compared to ipilimumab for BRAF mutation-negative advanced melanoma in Australia. The study estimated that compared to ipilimumab over 10 years, nivolumab would lead to an improvement in survival of 1.58 years and 1.30 QALYs per person at a discounted net cost of AUD$77,119 per person and AUD$59,311 per QALY saved. The full report of this study is not yet available therefore the ERG has not been able to critically appraise this study.

Cost-effectiveness analysis methods

The *de novo* cost effectiveness presented in the CS uses a semi-Markov model to estimate the cost-effectiveness of nivolumab compared with DTIC and ipilimumab for treatment-naive BRAF-mutation-negative patients and with dabrafenib, ipilimumab and vemurafenib for treatment naive BRAF-mutation-positive patients with advanced melanoma. The model adopted a lifetime horizon of 40 years and a cycle length of one week. The model consists of three health states: pre-progression, progression and death (CS Figure 49, p155).

As mentioned earlier, the clinical effectiveness estimates of nivolumab used in the economic are based on the CheckMate 066 trial.[4] The company conducted covariate-adjusted indirect comparisons between comparators using patient-level data. These data were used to estimate TTP, PPS and PrePS outcomes, which were used to derive the transition probabilities between health states. Survival curves for TTP, PPS and PrePS are shown in CS Figure 50, p166; CS

Figure 51, p167; and CS Figure 52, p168 respectively for the BRAF mutation-negative analysis. Overall survival for the BRAF mutation-negative analysis is shown in CS Figure 56, p172 and for the BRAF mutation-positive analysis.

The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS). The starting population of the model for patients in the BRAF mutation-negative analysis was based on the CheckMate 066[4] trial and the patient characteristics are shown in CS Table 59, p165. The starting population of the model for patients in the BRAF mutation-positive analysis were taken from the BRIM-3 trial[12] and are shown in CS Table 60, p173.

HRQoL was included in the model, using utility values collected from the CheckMate 066 trial.[4] HRQoL was applied according to the progression status and time to death (>=30 days before death; <30 days before death). These values were obtained from a data analysis of EQ-5D data (CS Table 67, p. 189). Disutility associated with adverse events was also included for endocrine disorders, diarrhoea (Grade 2+) and other adverse events (Grade 3+) (CS Table 65, p. 188).

Costs were included for treatments, adverse event, health state costs and end of life costs. The costs were sourced from MIMS,[29] NHS Reference costs 2013/4,[30] PSSRU 2014.[31] The unit drug costs and dosages are shown in CS Table 70, p193. The comparator treatments ipilimumab, dabrafenib and vemurafenib are subject to a patient access scheme (PAS) and have been offered to the NHS at a confidential discount. Resource use was estimated based on the MELODY study, an observational study of resource use in patients with advanced melanoma.[32] Resource use and unit costs are shown in CS Table 73, p. 196 and CS Table 74, p. 198. A covariate-adjusted time on treatment curve was used to estimate the proportion of patients on and off treatment for the nivolumab arm, with maximum treatment duration of two years assumed in the model (CS Figure 61, p. 179).

Deterministic sensitivity analyses were conducted on parameter estimates (CS p. 227-232) and additional scenario analyses were modelled (CS p. 235-240). Probabilistic sensitivity analyses (PSA) were also conducted and the input parameters are described in CS Table 79 (p. 202-204). Validation of the cost effectiveness analysis was conducted through external review by clinical experts and health economists. The CS provides a comparison between overall survival for patients treated with ipilimumab produced by the model compared to that from the clinical trials.

Cost effectiveness analysis results

Results from the economic model are presented (CS Section 5.7.1, p. 206-7) as incremental cost per QALY gained for nivolumab compared with its comparators for BRAF-mutation-negative for and BRAF mutation-positive patients. Total and incremental costs, life years gained (LYG) and QALYs were also reported, along with a breakdown of total costs. Results are presented with drug prices based on list prices and then for drug prices assuming PAS prices for the comparator treatments. Total costs are reported as commercial in confidence by the company for all treatments, in order to avoid calculation of the confidential PAS prices for ipilimumab and vemurafenib.

For BRAF-mutation-negative patients an incremental cost per QALY gained of £23,583 was reported for nivolumab versus DTIC (see Table 17). For BRAF-mutation-positive patients an incremental cost per QALY gained of £7,346 was reported for nivolumab versus ipilimumab (see Table 18).

Table 17 - Base case cost effectiveness results for BRAF mutation-negative patients (drug prices based on list price, CS Table 80)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
DTIC	[redacted]	1.23			
Ipilimumab	[redacted]	2.64	£48,429	1.41	Excluded due to extended dominance
Nivolumab	[redacted]	4.31	£72,578	3.08	£23,583

Table 18 - Base case cost effectiveness results for BRAF mutation-positive patients (drug prices based on list price, CS Table 81)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Ipilimumab	[redacted]	2.44			
Nivolumab	[redacted]	4.27	£13,374	1.82	£7,346
Dabrafenib	[redacted]	1.69	£6,228	-2.57	Excluded due to dominance
Vemurafenib	[redacted]	1.70	£24,659	-2.56	Excluded due to dominance

In the deterministic sensitivity analyses of nintedanib, the results were presented in terms of net benefit with a willingness to pay threshold of £50,000 per QALY. The analyses showed that the

model results were most sensitive to the parameters defining the fitted parameter curves for TTP, PPS and long-term OS (CS Table 97-98, p. 233-240).

The CS summarises the results of the PSA stating that there is a 87% and 99% probability of nivolumab being cost-effective for BRAF-mutation-negative patients at a threshold willingness to pay of £30,000 and £50,000 per QALY gained (CS Figure 67, p. 218), and a 100% probability of nivolumab being cost effective for BRAF-mutation-positive patients for both thresholds (CS Figure 68, p. 219).

The CS states that the base case analyses show that nivolumab is a cost effective option for all patients with advanced melanoma versus all comparators at a cost-effectiveness threshold as low as £30,000 per QALY in BRAF-mutation-negative and BRAF-mutation-positive patients.

4.2 Critical appraisal of the company's submitted economic evaluation

Critical appraisal of company's submitted economic evaluation

The ERG has considered the methods applied in the economic evaluation according to the critical appraisal questions listed in Table 19, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[33]).

Table 19 - Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well-defined question?	Yes	The decision problem is described in CS Table 1, p15.
Is there a clear description of alternatives?	Yes	The alternatives are listed in CS Table 56, p160
Has the correct patient group / population of interest been clearly stated?	Yes	However, analyses have been conducted for treatment naive patients but not for treatment experienced patients.
Is the correct comparator used?	Yes	However, DTIC has not been included within the analysis for BRAF mutation-positive patients. The ERG notes that pembrolizumab would now be another potential appropriate comparator but this was not included in the NICE scope.
Is the study type reasonable?	Yes	
Is the perspective of the analysis clearly stated?	Yes	Costs are considered from a National Health Service and Personal Social Services perspective. (CS Table 1, p15)
Is the perspective employed	Yes	Perspective is in accordance with the NICE framework.

appropriate?		
Is effectiveness of the intervention established?	Yes	Treatment effectiveness reported in the CheckMate 066 trial
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	Time horizon is for 40 years (CS Table 55, p159).
Are the costs and consequences consistent with the perspective employed?	Yes	
Is differential timing considered?	Yes	Costs and health benefits discounted at 3.5% per year
Is incremental analysis performed?	Yes	Presented in CS Table 80 and 81, p206 for list price
Is sensitivity analysis undertaken and presented clearly?	Yes	Presented in CS Figure 76-77, p228-232 and scenario analyses presented in CS Table 97-98, p233-240

NICE reference case

The NICE reference case requirements have also been considered for critical appraisal of the submitted economic evaluation in Table 20.

Table 20 - NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	However, the analysis only includes treatment-naive patients.
Comparator: Alternative therapies routinely used in the UK NHS	Yes	Discussed in Section 4.2.3. DTIC has not been included within the analysis for BRAF mutation-positive patients.
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	Yes	
Type of economic evaluation: Cost effectiveness analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	Discussed in Section 4.2.4
Measure of health benefits: QALYs	Yes	Discussed in Section 4.2.5
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes	Discussed in Section 4.2.5
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes	Discussed in Section 4.2.5
Source of preference data: Representative sample of the public	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	
PSS = personal social services; TTO = time trade off; SG = standard gamble		

Overall, the methods applied in the economic analyses were appropriate and reported transparently. The company's economic evaluation conformed to NICE methodological guidance and generally met the NICE scope with a couple of exceptions.

4.2.1 Modelling approach / Model Structure

The company developed a *de novo* semi-Markov survival model consisting of three health states: progression-free; progressed; and death. In addition, the model incorporated two states relating to time to death (≥30 days and <30 days) for modelling utility. Costs were included according to treatment, time from initiation of therapy and proximity to death. A schematic of the model is presented in Figure 5. The model was developed in Microsoft Excel. Costs, QALYs and life years were presented as outputs of the model.

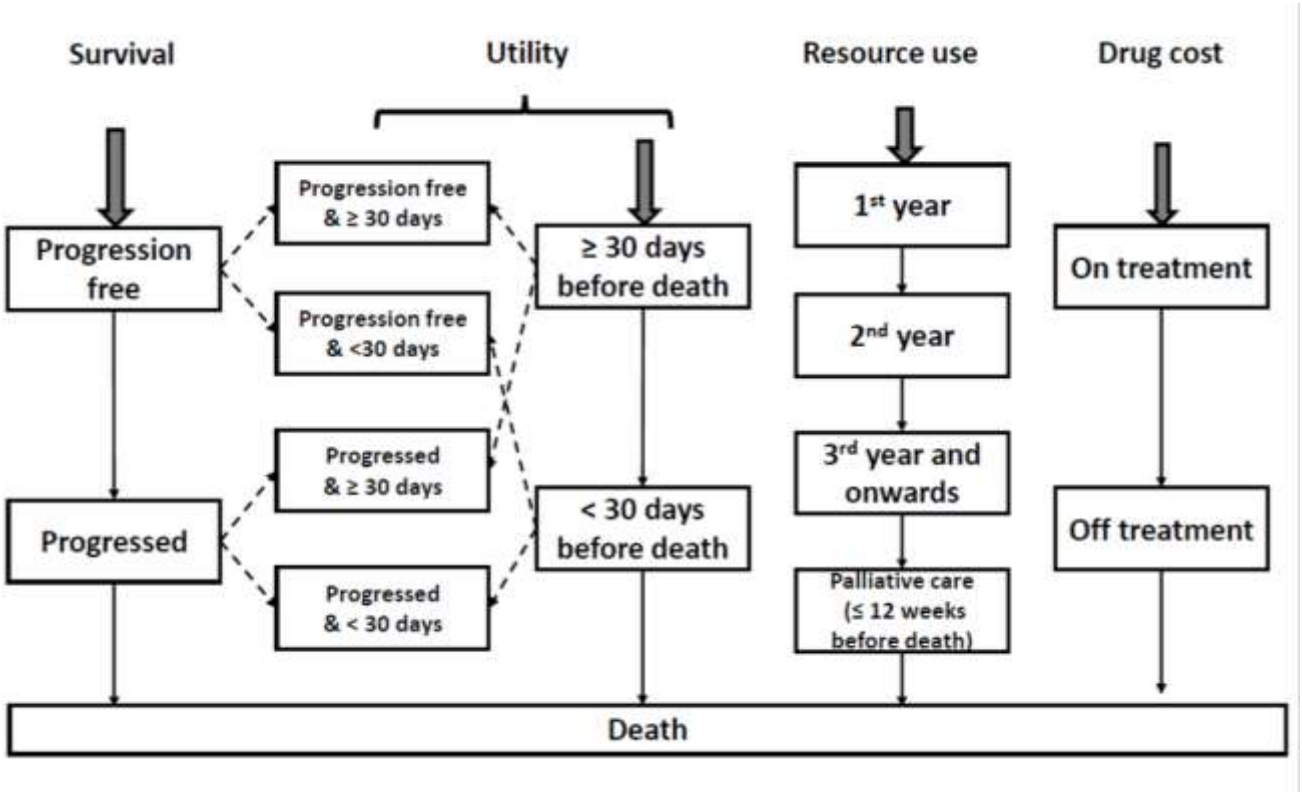

Figure 5 - A schematic of the model structure (reproduced from CS Figure 49, p 155)

The proportion of patients in each of the three health states were estimated using TTP, PPS and PrePS. Survival in the model was estimated by calculating TTP; PPS was used to estimate the time from progression to death; and PrePS was used to estimate time to death directly in instances where patients died before progression. Survival models were fit for TTP, PPS and

PrePs based on a covariate adjusted indirect comparison (described in more detail in section 3.17 and 4.2.4). The model estimated utility values based on progression-status and whether time to death was less than 30 days. The company stated that this approach was taken due to the issues arising for using RECIST criteria as a surrogate outcome for quality of life in CheckMate 066 trial.[4] The company, therefore, assigned utility values to four health states: progression-free and less than 30 days to death; progression-free and 30 or more days to death; progressed and less than 30 days to death; and progressed and 30 or more days to death. Resource use, on the other hand, was estimated based on time from treatment initiation where one-off costs were associated for treatment initiation and end of life care; and follow-up costs were used for the first year, second year, and third year after treatment initiation and for the last 12 weeks before death i.e. palliative care.

The NHS and PSS perspective was adopted in the economic model with a lifetime-horizon of 40 years and weekly cycles. This was considered as an appropriate time horizon given the median age of the patient population was 63 years for BRAF mutation-positive and 56 years for BRAF mutation-negative patients, respectively. The weekly cycle length provided sufficient time span to account for disease progression as well as treatment administration. A half-cycle correction was incorporated and costs and utilities were discounted at 3.5% p.a. as per NICE guidance.

The company cited three previous cancer technology appraisals (TA257;[34] TA258[35] and TA311[36]) as a rationale for using a state-transition method for modelling survival. Although none of these appraisals included patient groups who were treated for melanoma, the ERG agrees that state-transition modelling is a standard approach for modelling survival.

In one of the two previous NICE technology appraisals of ipilimumab (TA319),[16] a 'treatment-sequencing' approach was used to assess the cost effectiveness of ipilimumab in previously untreated melanoma in two patient groups: BRAF V600 mutation-positive (who received first-line treatment with ipilimumab, DTIC, or vemurafenib); and BRAF 600 mutation-negative patients (who received first-line treatment with ipilimumab or DTIC). The health states were defined by different lines of treatments that patients followed. The approach was criticised for some inherent inconsistencies with the evidence base, details of which are discussed elsewhere.[16] The other appraisal of ipilimumab for previously-treated melanoma patients (TA268)[20] used a 'partitioned-survival' model consisting of four health states: baseline disease, non-progressive disease, progressive disease and death. A Markov cohort model was

developed where one cohort received ipilimumab and the other cohort received best supportive care.

Broadly, the company's model structure follows a standard pattern of modelling patient transition in oncology. The disease pathway reflected the underlying clinical process of melanoma. The company validated their modelling approach with UK health economists and clinical experts. The model extrapolated short term outcomes obtained from the CheckMate 066 clinical trial to long-term outcomes by using survival models (discussed below). Overall, the ERG agrees with the company's modelling approach.

The company made a number of assumptions in relation to the model structure and model inputs on efficacy and safety, drug costs, resource use and HRQoL which are mentioned across different sections of the CS (some of these have been discussed earlier in this report). The key model assumptions are:

i. Data from trials CheckMate 066[4] and MDX010-20,[15] are used to conduct a patient-level indirect treatment comparison to obtain comparative efficacy of nivolumab, ipilimumab and DTIC based on the following assumptions (CS section 4.10, p.93, and Section 3.1.7 and Section 4.2.4 of this report):
   - DTIC and gp100 can be considered equivalent in terms of OS and PFS.
   - Line of treatment is not considered as an independent prognostic factor and is assumed not to independently affect treatment effectiveness
   - There is no difference between treatment effects by BRAF mutation status for nivolumab
   - There is equivalence of ipilimumab 3mg/kg+gp100 and ipilimumab 3mg/kg

ii. In the base case for BRAF-mutation-positive patients, the company assumed that vemurafenib had an equal efficacy to dabrafenib, based on NICE TA321[24] (CS section 5.2.2).

iii. Based on the evidence from the phase I of CheckMate 003 trial[7] and opinion of UK based clinical experts on melanoma, the company assumed that the maximum time on treatment for nivolumab was two years (CS section 5.2.2, p.156 and CS section 5.3.2).

iv. For OS, the company used pooled ipilimumab long-term data for nivolumab which showed a plateau effect in the OS for immunotherapies beginning around year three. The company also used alternative sources for long-term survival to extrapolate long-term OS for all the treatment arms. These included the use of melanoma registry data[37]

(from year two onwards for DTIC and BRAF inhibitors in the base case), long-term ipilimumab OS data[38] (from year 3 onwards for nivolumab and ipilimumab in the base case), and general UK population mortality as background mortality (CS section 5.2.2, p.156 and section 5.3.2 p.165).

Overall, the modelling approach adopted in this submission appears to be coherent. The model structure appears to be reasonable and there are no concerns regarding the techniques used with reference to the NICE methodological guidance.[39]

4.2.2 Patient Group

The characteristics of the patients in the model are based upon the patients in the CheckMate 066[4] trial for BRAF mutation-negative patients (CS Table 59, p. 165) and the vemurafenib arm of the BRIM-3[12] trial for BRAF mutation-positive patients (CS Table 60, p. 173). The patient population is consistent with the licensed indication and that population specified in the NICE scope. The ERG notes that economic analyses have only been conducted for treatment-naive patients but not for treatment-experienced patients. This is because the CheckMate 066 trial only included treatment-naive patients. The CS states that line of treatment has not been shown to independently impact treatment effect in advanced melanoma, and argue that there is no rationale for an alternative effect in the first- and subsequent-line settings. This assumption has been accepted in previous NICE appraisals of treatments for advanced melanoma. The ERG notes that it may have been possible to repeat the analysis using data from CheckMate 037 trial which included previously treated patients but this analysis was not presented.

4.2.3 Interventions and comparators

For patients with BRAF mutation-negative melanoma, nivolumab was compared to ipilimumab and DTIC. For patients with BRAF mutation-positive melanoma, nivolumab was compared to ipilimumab, vemurafenib, and dabrafenib. The comparators included within the CS economic evaluation correspond to NICE's scope, with the exception of DTIC which has not been included within the analysis for BRAF mutation-positive patients. The CS does not provide a rationale for this omission and the ERG suggests this may have been because few BRAF mutation-positive patients would be unsuitable for a BRAF inhibitor and therefore use of DTIC in this population would be rare. The ERG has conducted a scenario analysis with DTIC included as a comparator for BRAF mutation-positive patients (Section 4.3).

The CS does not include pembrolizumab, which has now received approval in advanced melanoma after disease progression with ipilimumab (NICE TA357),[3] and in patients not previously treated with ipilimumab. The ERG notes that pembrolizumab was not within the NICE scope for this appraisal.

4.2.4 Clinical Effectiveness

The following sections describe and critique the methods used to fit and extrapolate survival models to inform the economic model. For a description and critique of the indirect comparison used to estimate the comparative clinical-effectiveness and cost-effectiveness of nivolumab see Section 3.1.7 of this report.

Transition probabilities

The proportion of patients in the progression-free, progressed and death states in each Markov cycle were derived using TTP, PPS and PrePS. The transition from progression-free to progression is derived from TTP, and transition from progression-free to death from PrePS. The death rates for patients in the progression health state are derived from PPS. The parametric survival curves for TTP, PPS and PrePS were fitted based on a covariate-adjusted indirect comparison using patient-level data from trials (CheckMate 066[4] for nivolumab and DTIC and MDX010-20[15] for ipilimumab and gp100).

An advantage of using separate survival curves for TTP, PrePS and PPS is that the use of PFS as a composite endpoint is avoided. This allows the economic model to adopt a Markov-state transition approach, rather than an area under the curve partitioned survival method (CS p101-102). However to the extent that sample sizes are smaller for these endpoints than OS and PFS, the treatment effects will be estimated less precisely. Indeed, the ERG notes that for several analyses there are non-significant treatment effects, for example ipilimumab has a non-significant treatment effect at the 95% level in the Gompertz model for TTP post 100 days (CS Table 32) and the Cox proportional hazards model for PrePS (CS Table 35). Nivolumab has a borderline non-significant treatment effect in the log-logistic model for PPS (CS Table 34). The non-significance of these treatment effects may be due in part to covariate adjustment as well as a smaller sample size.

The analyses that describe the derivation of the survival curves used three types of patient-level data analyses: parametric survival modelling, Cox proportional hazards regression modelling

and Kaplan-Meier techniques. The parametric and Cox survival models were adjusted for treatment, trial and other covariates (CS Table 27). The parametric survival modelling included analyses for six different parametric distributions: exponential, Weibull, log-Normal, log-logistic, Gompertz and generalised gamma.

Survival curve modelling: BRAF mutation-negative patients

Time to progression (TTP)

As reported earlier in this report (Section 3.1.7), the TTP survival curve was modelled separately for the first 100 days, and then post 100 days. The CS comments that there is an unrealistic clustering of progression times in the studies which makes it difficult to fit meaningful parametric survival curves to these data near to the start of the curves and therefore the data were cut at Day 100 to allow a more clinically and statistically plausible shape to the progression curve. Day 100 was chosen to ensure in both studies, patients surviving from that point will have had their first tumour assessment. The ERG notes that the Kaplan-Meier curves for TTP (CS Figure 28) for nivolumab, DTIC and ipilimumab begin to diverge at around Day 100 and that by splitting this endpoint at this time the estimated treatment difference between nivolumab and the comparators is likely to be maximised. This is because an HR based on a survival model fitted to the whole time period is likely to be smaller than an HR obtained from a model fitted to data from Day 100 onwards, as treatment effects will be averaged over the entire time period.

TTP pre-100 days uses Kaplan-Meier data adjusted by a HR estimated from a Cox proportional hazards model using covariates to control for differences between trial arms and between trials. The parameters for the Cox proportional hazards model are shown in CS Table 30. Although the CS notes that proportionality of treatment effects clearly does not hold for TTP pre-100 days based on the Kaplan-Meier curves (CS Figure 29), a proportional hazard model which includes treatment effects is still used to estimate hazard ratios for the prognostic factors for this endpoint. The CS does not report if the proportional hazards assumption of this model was satisfied. The HR applied to the Kaplan-Meier data for TTP pre-100 days is 0.987 for nivolumab, 0.999 for DTIC and 0.891 for ipilimumab (values derived from company model). The ERG has examined the sensitivity of the economic model to covariate adjustment for this endpoint and found that the base case ICER for nivolumab compared to DTIC does not vary substantively when no adjustment is applied.

Standard parametric curves were fitted to the TTP post 100 days and the fitted curves are shown in CS Figure 31. Based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) values, the company stated that the Gompertz distribution provided the best fit of these distributions and was deemed to be clinically plausible and in line with long-term data available for ipilimumab. The parameters for the Gompertz distribution were derived through a covariate analysis. The indirect treatment comparison effect of nivolumab vs. ipilimumab was a HR of 0.356 (95% CI 0.165, 0.771), in favour of nivolumab. The CS comments that many of the covariates individually had modest effects on the outcome and were not statistically significant but were retained to fully adjust for prognostic factors.

Deterministic sensitivity analysis showed that the economic model was sensitive to TTP post 100 days for both nivolumab and ipilimumab (CS Figures 75 and 76).

The TTP survival curves used in the company model compared to the Kaplan-Meier data for the treatment arms are shown in Figure 6.

The ERG considers the general method used to estimate the TTP survival curves to be reasonable. The Gompertz distribution was chosen for each of the treatment arms and this provides a reasonable fit for the ipilimumab treatment arm, which has the longest time follow-up, but a poorer fit for the nivolumab treatment arms. A better approach would be to use the best-fitting distribution for each treatment arm. The effect of using alternative distributions is explored by the ERG in scenario analyses (see Section 0 of this report). The ERG also notes that the numbers of patients at risk for the DTIC and nivolumab arms are small (<5%) by day 400, which makes curve fitting more uncertain.

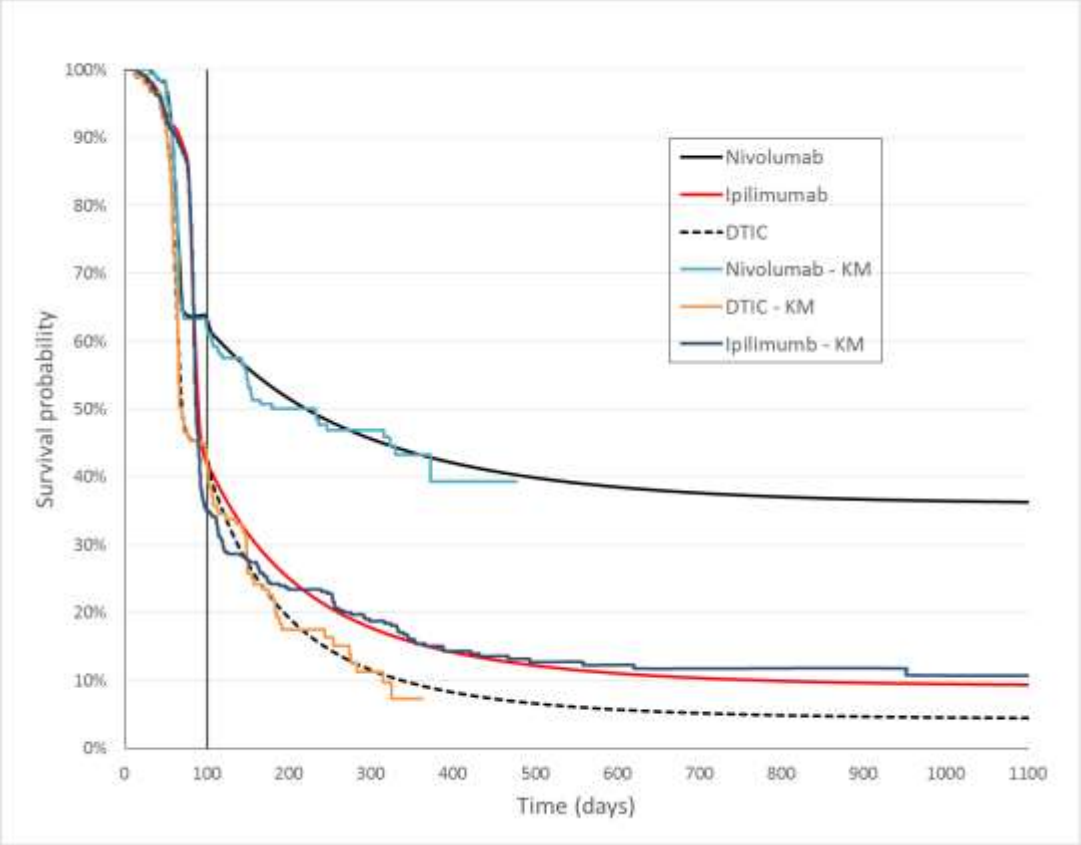

Figure 6 - Time to progression in the base case model for BRAF mutation-negative analysis over two years

Post-progression survival (PPS)

Covariate-adjusted parametric curves were also fitted to PPS for six parametric distributions. According to the AIC/BIC values, the company stated that the gamma, log-logistic and log-normal are all reasonable distributions and the company selected the log-logistic as the best-fitting/most appropriate model for use in the base case. CS Figure 51 shows the final modelled PPS for BRAF mutation-negative patients and shows PPS is similar for nivolumab and ipilimumab. The CS states that using the same model, the CS estimated the indirect treatment comparison effect of nivolumab vs ipilimumab for PSS of 0.98. The ERG notes that the choice of parametric curve has only a minor impact on the model results and considers the choice of the log-logistic distribution for PPS to be reasonable.

Pre-progression survival (PrePS)

PrePS was modelled using Kaplan-Meier data adjusted by covariates for the length of the trial follow-up. Parametric curves were fitted for PrePS, however the CS states that none of the

curves provided an acceptable visual fit to observed data. Beyond the trial follow-up duration, longer-term extrapolation was informed by the melanoma registry data,[37] long-term OS on pooled ipilimumab trials and the general population mortality. The length of the trial data varied from 477 days to 1565 days for nivolumab and ipilimumab respectively. The final modelled PrePS for BRAF mutation-negative patients is shown in CS Figure 52, p168. The CS states that the sensitivity of the economic model to assumptions around PrePS is limited due to the low number of events experienced and because the majority of the patients within the trials die following observed progression events. The ERG concurs with this statement.

Overall survival (OS)

The modelled OS for BRAF mutation-negative patients for the first three years combines the TTP, PPS, and PrePS outcomes and is presented in CS Figure 53. It indicates that, overall, the model has overall a reasonable fit to the observed data for ipilimumab and DTIC. After three years, pooled ipilimumab long-term OS[38] was used for nivolumab and ipilimumab. The CS notes that the pooled analysis showed a plateau in the OS curve beginning around year three using pooled ipilimumab trials with follow-up up to 10 years (CS Figure 55, p. 171). The long-term OS was assumed to be applicable to long-term OS for nivolumab due to similarity of mechanism of action (both are immunotherapies). Figure 7 shows the overall modelled survival for the treatment arms over a 40 year time span (CS Figure 56, p. 172). Expert clinical advice to the ERG suggested that there is some uncertainty whether nivolumab would have the same long-term plateau for OS as seen with ipilimumab. It may be that this OS plateau is unique to ipilimumab and trial evidence is not currently available for a long follow-up time period for nivolumab. The ERG tested this assumption in a scenario analysis in Section 0. OS is taken from the Melanoma registry OS by Balch and colleagues[37] for the DTIC arm from year two onwards.

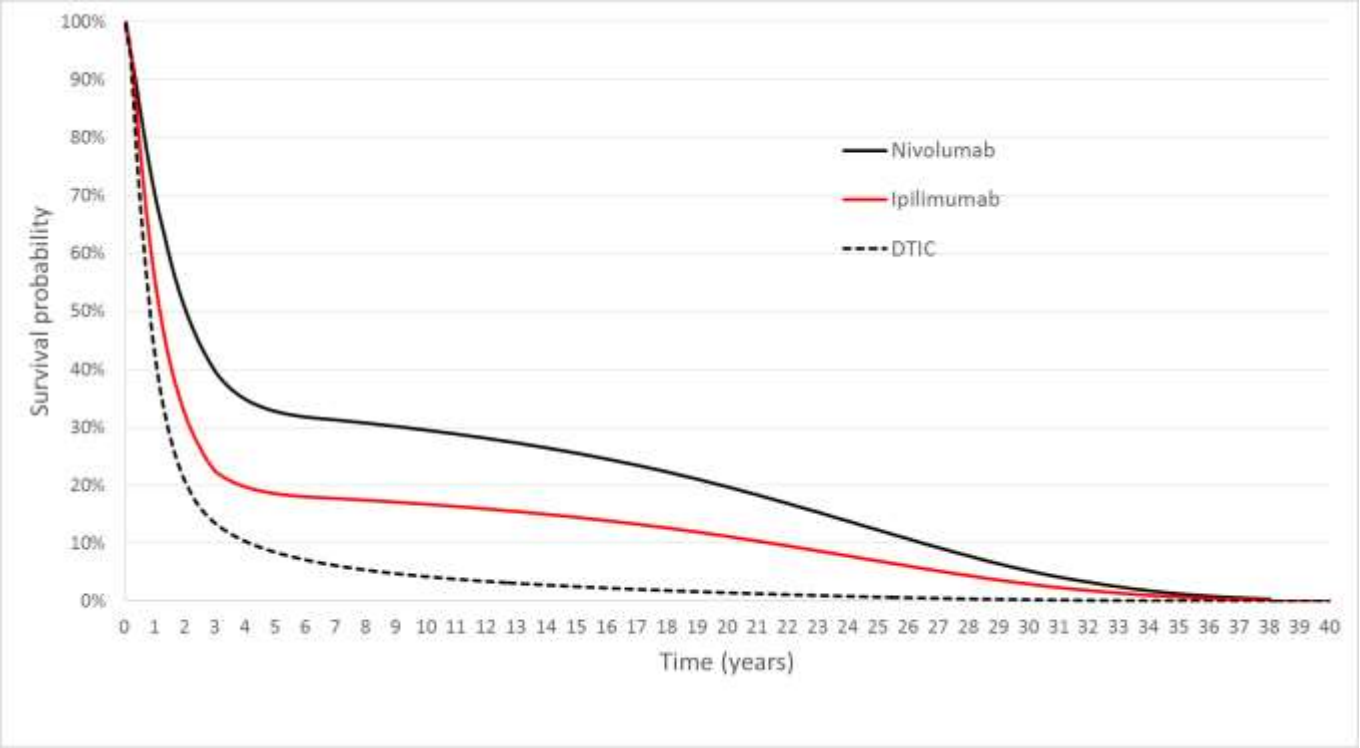

Figure 7 - Final overall survival in the base case model for the BRAF mutation-negative analysis over life time

Survival curve modelling: BRAF mutation-positive patients

The methods used for deriving transition probabilities for BRAF mutation-positive patients for nivolumab and ipilimumab-treated patients is similar to BRAF mutation-negative patients (described above), with patient characteristics in this instance based on the BRIM-3 trial.[12] As before, the survival curves are adjusted according to covariates based upon prognostic factors.

The BRAF inhibitors vemurafenib and dabrafenib were included in the analysis by fitting survival curves to Kaplan-Meier data for PFS and OS from BRIM-3[12] for vemurafenib. The company assumed that vemurafenib had an equal efficacy to dabrafenib by using a HR of 1 for OS and PFS for vemurafenib versus dabrafenib, based upon the NICE TA321[24] of dabrafenib where the Appraisal Committee determined that they have approximate equal efficacy (as discussed in Section 3.1.7 of this report).

In order to derive PFS and OS survival curves for vemurafenib, the Kaplan-Meier curves from the BRIM-3 trial were derived using digitisation software and estimating pseudo patient-level data using the Guyot 2012 method.[26] This is a method that maps from digitised curves back to Kaplan-Meier data by finding numerical solutions to the inverted Kaplan-Meier equations, using available information of events and numbers of patients at risk. As stated in Section 3.1.7 of this report, the ERG considers this to be an appropriate method to use in this circumstance. Parametric curves were then fitted to the pseudo-patient data and the log-normal distribution for OS and generalised-gamma distribution for PFS were chosen, based on the AIC/BIC values and visual fit. The proportions of patients in the model in the progression-free, progressed and dead health states were calculated directly from the PFS and OS survival curves by the area under the curve method. CS Figure 57 and CS Figure 60 show the OS and PFS in the base case model for BRAF mutation-positive analysis. The ERG notes that the costs for vemurafenib and dabrafenib are sensitive to the survival curve chosen for PFS. For example, the total costs for vemurafenib in the base case analysis was £117,655 (based on the generalised-gamma distribution), whilst using a PFS survival curve with the log-normal distribution gave total costs of £99,227. According to the AIC/BIC values, the log-normal also provided a good fit for PFS.

Time on treatment

The time spent receiving nivolumab treatment has been derived from patient-level data from the CheckMate 066 trial. Parametric curves were fitted to the data and the log-logistic curve was chosen based on the AIC/BIC scores and clinical plausibility of the distribution tail. The CS states that Gompertz curve provided the best fit but was not used in the base case because the tail of the predicted curve becomes almost horizontal from year 2 onwards and this may not be clinically plausible. The ERG notes that for TTP the company uses the Gompertz curve and considers intuitively the same curves should be used for both TTP and time on treatment. However, as noted above the ERG considers that the Gompertz should not be used for TTP. The company has provided scenario analyses using alternative distributions for time on treatment (CS Table 97, p234) which show the choice of survival curve for time on treatment has only a small effect on the model results.

The model assumes a maximum time on treatment of two years. The CS comments that treating until progression is not necessarily a realistic approach in UK clinical practice and that it would be reasonable to assume maximum treatment duration of two years in clinical practice instead. The CS reports sensitivity analyses that show that varying the maximum treatment

duration has a large effect on the model results. For example, removing the maximum treatment duration assumption increases the ICER to £68,883 per QALY. The ERG notes that the marketing authorisation for nivolumab recommends that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Expert clinical advice to the ERG suggests that clinicians and patients may be reluctant to stop treatment before disease progression, given the marketing authorisation. Expert clinical advice also suggests that patients may continue to derive benefit after they have stopped treatment and it is not clear whether patients need to be continued on treatment beyond an initial period (e.g. three months). The ERG considers that the assumption related to the treatment duration is a key issue of uncertainty in the model and investigates the effect of this uncertainty in section 0.

The dosing for ipilimumab used in the model is shown in CS Table 57 and is based on the CA184-024 trial[14] trial for doses one to four (induction 1) and MDX010-20 trial for re-induction (Induction 2 to 4). The CS notes that ipilimumab is used for a maximum of 4 doses in the UK, rather than the 16 doses used in the model.

For dabrafenib, vemurafenib and DTIC the model assumes that treatment will continue until disease progression.

Adverse events

The CS model included adverse events for endocrine disorder (any grade), diarrhoea (grade 2+) and other AEs (grade 3 +). Patient-level AE data from CheckMate 066 were used to calculate the proportion of AEs for patients in the nivolumab and DTIC arms (CS Table 61). These values differ from those reported in the trial publication and CS Table 47. The company clarified to the ERG that the values used in the model were derived from a different ad hoc analysis and that the categorisations of AEs and thresholds differed between the analyses (clarification question B5). This ad hoc analysis was done as the company's clinical advisory board felt that the reporting of the adverse events in the CSR did not capture all adverse events of relevance to clinical practice. Patient-level data for the number of hospital bed days associated with each AE from the trial was also included.

The AEs incidence for patients treated with ipilimumab is calculated as a proportion of those for nivolumab, using the ratio of adverse event rates observed in CheckMate 067. A similar method

was used to calculate the incidence of patients for dabrafenib and vemurafenib compared to DTIC using the BREAK-3 and BRIM-3[12] trials respectively.

Overall, the ERG considers that the company's approach to populate the economic model with clinical effectiveness data to be reasonable although due to the complexity of the analyses, the approach taken may appear difficult for non-statisticians to understand (and therefore suffers from a lack of accessibility and transparency) and that other, simpler, approaches may obtain similar results. As stated earlier in this report, the ERG notes that the CheckMate 067 trial data have not been used in the derivation of the survival curves due to lack of available follow-up OS data. The CheckMate 067 contains a direct comparison between nivolumab and ipilimumab and provides a key data source that has been omitted from the company's analysis. The ERG notes that there is considerable uncertainty around model results with respect to the assumptions adopted for long-term OS and time on treatment for nivolumab (explored in ERG scenario analyses – Section 4.3)

4.2.5 HRQoL

The company reports one systematic review based on the original systematic review from the NICE TA319[16] of ipilimumab, and then an update review (November 2014), for utility values and HRQoL studies for patients with advanced melanoma. The inclusion criteria specified studies reporting utilities and HRQoL data, not limited to EQ-5D.

Fifteen studies were included in the review (CS Table 64, p. 185 to 187). Thirteen studies were included from the first systematic review and two in the systematic review update. From these nine were studies directly measuring quality of life and six were cost-effectiveness studies using utilities from published articles (CS Table 64, p. 185 to 187). Details on studies found in the systematic review are provided in Appendix 13.

HRQoL was incorporated for the health states in the economic model using data from the CheckMate 066 trial[40]. Table 21, shows the mean utility values from the trial that were used to predict the utility values used within the cost effectiveness model (supplied to the ERG by the company on request, clarification question B4). The utility values, derived from EQ-5D values, defined by progression status and time to death are presented in Table 22, (CS Table 67, p. 189). Comparing these two tables it is apparent that moving from the pre-progression to post-progression states, the reduction in HRQoL observed during the trial, for both nivolumab and

DTIC is much smaller than the reduction in HRQoL predicted from the statistical model (0.03 vs 0.08).

Table 21 - Mean utility values from the CheckMate 066 trial

Mean utility by treatment arm and progression status	Utility
Nivolumab arm pre-progression	0.7892
Nivolumab arm post-progression	0.7548
DTIC arm pre-progression	0.6963
DTIC arm post-progression	0.6565

Table 22 - Quality of life (utility values) used in the company's cost effectiveness model

Health states (base case)	Mean EQ-5D utility	Range	Number of observations
Pre-progression + days left >=30 days	0.8018	Uncertainty was addressed by sampling from variance-covariance matrices assuming multivariate-normal distribution	Sample size 288 (1125 utility observations)
Pre-progression + days left >30 days	0.7795		
Post-progression + days left >=30 days	0.7277		
Post-progression + days left >30 days	0.7054		

EQ-5D data from the CheckMate 066 trial was obtained on days 1, 15, 22, and 29, continuing every six weeks for the first 12 months, and then every 12 weeks until disease progression or treatment discontinuation. For patients in the discontinued category, assessments continued every three months for the next 12 months, and then every six months thereafter.

The CS states that there were a total of 1,540 visits involving 362 patients (CS p. 182). The company conducted a statistical analysis based on this data to predict the utilities used in the model for each health state. The regression model reported was derived from a sample of 288 patients, with a total of 1125 observations. The sample size for the CheckMate 066 trial however, was a total of 418 patients for both arms and it is not clear from the CS, whether the

missing data was taken into account and how this was incorporated into the prediction model to avoid potential bias.

The utility values for health states from the regression analysis were defined by progression status and time to death and were used for all treatment arms (CS Table 67, p. 189). The CS Appendix 14 provides information regarding the statistical model used. The CS also states that utilities used in the recent ipilimumab NICE appraisal were tested in a scenario analysis.

The company reported that the final model predicts utility values using post-progression and time to death < 30 days as explanatory variables, adjusted for baseline EQ-5D values and DTIC therapy to see if there is a residual treatment effect not captured by the model. The company supplied additional information on these data upon request from the ERG that clarified that the significance cut-off used on their statistical models was 0.1.

The ERG agrees with the approach taken but expresses its reservations regarding the limited information provided on the fit of models tested. The ERG is unclear for the reason for the discrepancy between the mean trial data and the data used in the model. The ERG investigated running the model using the mean utility values from the trial, however the model results were not sensitive to changes in the utility values. An additional issue is the large amount of missing EQ-5D data, as this might have introduced bias into the estimated utility model. The ERG also notes that although the company has data for both treatment arms, they have not attempted to estimate the any differences in quality of life related to the treatments.

The impact of adverse events (AEs) on quality of life was assessed by applying a one-off utility decrement. Utility decrements for the AEs considered in the model were taken from a study by Beusterien and colleagues.[41] in which a sample of the general public evaluated outcomes for advanced melanoma in the UK and Australia.

The utility decrements for the AEs considered in the model include endocrine disorder (any grade), (disutility of -0.11), diarrhoea (Grade 2+), (disutility of -0.06) and other AEs (Grade 3+), (disutility of -0.12), (CS Table 65, p. 188). The utility decrement for other AEs associated with treatment toxicities is a mean value taken from the Beusterien and colleagues [41], consisting of a -0.11 decrement for symptomatic melanoma and -0.13 decrement for 2-5 days hospitalisation for severe toxicity. The company supplied additional information on these data upon request

from the ERG (clarification question B3). The company states that the definitions of AEs for the utility decrements had a limited match to the reported data by Beusterien and colleagues[41], so the assumptions were derived from clinical opinion received as part of the work for the company's submission of ipilimumab to NICE (TA268).[20] The assumptions used by the company are presented in Table 23**Error! Reference source not found.** in this report.

Table 23 - Assumptions used estimating utility decrements for AEs

	Model inputs	**Assumptions**
Endocrine disorder (any grade)	-0.11	UK decrement for 1-day in-/outpatient stay for severe toxicity (grade III/IV)
Diarrhoea (Grade 2+)	-0.06	UK decrement for Grade I/II diarrhoea
Other AEs (Grade 3+)	-0.12	Assumes 50:50 split between UK decrement for 1-day in-/outpatient stay for severe toxicity (grade III/IV) & 2–5-day hospitalisation for severe toxicity (grade III/IV)

The proportion of patients experiencing these events, and therefore the proportion of patients that these dis-utilities were applied to, were derived from CheckMate 066[40] in the nivolumab and DTIC arms. For the ipilimumab, dabrafenib and vemurafenib arms these data were estimated by deriving the proportions of patients expected to experience the adverse events in CheckMate 067[5] and applying these ratios to the BREAK-3[13] and BRIM-3[12;12] trials (CS Table 62, p. 181). These AEs' related decrements for each arm were estimated to be -0.0239 for nivolumab, -0.0325 for ipilimumab, -0.0236 for DTIC, -0.0279 for dabrafenib, and -0.0218 for vemurafenib.

The CS states that these utility decrements were applied at the start of the model, and then periodically to patients who are still on treatment, where the cycle to apply the decrement was determined by the follow-up data from the CheckMate 066[40] trial (i.e. 35 weeks). Given that the prediction model uses aggregate EQ-5D data to predict the HRQoL within each health state, an additional issue of concern, which is not clearly defined within the CS, was how the effect of AEs was marginalised avoiding double counting. The ERG notes that the treatment duration for the adverse events is based upon an annual disutility, i.e. the effect of the adverse event lasts for a year, however the company provides evidence that the adverse events last for a significantly shorter time period. The ERG is also unclear why the disutility has been applied every 35 weeks to patients. The ERG considers that the disutility has been incorrectly applied in

the model. However, the ERG notes that as the disutility is similar across all treatments, correction to the disutilities has minimal impact on model results.

Overall, the main concern for the ERG is related to the method used to incorporate HRQoL data from the trial which captures the change associated with health states but does not capture any impact of treatment on HRQoL within the health state. The ERG considers that the disutility has not been applied correctly in the economic model.

4.2.6 Resource use and costs

The main resource use and cost categories included by the company were treatment (including drug costs, cost for type of administration, one-off costs for treatment initiation and end-of-life), health state resource use such as for pre-palliative and palliative care, and resources for treating AEs.

The company conducted a systematic literature search to identify costs and resource use studies for advanced melanoma. This includes the original systematic review from the NICE TA319[16] of ipilimumab; and an update conducted up to November 2014. Overall eight studies were identified as meeting the eligibility criteria. Three of them reported only drug costs and five reported a wide range of costs and resource use. The CS however, reports that none of the studies reported on the costs or resource use associated with disease management of the newly available immunotherapies or BRAF inhibitors.

Resource use and costs for patients with advanced melanoma were included by identifying one-off resource use for treatment initiation and end of life and resource use by cycle for patients in the pre-palliative (year 1 – 3 and beyond) and palliative care period. The one-off resource use and costs for treatment initiation and end of life states were obtained from NHS Reference costs[42] and PSSRU[31] (as in NICE appraisal TA319[16] of ipilimumab).[16] While resource use and costs for patients in the pre-palliative and palliative care states were obtained from the NHS Reference case,[42] PSSRU,[31] and the Oxford Outcomes Melanoma Resource Use report.[32] Resource use data for AEs were based on patient-level CheckMate 066[40] trial data. The same sources were used to identify the unit costs for AEs, CS Table 76 (CS, p. 200) presents the unit costs and resource use for AEs. The CS reports that the unit cost data and resource use for the one-off treatment initiation and end of life costs sources used were updated according to UK clinical opinion to match current treatment practice based on responses of an advisory board

including four leading UK clinicians. They also report that these sources were used in the recent NICE appraisal TA319[16] of ipilimumab.

The resource use is modelled by dividing the patient's lifetime into health states as: first year after treatment initiation, second year, third and subsequent years following treatment initiation, and 12 weeks palliative care before death. Resource use data, proportion of patients and unit costs used in the economic model are presented in CS Table 73 for one-off resource use for treatment initiation and end of life, and CS Table 74 for cycle resource use for patients in the pre-palliative and palliative periods (CS, p. 196 to 199). The same approach as for quality of life estimates was adopted incorporating AE resource use in the model by applying this cost at the start of the model, and then periodically for patients who are still on treatment (i.e. 35 weeks).

The dosing regimen for each treatment is presented in CS Table 56 (CS, p. 160). Nivolumab is administered every two weeks by IV and the dose per administration is 236mg (i.e. 3mg/Kg, in the base case using UK patient-level weight data from the CheckMate 066 and CheckMate 067 trials, and the CA184-024 trial[14]). The recommended dosing schedule per administration for nivolumab, ipilimumab, and DTIC and the recommended daily dose for dabrafenib and vemurafenib and the drug administration costs are stated in CS Table 71 (CS, p. 194). The dose per administration and drug costs are summarised here in Table 24.

The company states that the drug unit costs of the treatments are based on the list price for nivolumab and all comparators (CS, Table 70, p. 193), with PAS discount rates explored in a scenario analysis. The list prices for drug costs have been identified from MIMS, and EMIT. The administration cost assumptions used for ipilimumab, DTIC and vemurafenib were the same as those used within the NICE TA319[16] of ipilimumab.

The administration cost was taken from NHS reference costs[42] and the treatments were assumed to be given in day care settings, every two weeks. The administration cost assumptions for ipilimumab, DTIC, and vemurafenib are the same as those within the previous ipilimumab NICE TA319[16] of ipilimumab. The active cost per administration was estimated £2,809 per infusion for nivolumab, £19,574 for ipilimumab, and £48.21 for DTIC; while, the cost per day for dabrafenib and vemurafenib was £200 and £250, respectively (Table 24). The cost for each type of administration regime was from NHS Reference Costs (2013/14).[42]

Table 24 - Dose per administration and drug costs

Drug	Dosing regimen	Dose per administration	Drug cost per administration (without PAS)	Drug cost per administration (with PAS)
Nivolumab	3mg/kg, every 2 weeks by IV	236mg	£2,809.47 per IV	n/a
Ipilimumab	3 mg/kg	236mg	£19,574.00 per IV	[redacted]
DTIC	1000mg/m2, every 3 weeks by IV	1902mg	£48.21 per IV	n/a
Dabrafenib	300mg, daily oral	300mg	£200.00 per day	[redacted]
Vemurafenib	1920mg, daily oral	1920mg	£250.00 per day	[redacted]

A one-off cost is included for BRAF inhibitors as oral chemotherapy at treatment initiation. A complete metabolic panel laboratory test cost is also added based on test requirements in the product Summary of Product Characteristics. No other additional resource use is discussed. The assumptions seem to follow the recent NICE submission TA319,[16] new assumptions are adequately described.

Overall the ERG considers the approach for costing to be reasonable. In general, the values used have been taken from standard sources and the estimates have been appropriately reported. However, there are some resource data based upon expert opinion and aspects on the adverse events and dosing information from the CheckMate 066[40] trial that the ERG is not able to check.

4.2.6 Consistency/ Model validation

The company presented a number of steps to assess the robustness of the economic model. Both health economic and clinical experts were consulted and their feedback was incorporated in the estimation of long-term survival, the treatment continuation rule for nivolumab and resource use.

The company did not report whether any checklist was used for internal validation. The company stated that the health economic and clinical experts assessed the following aspects of modelling methods and inputs (CS section 5.9, p.241-2):

Methods:

- The Markov state transition for modelling OS and PFS
- Indirect comparison of efficacy between nivolumab and ipilimumab

- Modelling time on treatment for nivolumab and the treatment discontinuation rule
- Data extrapolation beyond the trial duration and the use of external data for long-term survival

Inputs:

- Estimating utilities based on progression status and time to death
- Costs and resource use
- Safety and adverse events

Furthermore, the company verified the estimated clinical model results against those obtained from the clinical trials (CS Table 84, p. 208). For BRAF mutation-negative patients, the short term model results were compared with the trial results based on CheckMate 066[4] and results based on the BRIM-3[12] trial were used to compare the results for BRAF mutation–positive patients. Long-term model results were compared against pooled ipilimumab data. Although the short term model results for OS and PFS were comparable with those obtained from the clinical trials, the long-term model estimation of OS for ipilimumab at year 10 varied when compared to the clinical results (clinical trial results: 18%; model results: 16.8% (BRAF negative) and 13.9% (BRAF positive)). The lower OS obtained in the model estimations was explained to have resulted from small numbers of patients at risk at year 10 in the pooled analysis.

For both the patient groups, the company presented disaggregated results for both health outcomes (including QALY gains and life year gains) as well as for costs by the health states (CS Tables 85-92 p.212-7).

The company did not describe any basic input and output verification checks of the model. The ERG conducted a list of extreme value checks of the model inputs and their expected outputs to examine if the model was coded correctly. Setting the resources used to zero resulted in no costs as expected, as did using zero values for all the types of costs. Similarly, using zero value for all health state utilities and adverse events disutilities resulted in no health outcomes whereas using the value of one matched the QALYs to life years. Total costs and QALYs decreased with an increase in the discount rates which is logical and consistent. The ERG did not detect any input errors and the model calculations appeared to function correctly. Although a minor error was identified in reporting incremental costs, incremental life years gained and incremental QALYs for PAS base case results in BRAF mutation-positive patients (CS Table 83, p. 207), the model however appeared to estimate the results correctly. The logical flow of the

model appeared to work as intended and no errors were found. Overall, the model is clearly laid out, well presented, easy to navigate through and on re-running, produced results as expected.

The company has compared the modelled OS and PFS survival curves to those observed in the CheckMate 066 trial. CS Figure 53 compares the economic model predictions of OS in the base case for the first three years with observed data. It indicates that the model has overall a reasonable fit to the observed data for ipilimumab and DTIC. CS Figure 59 indicates that there is a very good fit between observed Kaplan-Meier data and PFS from the economic model for both DTIC and nivolumab (CS p. 177).

In the company's clarification response to the ERG (clarification question B2), the company has provided an analysis using the CheckMate 066 trial only, without adjusting survival curves for covariates. The analyses show similar results to those presented in the base case analysis with an ICER of £28,583 per QALY for nivolumab versus DTIC.

For external validation, the company reported that they had compared the PAS based cost-effectiveness results of the current submission with the results obtained from the PAS based analyses of the previous NICE appraisal TA319[16] of ipilimumab. Although the results of the current submission were stated to be comparable with the results in TA319, the ERG could not check this due to the commercial-in-confidential nature of the PAS price discount for ipilimumab in NICE TA319. The ERG, however, cross-checked the list price base case results of the two submissions and found significant discrepancies in the two sets of results in the submissions as shown in Table 25 and Table 26. In the BRAF mutation-negative patients, the ICERs (ipilimumab vs DTIC) obtained in TA319 were lower than that obtained by the company in the current submission. However, in the BRAF mutation-positive patients, both the analyses found vemurafenib to be dominated when compared against ipilimumab.

4.2.7 Assessment of uncertainty

The company conducted a range of sensitivity analyses including one-way sensitivity analyses, scenario analyses and PSA. Structural uncertainty was tested in the scenario analyses and heterogeneity was dealt with to some extent by running the model separately for the two patient groups: BRAF mutation-positive and BRAF mutation-negative.

Table 25 - Comparison of results obtained in the CS with TA319 for BRAF mutation-negative patients

Company submission: BRAF mutation-negative					
Treatment	**Costs**	**QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER (vs DTIC)**
DTIC	[redacted]	1.23			
Ipilimumab	[redacted]	2.64	£48,429	1.41	£34,261
Nivolumab	[redacted]	4.31	£72,578	3.08	£23,583
TA319: BRAF mutation-negative (based on CA 184-024 data for ipilimumab)					
Treatment	**Costs**	**QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER (Ipilimumab vs comparator)**
Ipilimumab	[redacted]	2.35			
DTIC	[redacted]	1.56	£13,493	0.80	£16,957
TA 319: BRAF mutation-negative (based on pooled chemotherapy naive data for ipilimumab)					
Treatment	**Costs**	**QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER (Ipilimumab vs comparator)**
Ipilimumab	[redacted]	2.50			
DTIC	[redacted]	1.55	£16,948	0.95	£17,866

Table 26 - Comparison of results obtained in the CS with TA319 for BRAF mutation-positive patients

Company submission: BRAF mutation-positive					
Treatment	**Costs**	**QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER (vs ipilimumab)**
Ipilimumab	[redacted]	2.44			
Nivolumab	[redacted]	4.27	£13,374	1.82	£7,346
Dabrafenib	[redacted]	1.69	£19,602	-2.57	Dominated
Vemurafenib	[redacted]	1.70	£38,033	-2.56	Dominated
TA 319: BRAF mutation-positive (based on CA 184-024 data for ipilimumab)					
Treatment	**Costs**	**QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER (Ipilimumab vs comparator)**
Ipilimumab	[redacted]	2.31			
DTIC	[redacted]	1.56	£23,766	0.75	£31,558
Vemurafenib	[redacted]	2.13	-£12,625	0.18	Dominated
TA319: BRAF mutation-positive (based on pooled chemotherapy naive data for ipilimumab)					
Treatment	**Costs**	**QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER (Ipilimumab vs comparator)**

Ipilimumab	[redacted]	2.45			
DTIC	[redacted]	1.55	£25,525	0.90	£28,465
Vemurafenib	[redacted]	2.10	-£9,814	0.35	Dominated

Across most of the scenario and sensitivity analyses, nivolumab was cost-effective compared to ipilimumab and DTIC at list price for BRAF-mutation-negative patients. Similarly, in BRAF-mutation-positive patients, nivolumab represented a cost-effective option when compared to ipilimumab, dabrafenib and vemurafenib at the list price for a majority of the analyses conducted. The exception to this was for scenarios related to treatment discontinuation in the nivolumab arm. [redacted]

One-way sensitivity analyses

The company conducted 53 one-way sensitivity analyses for BRAF mutation-negative patients and 58 analyses for BRAF mutation-positive patients. The parameters were varied between their upper and lower 95% confidence intervals bounds. A variation of 20% around the mean was assumed for parameters with no distribution, as stated in the model. Details of the parameters included in the analyses are listed within the model. These can be grouped under the following categories:

- Administration costs
- Patient dosing parameters including weight and height
- Proportions of patients receiving different doses of ipilimumab
- AE costs
- Resource use and costs
- Utilities (which included utility coefficients for the regression equation)
- Treatment duration
- Efficacy parameters

The results of the sensitivity analyses are presented as tornado diagrams that illustrated the 20 most influential parameters for both the patient groups (CS Figure 75 and Figure 76, p. 228-232) with the effect expressed in terms of incremental net benefit. The figures for the PAS based analyses are presented in CS Appendix 16. The model has the built-in flexibility to select up to 50 parameters in the tornado diagrams. The ICER values for the analyses are also presented in the model. The company used a willingness to pay threshold of £50,000 per QALY

for the estimation of incremental net benefit on the basis that nivolumab qualifies as an end-of-life treatment (see Section 5 of this report for discussion of end of life criteria).

Based on the company's findings, the economic model was found to be most sensitive to the parameters that defined the fitted parametric curves for TTP, PPS, long-term OS, OS/PFS for vemurafenib and time on treatment, as well as utility parameters and administration cost. The ERG considers the company's conclusions relating to the influential parameters impacting the base case results to be reasonable.

Scenario Analysis

The company also included 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 trial evidence (comparing the CheckMate 066[4] trial with the CA184-024 trial[14], rather than the MDX010-20 trial[15]) and PPS data (based on combined PPS for nivolumab and ipilimumab).
- treatment discontinuation and maximum length of treatment duration
- alternative approach to modelling dosing, drug cost and utilities
- time horizon
- discount rates

The results of the analyses are tabulated in CS Table 97 p. 233-236 (for BRAF mutation-negative) and CS Table 98 p. 237-240 (for BRAF mutation-positive) for the list price and PAS price. The findings of the company's analyses indicate that a majority of the scenarios tested did not influence the base case results and nivolumab remained cost-effective compared to the comparator drugs in both the patient groups. The exceptions were scenarios examining the effect of changing the proportion of patients continuing treatment at two years: the number of years of maximum treatment duration for nivolumab, and reducing the model time horizon to 10 years.

The scenarios relating to treatment discontinuation and maximum length of treatment discontinuation for nivolumab have the most impact on model results. The marketing authorisation for nivolumab states that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (CS p. 158). The company

considered treating patients until disease progression occurs as an unrealistic approach, as a result of which they assumed that the maximum treatment duration for nivolumab was two years. The treatment duration was altered to three, four, and five years and to no maximum duration in the company scenario analyses, with ICERs increasing according to increased treatment duration.

The ERG has included additional scenario analyses to test some of the key assumptions and input parameters associated with uncertainty in the economic model (Section 4.3).

Probabilistic Sensitivity Analysis

The company performed PSA for 1000 simulations and presented the results using scatter plots (CS Figure 71-74, p. 221-224) and cost-effectiveness acceptability curves (CS Figure 67-70, p.218-220). The list of the input parameters for the analysis is presented in CS Table 79, p.202-204 and within the model. The company used normal distribution for resource use and costs; beta distribution for patient dosing parameters, proportion of patients receiving different doses of ipilimumab, and adverse event disutilities; and multivariate normal distributions for the coefficients of the regression analysis for utility. The ERG considered the assigned distributions to be appropriate; although the use of the gamma distribution for costs would have been preferable. The ERG re-ran the PSA using 1000 simulations which took approximately 10 minutes to run.

Based on the PSA results, the company concluded that in BRAF mutation-negative patients, the probabilities of nivolumab being cost effective at willingness to pay thresholds of £30,000 and £50,000 are 87% and 99% respectively for the list price and the probabilities for PAS analyses are [redacted] respectively. In the BRAF mutation-negative patients, the probabilities of the drug being cost effective at these thresholds are 100% and 100% respectively at the list price and at the PAS price the probabilities are [redacted] respectively.

The PSA results are found to be similar to those obtained in the deterministic analysis (CS Table 93-96, p.225-226).

Overall, the ERG considers that the company included a reasonable list of parameters in the PSA and the distributions used for the model parameters were appropriate.

4.2.8 Comment on validity of results with reference to methodology used

The structure of the economic model was appropriate, comprehensive and reflected the clinical pathway for patients with advanced melanoma. The economic model, developed in Microsoft Excel, was well-structured and provided the relevant data sources in a transparent way. Furthermore, the model provided graphs to enable comparison between the model results and the trial data which aided validation. The ERG did not find any errors in the coding of the model structure.

The methods chosen for the analysis were generally appropriate and conformed to NICE methodological guidelines. In general, the methods chosen to derive the survival curves were more complex than traditional methods and the complexity of the analyses may appear difficult for non-statisticians to understand and therefore limit accessibility and transparency.

The ERG identified several areas where choice of parameter was not sufficiently justified or uncertainty was not insufficiently explored. Where these concerns were identified, the ERG has conducted additional analyses, where possible, to address the uncertainty surrounding these parameters.

The ERG observed that the CheckMate 067 trial data have not been used in the derivation of the survival curves due to lack of available follow-up OS data. The CheckMate 067 contains a direct comparison between nivolumab and ipilimumab and would provide a better estimate of the comparison between these treatments that using an indirect comparison.

The ERG noted that DTIC has not been compared as a comparator in the analysis of BRAF mutation-positive patients, although it was within the NICE scope.

The ERG had reservations of the choice of survival curve used in the model for TTP for nivolumab. The model uses the Gompertz survival for all treatment comparators but the ERG suggests that other survival curves may be plausible for nivolumab.

The model assumes that the long-term survival of patients treated with nivolumab would follow a similar pattern to ipilimumab, i.e. beyond two years most patients remain alive, however there is uncertainty at present, from the trial data, whether this would indeed be the case.

For BRAF positive patients, the cost of the BRAF inhibitors was sensitive to the type of survival curve chosen for the BRAF inhibitors. The ERG noted that other survival curves are plausible that give more favourable results for the BRAF inhibitors.

4.3 Additional work undertaken by the ERG

The ERG observed a number of issues and uncertainties in the CS which are explored in this section. The additional work undertaken by the ERG is based around the following aspects:

1. Type of survival model chosen for treatment efficacy
    i. Time to progression: using the Weibull, lognormal, log-logistic and generalised gamma distributions for nivolumab patients and Gompertz distribution for DTIC and ipilimumab
    ii. Progression-free survival: using the exponential, Gompertz, log-logistic, lognormal and Weibull distributions for BRAF inhibitors (vemurafenib assumed to be same as dabrafenib)
2. Modelling method: using the data extrapolation method to model long-term survival for nivolumab
3. Using DTIC as a comparator in BRAF mutation-positive patients
4. Presentation of the ERG's preferred scenarios which includes a combination of scenarios (1), (2) and (4) outlined above and between two years and no maximum treatment duration for nivolumab.

4.3.1 Modelling TTP for nivolumab patients with the Weibull, lognormal, log-logistic and generalised gamma and Gompertz distribution for DTIC and ipilimumab

As discussed in Section 4.2.4 of this report, the ERG observed that although the Gompertz distribution provided a reasonable fit for modelling TTP for the ipilimumab arm a preferable approach to model this parameter would be to use the best fitting distribution for each treatment arm. The ERG therefore fitted the Weibull, lognormal, log-logistic and generalised gamma distributions for nivolumab, without changing the company's assigned Gompertz distribution for the DTIC and ipilimumab arms. The results are presented in Table 27 and Table 28 for BRAF mutation-negative and BRAF mutation-positive patients respectively.

Changing the survival model for nivolumab had a small impact on the incremental costs and QALYs in BRAF mutation-negative patients, increasing the ICERs (nivolumab vs DTIC) marginally, ranging from £26,483 to £27,027 from the base case ICER of £23,583. In BRAF

mutation-positive patients, the impact was similar with ICERs (nivolumab vs ipilimumab) ranging from £8,836 to £9,144, deviating from the base case ICER of £7,346.

Table 27 - Using the Weibull, log-normal, log-logistic and generalised distributions for the nivolumab arm to model time to progression at list price (BRAF mutation-negative patients)

Treatment	Distribution	Incremental Costs (vs DTIC)	Incremental QALYs (vs DTIC)	ICER (vs DTIC)	ICER (vs ipilimumab)
Nivolumab	Base case[1]	£72,578	3.08	£23,583	£14,513
Nivolumab	Weibull	£72,237	2.73	£26,483	£18,117
Nivolumab	Lognomal	£72,085	2.67	£27,027	£18,874
Nivolumab	log-logistic	£72,137	2.69	£26,829	£18,594
Nivolumab	generalised gamma	£72,098	2.67	£26,980	£18,806

1: Gompertz

Table 28 - Using Weibull, log-normal, log-logistic and generalised gamma distributions for the nivolumab arm to model time to progression at list price (BRAF mutation-positive patients)

Treatment	Distribution	Incremental Costs (vs ipilimumab)	Incremental QALYs (vs ipilimumab)	ICER (vs ipilimumab)
Nivolumab	Base case[1]	£13,374	1.83	£7,346
Nivolumab	Weibull	£13,060	1.48	£8,836
Nivolumab	Lognomal	£12,890	1.41	£9,144
Nivolumab	log-logistic	£12,947	1.43	£9,025
Nivolumab	generalised gamma	£12,903	1.41	£9,120
Nivolumab dominates dabrafenib and vemurafenib for all analyses				

1: Gompertz

4.3.2 Modelling progression-free survival using a range of distributions for BRAF inhibitors

For PFS, it was observed that the type of survival curve chosen for the BRAF inhibitors influenced the costs associated with the treatment arms in BRAF mutation-positive patients. The ERG explored this further by assigning a range of distributions (exponential, Gompertz, log-logistic, log-normal and Weibull) to the PFS in the BRAF inhibitors. Assigning different distributions influenced the total costs for both dabrafenib and vemurafenib but total QALYs in both the treatment arms remained similar to the base case values as shown in Table 29. As in the base case, the ICERs for both the BRAF inhibitors (vs ipilimumab) remained dominated for the scenarios with different survival distributions.

Table 29 - Using a range of distributions to model PFS for the BRAF inhibitors at the list price (BRAF mutation-positive patients)

Treatment		Incremental Costs (vs ipilimumab)	Incremental QALYs (vs ipilimumab)	ICER (vs nivolumab)
Dabrafenib	base case[1]	£19,602	-0.75	Dominated
Dabrafenib	exponential	£5,950	-0.75	Dominated
Dabrafenib	Gompertz	£1,783	-0.76	Dominated
Dabrafenib	log-logistic	£37,002	-0.74	Dominated
Dabrafenib	log normal	£4,860	-0.75	Dominated
Dabrafenib	Weibull	£1,538	-0.76	Dominated
Vemurafenib	base case[1]	£38,033	-0.74	Dominated
Vemurafenib	exponential	£20,964	-0.74	Dominated
Vemurafenib	Gompertz	£15,757	-0.75	Dominated
Vemurafenib	log-logistic	£59,778	-0.73	Dominated
Vemurafenib	lognormal	£19,605	-0.74	Dominated
Vemurafenib	Weibull	£15,452	-0.75	Dominated

4.3.3 Using the data extrapolation method to model long-term survival for nivolumab

The company's long-term OS analysis, based on pooled ipilimumab data showed a plateau effect for ipilimumab beginning around year three. The company assumed the same effect for the nivolumab arm in their analyses (for details, see Section 4.2.4 of this report) which might not reflect the clinical trajectory of overall survival for the nivolumab treatment arm. The ERG explored the impact of using extrapolated long-term survival data for the nivolumab arm (using the Gompertz survival curve), rather than using the pooled ipilimumab data. As shown in Table 30 and Table 31, changing the modelling method reduced the total costs of nivolumab by approximately £2,000 and reduces the QALYs gained for nivolumab in both the patient groups from the base case values.

Table 30 - Using the data extrapolation method to model long-term survival for nivolumab at the list price (BRAF mutation-negative patients)

Treatment	Costs	QALYs	Incremental Costs (vs DTIC)	Incremental QALYs (vs DTIC)	ICER (£/QALY)
DTIC	[redacted]	1.23			
Ipilimumab	[redacted]	2.64	£48,429	1.41	£34,261
Nivolumab	[redacted]	3.25	£70,761	2.02	£36,072

The ICERs for nivolumab vs DTIC increased from £23,583 in the base-case to £36,072 in BRAF mutation-negative patients. The ICERs for nivolumab compared to ipilimumab increased from £7,346 in the base case to £27,171 in BRAF mutation-positive patients.

Table 31 - Using data extrapolation method to model long-term survival for nivolumab at the list price (BRAF mutation-positive patients)

Treatment	Costs	QALYs	Incremental Costs (vs ipilimumab)	Incremental QALYs (vs ipilimumab)	ICER (£/QALY)
Ipilimumab	[redacted]	2.44			
Nivolumab	[redacted]	2.85	£10,978	0.40	£27,171
Dabrafenib	[redacted]	1.69	£19,602	-0.75	Dominated
Vemurafenib	[redacted]	1.70	£38,033	-0.74	Dominated

4.3.4 Including DTIC as a comparator in BRAF mutation-positive patients

The ERG observed that the company did not include DTIC as a comparator in BRAF mutation-positive patients, as discussed in Section 4.2.3 of this report. The ERG, therefore conducted a scenario analysis in which DTIC was included as one of the comparator arms, the results of which are presented in Table 32. In this scenario, nivolumab was the most cost-effective option with an ICER (nivolumab vs DTIC) of £21,201.

Table 32 - Including DTIC as a comparator arm in the BRAF mutation-positive analysis at list price

Treatment	Costs	QALYs	Incremental Costs (vs DTIC)	Incremental QALYs (vs DTIC)	ICER (£/QALY)
DTIC	[redacted]	1.10			
Ipilimumab	[redacted]	2.44	£53,793	1.35	Extendedly dominated
Nivolumab	[redacted]	4.27	£67,167	3.17	£21,201
Dabrafenib	[redacted]	1.69	£73,396	0.60	Dominated
Vemurafenib	[redacted]	1.70	£91,826	0.61	Dominated

4.3.5 Combination scenario with varying maximum treatment duration for nivolumab

The ERG conducted a combination scenario analysis whereby the following assumptions were simultaneously made to the cost-effectiveness model:

- Using a Weibull distribution for modelling TTP for nivolumab patients (the ERG considered this to be the best visual fit)
- Modelling PFS using the lognormal distribution for BRAF inhibitors (the ERG considered this to be the best visual fit)
- Using the data extrapolation method to model long-term survival for nivolumab
- Treatment duration ranging from two years to no maximum treatment duration.

The results of the combination scenarios (shown in Table 33, Table 34, Table 35,

Table 36 Table 37, and Table 38) show that nivolumab is dominated by ipilimumab in both BRAF mutation-negative and BRAF mutation-positive patients. The cost of nivolumab is almost double in the scenario with no maximum treatment duration compared to using maximum treatment duration of two years.

Table 33 - Combination scenario at list price (BRAF mutation-negative) 2 years treatment duration

Treatment	Costs	QALYs	Incremental Costs (vs DTIC)	Incremental QALYs (vs DTIC)	ICER (£/QALY)
DTIC	[redacted]	1.23			
Ipilimumab	[redacted]	2.64	£48,429	1.41	£34,261
Nivolumab	[redacted]	2.55	£69,725	1.32	Dominated

Table 34 - Combination scenario at list price (BRAF mutation-positive) 2 years treatment duration

Treatment	Costs	QALYs	Incremental Costs (vs ipilimumab)	Incremental QALYs (vs ipilimumab)	ICER (£/QALY)
Ipilimumab	[redacted]	2.44			
Dabrafenib	[redacted]	1.69	£4,860	-0.76	Dominated
Nivolumab	[redacted]	2.27	£5,267	-0.17	Dominated
Vemurafenib	[redacted]	1.70	£19,606	-0.75	Dominated

Table 35 - Combination scenario at list price (BRAF mutation-negative) 3 years treatment duration

Treatment	Costs	QALYs	Incremental Costs (vs DTIC)	Incremental QALYs (vs DTIC)	ICER (£/QALY)
DTIC	[redacted]	1.23			
Ipilimumab	[redacted]	2.64	£48,429	1.41	£34,261
Nivolumab	[redacted]	2.54	£84,257	1.31	Dominated

Table 36 - Combination scenario at list price (BRAF mutation-positive) 3 years treatment duration

Treatment	Costs	QALYs	Incremental Costs (vs ipilimumab)	Incremental QALYs (vs ipilimumab)	ICER (£/QALY)
Ipilimumab	[redacted]	2.44			£43,603
Dabrafenib	[redacted]	1.69	£4,860	-0.76	Dominated
Vemurafenib	[redacted]	1.70	£14,746	-0.75	Dominated
Nivolumab	[redacted]	2.26	£22,574	-0.18	Dominated

Table 37 - Combination scenario at list price (BRAF mutation-negative) maximum treatment duration

Treatment	Costs	QALYs	Incremental Costs (vs DTIC)	Incremental QALYs (vs DTIC)	ICER (£/QALY)
DTIC	[redacted]	1.23			
Ipilimumab	[redacted]	2.64	£48,429	1.41	£34,261
Nivolumab	[redacted]	2.51	£155,177	1.28	Dominated

Table 38 - Combination scenario at list price (BRAF mutation-positive) maximum years treatment duration

Treatment	Costs	QALYs	Incremental Costs (vs ipilimumab)	Incremental QALYs (vs ipilimumab)	ICER (£/QALY)
Ipilimumab	[redacted]	2.44			£43,603
Dabrafenib	[redacted]	1.69	£4,860	-0.76	Dominated
Vemurafenib	[redacted]	1.70	£14,746	-0.75	Dominated
Nivolumab	[redacted]	2.24	£83,858	-0.21	Dominated

4.4 Summary of uncertainties and issues

The CS reports that nivolumab is cost effective compared to its comparators at a cost effectiveness threshold of £30,000 per QALY and the base case results are robust to uncertainties of key model parameters and assumptions. However there are some uncertainties with regard to the modelling assumptions and data. The ERG notes that incorporating changes to the method used to estimate OS, the maximum treatment duration and TTP have significant impact on the model results. In the ERG combination scenario analysis, nivolumab is no longer cost effective and is dominated by ipilimumab. Furthermore, the ERG notes that a key trial,

CheckMate 067, has not been included in the company's analysis due to lack of available OS data.

5 End of life

The CS discusses the end of life criteria in Table 52 and states that advanced melanoma is associated with a short life expectancy, with median survival estimates of 6-10 months. Survival analyses of CheckMate 066 trial data indicate that nivolumab offers an extension to life of at least three months compared to palliative chemotherapy (DTIC). However, the survival benefit compared to ipilimumab is not yet fully established, pending follow-up OS data from CheckMate 067.[5] The CS reported that the expected number of new cases and relapsed cases of advanced melanoma in England in 2016 is 1,577. The CS therefore concluded that nivolumab is suitable for consideration as a life-extending treatment at the end of life.

The ERG also notes that in TA319[16] for ipilimumab for advanced melanoma, the Appraisal Committee was satisfied that ipilimumab met the criteria for being a life-extending, end of life treatment.

6 Innovation

The CS states that nivolumab should be considered innovative, representing a step-change in the management of advanced melanoma. The arguments in support of this include the stated significant clinical improvement associated with the drug, demonstrated through 45-50% of patients estimated to still be in remission two years after treatment initiation, based on extrapolation from the on-going Phase III RCTs. Furthermore, the CS reports that the Medicines and Healthcare products Regulatory Agency awarded nivolumab a Promising Innovative Medicine (PIM) designation for the treatment of advanced melanoma. Nivolumab was also approved to treat locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) through the Early Access to Medicines Scheme. The criteria for drugs to be supported under this scheme include evidence that the product is likely to offer significant advantage over methods currently used in the UK.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The clinical effectiveness evidence for nivolumab is based on three on-going phase III RCTs. The trials were conducted internationally, though a small proportion of UK patients were

included in two of them. The ERG considers the trials to be well-designed and unlikely to be at high risk of bias.

The currently available evidence shows that nivolumab is associated with a significant reduction in mortality compared to DTIC. However, the impact of nivolumab on overall survival compared to ipilimumab is not yet reported. Nivolumab also increased PFS compared to DTIC or ipilimumab. In terms of treatment response (ORR) there was significant benefit of nivolumab over comparator drugs in all three CheckMate trials. From the limited currently available nivolumab does not impair HRQoL. However, there is no current evidence that nivolumab leads to a consistent and sustained improvement in HRQoL. Nivolumab has a favourable AE profile with a lower incidence of high grade and serious AEs in compared to comparators, although nearly all trial participants experienced AEs (of any grade or category). Expert clinical advice to the ERG suggested that the benefits seen so far are very clinically significant.

A mixed treatment comparison of all comparators to inform economic modelling was not possible, necessitating an indirect comparison using selected RCTs from the company's systematic review of clinical effectiveness. Two separate evidence networks were created for BRAF mutation-positive and BRAF mutation-negative patients, respectively. A complex process was followed based on extraction of patient-level data from the trials ('pseudo patient-level data' from the BRAF inhibitor trials), using TTP, PrePS, and PPS outcomes to estimate PFS and OS (where available long-term data are currently unavailable). Covariate-adjusted parametric survival models, to adjust for differences between the trials, were created to inform transitions between states in the economic model. As summarised earlier in this report, the ERG considers that, in the circumstances, the approach taken was reasonable (subject to caveats for possible uncertainties, such as small sample sizes and numbers of events for some of the outcomes included), with some of the assumptions underpinning the indirect comparison having been accepted in previous NICE appraisals of treatments for advanced melanoma. However, there may be uncertainty around the assumption that there is no difference in treatment effect for nivolumab by BRAF mutation status. This is of significance because the cost-effectiveness estimates for BRAF-mutation positive patients are informed by the results of the CheckMate 066 trial which only included BRAF-mutation negative patients.

One of the biggest limitations was the omission of the pivotal CheckMate 067 trial from the indirect comparison evidence networks as this would have provided a direct comparison

between nivolumab and ipilimumab. The company clarified that it was not possible to have used data for the alternative outcomes from this trial (i.e. TTP, PrePS and PPS) as had been done for CheckMate 066 as this requires both PFS and OS events to be available. This appears to be a reasonable argument.

7.2 Summary of cost effectiveness issues

The CS includes evidence on the cost effectiveness of nivolumab compared with DTIC and ipilimumab for BRAF-mutation-negative patients and with dabrafenib, ipilimumab and vemurafenib for BRAF-mutation-positive patients with advance melanoma. The methods adopted for the economic evaluation are reasonable and are generally appropriate. The model structure and model parameter inputs are consistent with the clinical disease pathways and the available clinical trial evidence. However, the CS has not used direct evidence from the CheckMate 067 trial for nivolumab versus the ipilimumab and instead has conducted an indirect comparison. There is also some uncertainty regarding the maximum treatment duration for nivolumab.

The company performed a wide range of sensitivity analyses including one-way, probabilistic and scenario analyses to assess model uncertainty. Across most of the scenarios and sensitivity analyses, nivolumab was found to be cost effective in both BRAF mutation-positive and BRAF mutation-negative patients. The model results from the PSA suggest that in BRAF mutation-positive patients, the probabilities at list price were 100% at both £30,000 and £50,000 willingness-to-pay thresholds respectively and at estimated PAS prices, the probabilities were [redacted] respectively. In BRAF mutation-negative patients, the probabilities of nivolumab being cost-effective at list price were 87% and 99% at willingness-to-pay thresholds of £30,000 and £50,000 respectively and the probabilities for the PAS analyses were [redacted] respectively. The key model drivers in the one-way sensitivity analyses were: parameters that defined the fitted parametric curves for TTP, PPS, long-term OS; OS/PFS for vemurafenib; time on treatment; utility parameters; and administration cost.

The company has implemented two important assumptions: (i) that the long-term overall survival will be similar to seen with ipilimumab, i.e. an OS plateau, however this may not be the case and other distributions for long term OS may be more appropriate; and (ii) that the maximum treatment duration should be two years, although the marketing authorisation

specifies that treatment should continue as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

The ERG believes that the comparative efficacy of nivolumab with the comparator treatments in the NICE scope is uncertain due to a lack of head-to-head data from clinical trials. Furthermore changes to the method used to estimate OS, the maximum treatment duration and TTP have significant impact on the model results.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Nivolumab for treating advanced (unresectable or metastatic) melanoma [ID845]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre (SHTAC) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 6th November 2015** 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 Maximum duration of treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 of the report states that: "The time spent on treatment is a key factor influencing cost effectiveness results but the maximum duration of treatment likely in practice is unclear." This statement is repeated elsewhere in the report. These statements are misleading because there is, in fact, no fixed maximum duration of	We would propose that this text/conclusion is reworded throughout the ERG report to make it clear that there is a distinction between clinical uncertainty and economic uncertainty, using the following wording, or similar: "The point at which nivolumab	To clarify, there is no fixed maximum duration of treatment. The decision to stop treatment is very much an individual decision between clinician and patient. Based on review of data from the Checkmate 003 study, when treatment was discontinued at 96 weeks (1.85 years), the clinical advice we received indicated that 6 months, 1 year and 2 years were all time-points at which	This is not a factual inaccuracy. The assumptions used in the economic modelling regarding time on treatment has a large effect on cost effectiveness results.

treatment that will apply to every patient. For the purposes of cost-effectiveness modelling, however, we took a pragmatic (and conservative) approach in assuming that all patients would discontinue treatment (at 2 years in the base case).	treatment might be discontinued is an individual decision between the clinician and patient, and is likely to vary in clinical practice."	clinicians might be willing to consider stopping treatment, particularly if the patient had had either a complete or partial response prior to that point. Part of the mechanism of action of immunotherapies like nivolumab is to stimulate the person's own immune system to target the cancer cells. Consequently, it is not unreasonable to consider stopping treatment in patients in whom a complete or partial response is observed. This is precisely because the fact that a response has been triggered is indicative of the treatment having been successful in stimulating the immune system. It is worth noting that a number of recent and ongoing clinical trials for immumotherapies are now incorporating a maximum duration of treatment into the trial protocol. Irrespective of which time period is chosen, physicians indicated to us that decisions to stop treatment would be made on an individual patient basis. This decision would be likely to involve observation of the patient on treatment, and at least two consecutive on-treatment scans confirming either a complete response, or stable disease following an initial good partial response (thus aligning with the marketing authorisation which proposes treatment until no further clinical benefit is observed). For the purposes of the cost-effectiveness modelling, however, we took a pragmatic (and conservative) approach in the Company Submission (CS) and assumed that all patients would discontinue treatment at 2 years as the base case. This decision is consistent with what was observed in Checkmate 003, as well as the nivolumab	

		RCTs. The mean time on treatment in the Checkmate RCTs is 8 months and none of the patients in the trials have yet reached two years on treatment. Recognising that there was uncertainty around the base case assumption, however, we undertook sensitivity analyses, which varied the maximum duration of treatment to 3, 4 and 5 years, as well as the proportion of patients discontinuing treatment at 2 years. Nivolumab was cost-effective at a threshold of £50k/QALY in all of those sensitivity analyses.	

Issue 2 Innovative nature of the technology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 108. The report states "Nivolumab was also approved to treat locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) through the Early Access to Medicines Scheme." This statement is only partially correct.	Nivolumab was approved to treat both NSCLC and advanced melanoma through the Early Access to Medicines Scheme. We would propose that the text is corrected accordingly.	It is important that the Appraisal Committee appreciates that the technology that is the subject of this appraisal was made available to UK patients prior to marketing authorisation through the Early Access to Medicines Scheme.	The report has been amended to state that the Early Access to Medicine's Scheme approved Nivolumab for advanced melanoma.

Issue 3 Transcription or typographical errors in reporting numbers or facts

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23. The ERG report states that: "CheckMate 067 recruited treatment naïve patients with any BRAF mutation status.	We would propose correcting the text to read: "…and a combination of nivolumab	The description of the combination arm in the	The proposed amendment is not apparent in the company

This was a three arm trial and the two comparator treatments were ipilimumab 3mg/kg administered every three weeks, and a combination of nivolumab at a dose of 1mg/kg and ipilimumab 3mg/kg, administered every three weeks."	1mg/kg plus ipilimumab 3mg/kg, administered every 3 weeks for 4 doses, followed by nivolumab at a dose of 3mg/kg, administered every two weeks."	Checkmate 067 study is incorrect.	submission therefore this is not a factual error in the ERG report.
Page 24. Table 1. PD-L1 status classification is described as being "positive, negative, or intermediate". This is incorrect.	We would propose correcting the text to read "positive, negative or indeterminate"	The description of PD-L1 status classification in Table 1 is incorrect.	This typographical error has now been corrected
Page 52. Table 8. The footnote associated with unweighted ORR difference for Checkmate 067 should be d (not c)	We would propose correcting this footnote, changing c for d	This amendment will facilitate reader navigation through the report.	This typographical error has now been corrected
Page 59. Line 6 of the first paragraph reads: "…whereas there was no difference between nivolumab and DTIC for the time to first decline of EQ-5D VAS scores (HR=0.82 [95% CI 0.59 to 1.14])." This is incorrect.	We would propose correcting the text to read "whereas there was no significant difference between nivolumab and DTIC for the time to first decline…"	The statement is incorrect as currently written.	This has now been corrected
Page 62. Table 11. The percentage of PD-L1 positive patients in the ipilimumab arm of Checkmate 067 is stated incorrectly.	The percentage of PD-L1 is 23.8%.	The stated percentage of PD-L1 positive patients in the ipilimumab arm of Checkmate 067 is incorrect.	This has now been corrected
Page 64. Section 3.3.5 states "Adverse events (AE) are reported in CS section 4.2". This is incorrect.	We would propose correcting the text to state that adverse events are reported in CS section 4.12**.**	This amendment will facilitate reader navigation through the report.	This typographical error has now been corrected
Page 73. Penultimate line reads: "In the deterministic sensitivity analyses of nintendanib…" This is incorrect.	The word "nintendanib" should be replaced with "nivolumab".	The reference to nintendanib is a typographical error.	This typographical error has now been corrected
Page 91. Line 5. The hyperlinked reference to Table 23 does not work correctly.	We would propose reinserting the hyperlink.	This amendment will facilitate reader navigation through the report.	The hyperlink works in our version of the report.

Page 103. The penultimate line reads: ”the ICERs for both the BRAF inhibitors (vs. ipilimumab) remained dominated for the scenarios with different survival distributions.” This is incorrect.	We would propose correcting the text to read: ”the ICERs for both the BRAF inhibitors (vs. nivolumab) remained dominated…”.	The statement is incorrect as currently written.	This typographical error has now been corrected
The report contains several references to section 0, which does not seem to exist.	We would propose correcting these section cross-references.	This amendment will facilitate reader navigation through the report.	These do not appear in our version of the report.

Issue 4 Estimation of quality of life between treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 90 states that: “The ERG also notes that although the company has data for both treatment arms, they have not attempted to estimate the any differences in quality of life related to the treatments.”	We would propose that this sentence be removed from the ERG report.	The treatment arm is a covariate (Treatment DTIC) in the utility regression model (mainly for the purpose of controlling utility difference between treatment arms and to increase the robustness/accuracy of estimated effects on progression status and time to death) and the estimated coefficient (-0.0689) was reported in Table 66 in the submission. We believe a conservative approach was implemented in the CS by not having this treatment effect incorporated into the model (as to do so would have benefitted the nivolumab arm). Moreover, the NICE reference case suggests that a good reason is needed to	This is not a factual inaccuracy. No action taken.

		justify estimating utility based on treatment effect and it would not have been possible to assign a treatment effect to the BRAF-inhibitors or DTIC without making significant assumptions.	

Issue 5 Combination scenario performed by the ERG appears to give counter-intuitive and clinically-implausible results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106. The results presented in Tables 33 and 34 are counter-intuitive and clinically implausible.	We would propose that this combination scenario is removed from the ERG report in its entirety.	In Table 33 and Table 34 where ERG present the results based on a combination scenario performed by the ERG, the total QALYs for nivolumab are less than total QALYs for ipilimumab (2.55 vs. 2.64 in Table 33 and 2.27 vs. 2.44 in Table 34). We are still in the process of reviewing the ERG's analytical work; however, we believe that these results are counter-intuitive and clinically implausible given the superior efficacy results for nivolumab compared to ipilimumab in CheckMate 067 (median PFS 6.9 months in the nivolumab group vs. Median PFS 2.9 months in the ipilimumab group; HR for death or disease progression: 0.57 [95% CI:	The results are obtained in the company economic model using alternative assumptions specified. Not a factual inaccuracy.

		0.43, 0.76); p<0.001], see page 13 in the CS) and the long-term OS data for nivolumab (CheckMate 003 phase I trial) showing 42% and 32% patients still alive at year 3 and year 4 (see Figure 44 in the CS). The assumption of similar long-term OS benefit for all immunotherapies (including both nivolumab and ipilimumab) was also validated by the UK clinicians and health economic experts in the advisory board meeting (see Section 5.9 in the CS).	

Issue 6 Adjusted treatment comparison - Use of the Weibull parametric model for comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43 of the report states that: "The ERG also notes that no justification is given for use of the Weibull parametric model in CS Table 36 for comparison with the adjusted indirect comparison…. Therefore, a justification for use of this model in the CS would have been informative."	We would propose that this paragraph be removed from the report.	The use of log-logistic treatment effects for comparison with the adjusted indirect comparison hazards ratios cannot be used. The reason for this is log-logistic models are accelerated failure time models rather than proportional hazards models, and so do not produce hazard ratios.	We note that the company have justified using a single parametric model, but has not justified choosing the Weibull parametric model compared to the Gompertz model, or exponential model, both of which report hazard ratios. To make our critique clearer we have amended

			the following sentence: "The ERG also notes that no justification is given for use of the Weibull parametric model instead of other parametric models which also report in the hazard ratio metric in CS Table 36 for comparison with the adjusted indirect comparison…." And removed the following sentence: "Likewise, use of the log-logistic HR for PPS (used in the economic model) of 0.98 instead of the HR of 0.95 from the Weibull model would have been less comparable to the HR of 0.92 in the adjusted indirect comparison"

Issue 7 Modelling the TTP survival curve pre- and post-100 days

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 81 of the ERG report comments on the company's approach to modelling survival curves (time to progression) in the BRAF-mutation negative patients, and specifically the separation for the first 100 days, and then post 100 days.	We would propose adding the following sentence to the end of the first paragraph on this page: "This method was adopted by the company to allow sensible curve shapes to assist extrapolation, by removing the trial design driven cluster of events just before 100 days."	This method was adopted to allow sensible curve shapes to assist extrapolation, by removing the trial design driven cluster of events just before 100 days.	Not a factual inaccuracy. The clustering of events before 100 days has already been mentioned in the first paragraph on p81 of the ERG report.

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Nivolumab for treating advanced (unresectable or metastatic) melanoma

ERRATUM

Replacement pages following the factual accuracy check by
Bristol Myers Squibb

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Date completed 16th November 2015

- arm is outside of the NICE final scope and thus is not reported on in detail in the CS. The ipilimumab 3mg/kg arm of this trial allows a direct comparison between nivolumab and ipilimumab. A total of 945 patients were randomised, 316 to nivolumab and 315 to ipilimumab, as shown in CS Figure 8, p. 62. The remaining 314 patients were randomised to the combination therapy.
- CheckMate 037[9] recruited patients who progressed on or after prior anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy (ipilimumab) and (if BRAF mutation-positive) BRAF inhibitor therapy. This was an open-label study with the comparator the investigator's choice of one of two chemotherapy options, either DTIC 1000mg/m2 or carboplatin area under the curve 6 + paclitaxel 175mg/m^2. Both comparators were administered every three weeks. In total 405 patients were randomised (272 to nivolumab and 133 to ICC (CS Figure 9, p. 63).

The ERG presents a summary of trial characteristics in
Table 1.

Table 1 - Summary of characteristics of the included trials

	CheckMate 066 (n=418)	**CheckMate 067 (n=631)[a]**	**CheckMate 037 (n=405)**
Phase	Phase III	Phase III	Phase III
Blinding	Double blind	Double blind	Open label
Population	Previously untreated patients with advanced melanoma	Previously untreated patients with advanced melanoma	Previously treated patients with advanced melanoma
BRAF mutation status	Without BRAF mutation	With or without BRAF mutation	With or without BRAF mutation
PD-L1 status	PD-L1-positive, negative or indeterminate classification	PD-L1-positive, negative or i indeterminate classification	PD-L1-positive, negative or indeterminate classification
Comparator	DTIC	Ipilimumab	ICC
Primary outcome(s)	OS	OS, PFS	ORR, OS
Start date	January 2013	June 2013	December 2012
Status	Terminated[b]	Ongoing	Ongoing
Cut-off (database lock)	5 August 2014	17 February 2015	30 April 2014 (clinical database lock) 20 May 2014 (IRRC database lock)
Currently available primary/survival outcomes	1 year OS PFS	PFS	ORR PFS
Expected availability of further data	18 month OS: November 2015; 2 year OS: Q4 2016	OS and PFS: Q4 2016	OS and PFS: November 2015; OS extended follow/up: June 2016

DTIC = dacarbazine; ICC = investigator's choice chemotherapy (dacarbazine or carboplatin plus paclitaxel; IRRC = independent radiology review committee; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q4 = quarter 4.

[a] Nivolumab monotherapy and ipilimumab monotherapy arms. The trial included a third arm of combined nivolumab and ipilimumab treatment, which not included in this ERG report.

preserve randomisation through inclusion of the trial as a covariate in the analyses. Both methods are therefore appropriate in this respect.

The ERG also notes that no justification is given for use of the Weibull parametric model instead of other parametric models which also report the HR metric, in CS Table 36 for comparison with the adjusted indirect comparison. Use of the Gompertz model for TTP post 100 days (as used in the economic model) would have produced an HR of 0.35 compared to the HR of 0.38 for the Weibull model, which was slightly less comparable to the 0.37 HR in the adjusted indirect comparison. Gompertz model-based HRs might have been used throughout Table 36 instead, for example, and might not have given such a favourable comparison to the adjusted indirect figures as the Weibull model. Therefore, a justification for use of this model in the CS would have been informative.

(ii) Indirect comparison of nivolumab to BRAF inhibitors

This comparison informed the cost-effectiveness analysis for BRAF mutation-positive patients, and also comprises comparisons of treatments from trials using a common comparator. CS Table 25 describes the comparisons made and CS Figure 35 illustrates the network diagram, replicated in Figure 1 in this report. For nivolumab compared to vemurafenib, patient-level data from CheckMate 066[4] (nivolumab arm) was compared to aggregate data from the BRIM-3 trial[12] (vemurafenib arm) linked together by DTIC, which was a comparator in both trials. The ERG assumes that patient-level data from the BRIM-3 trial were not available to the company, whereas patient-level data were available for both nivolumab and ipilimumab in the BRAF mutation-negative network, since the company markets both drugs. However, the CS goes on to describe a process to create pseudo patient-level data for vemurafenib from Kaplan-Meier curves (CS P. 118, and see below).

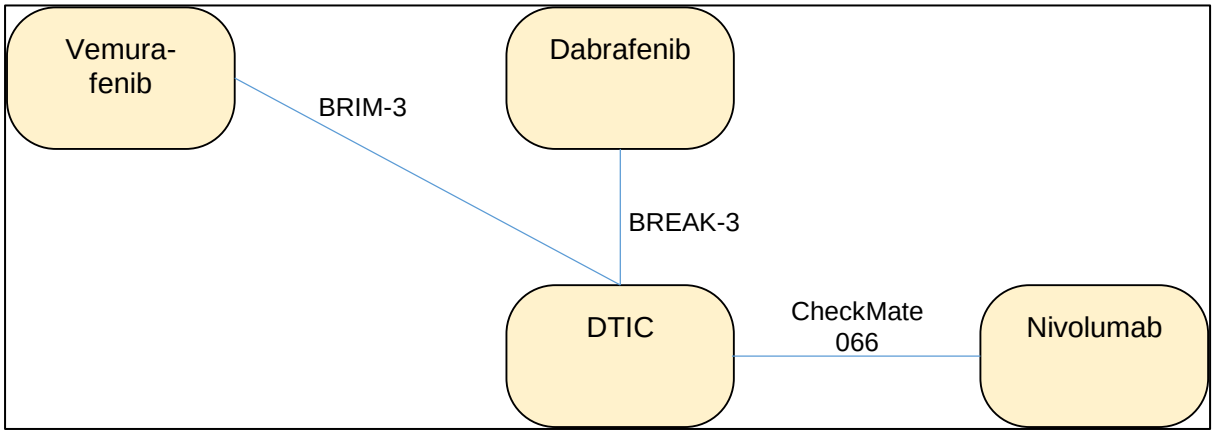

Figure 1 - Network diagram for nivolumab and BRAF inhibitors

Table 2 - Response analysis

	CheckMate 066		CheckMate 067		CheckMate 037	
	Nivolumab (n=210)	**DTIC (n=208)**	**Nivolumab (n= 316)**	**Ipilimumab (n= 315)**	**Nivolumab[a] (*PP*: n= 120) (*ITT*: n=122)**	**ICC (*PP*: n= 47) (*ITT*: n=60)**
Objective response rate (ORR)						
Responders, n (%) (95% CI)	84 (40.0)[b] (33.3, 47.0)	29 (13.9)[b] (9.5, 19.4)	138 (43.7)[b] (38.1, 49.3)	60 (19.0)[b] (14.9, 23.8)	*PP*: 38 (31.7)[c] (23.5, 40.8)	5 (10.6)[c] (3.5, 23.1)
					ITT: 38 (31.1)[c] (23.1, 40.2)	5 (8.3)[c] (2.8, 18.4)
Best overall response CR, n (%) PR, n (%)	16 (7.6) 68 (32.4)	2 (1.0) 27 (13.0)	28 (8.9) 110 (34.8)	7 (2.2) 53 (16.8)	*PP*: 4 (3.3) 34 (28.3)	0 5 (10.6)
					ITT: 4 (3.3) 34 (27.9)	0 5 (8.3)
Unweighted ORR difference, % (95% CI)	26.1 (18.0, 34.1)		24.7[d]		*PP*: 21.0 (6.8, 31.7)	
					ITT: 22.8 (10.5, 32.7)	
Estimated odds ratio (95% CI) p-value	4.06 (2.52, 6.54) <0.0001		3.40 (2.02, 5.72) <0.0001		Not reported	
Duration of response						
Median (range), months	Not reached (0.0, 12.5)	5.98 (1.1, 10.0)	Not reached	Not reached	*PP*: Not reached (1.4+, 10.0+)	3.5 (1.3+, 3.5)
Time to treatment response						
Median (range), months	2.10 (1.2, 7.6)	2.10 (1.8, 3.6)	2.8 (2.3, 12.5)	2.8 (2.5, 12.4)	*PP*: 2.1 (1.6, 7.4)	3.5 (2.1, 6.1)

CI = confidence interval; CR = complete response; DTIC = dacarbazine; ITT = intention-to-treat; ORR = Objective response rate; PP = per-protocol; PR = partial response rate.
[a] CheckMate 037[9] reports both ITT and PP analyses for tumour response. [b] Confirmed response (CR+PR) as per RECIST v1.1 criteria, investigator-assessed.
[c] Confirmed response (CR+PR) as per RECIST v1.1 criteria, assessed by independent radiological review committee. [d] 95% CI not reported in the CS or in the trial publication.[5]

p<0.001), and constipation (HR=0.51 [95% CI 0.34 to 0.76]; p<0.001). Subscales of the EORTC QLQ-C30 that demonstrated no significant difference in time to first decline between nivolumab and DTIC were fatigue (HR=0.74 [95% CI 0.55 to 1.00]), diarrhoea (HR=0.87 [95% CI 0.53 to 1.43]), and financial difficulties (HR=0.66 [95% CI 0.41 to 1.05]). The time to first decline in the EQ-5D utility index favoured nivolumab (HR=0.55 [95% CI 0.38 to 0.80]; p=0.002) whereas there was no significant difference between nivolumab and DTIC for the time to first decline of EQ-5D VAS scores (HR=0.82 [95% CI 0.59 to 1.14]).

In contrast to the time to first decline in HRQoL, the CS provides only a brief summary of the Cox proportional hazards regression analysis results for time to first improvement in HRQoL (CS p. 88). The CS reports that time to first improvement favoured nivolumab over DTIC (i.e. HR > 1.0) for four of the 15 subscales of the EORTC-QLQ-C30. These were: global health (HR=1.52; p=0.043); physical functioning (HR=1.92; p=0.027); fatigue (HR=1.69; p=0.008); and dyspnoea (HR=2.20; p=0.013) (no 95% CI for the HR were reported). The CS also reports that time to first improvement in the EQ-5D utility index favoured nivolumab (HR=1.86; p=0.002).

Although time to first decline appears to favour nivolumab for most of the HRQoL scales assessed, including the EQ-5D utility index, the ERG notes that the method of analysis is not clearly explained in the CS, particularly with regard to whether unbalanced attrition between the trials arms after week 13 could have influenced the reported outcomes (the CS does not explicitly state which time periods are covered by the regression analyses). The ERG also notes that any initial improvements in HRQoL suggested by these Cox proportional hazards regression analyses did not appear to translate into longer-term HRQoL benefits to patients. For these reasons, and given the interim nature of the analyses, the ERG suggests that these findings should be interpreted with caution.

In summary, based on the interim HRQoL evidence presented in the CS and in the company's clarification response, the ERG agrees with the company's conclusion that nivolumab does not impair HRQoL (relative to baseline), but the ERG notes that there is no current evidence that nivolumab leads to a consistent and sustained improvement in HRQoL. Although the company's analyses suggest that nivolumab has a favourable time to first decline in HRQoL and, to a lesser extent, favourable time to first improvement in HRQoL when compared to DTIC, the best available evidence from the initial analyses does not currently suggest that this translates into longer-term HRQoL benefits.

Table 3 - Objective response rate by PD-L1 expression status

	CheckMate 066 ITT analysis		**CheckMate 067** Post-hoc ITT analysis		**CheckMate 037** PP objective response set IRRC assessment	
	Nivolumab n=(210)	**DTIC n=208)**	**Nivolumab (n=316)**	**Ipilimumab (n=315)**	**Nivolumab (n=120)**	**ICC (n=47)**
PD-L1-positive patients, n (%)	74 (35.2)	74 (35.6)	80 (25.3)	75 (23.8)	55 (45.8)	22 (46.8)
Responders, n (%)(95% CI)	39 (52.7) (40.8, 64.3)	8 (10.8) (4.8, 20.2)	-	-	24 (43.6) (30.3, 57.7)	2 (9.1) (1.1, 29.2)
Unweighted ORR difference, % (95% CI)	-		-		34.5 (12.2, 49.2)	
ORR %	-	-	57.5	21.3	-	-
Odds ratio (59% CI)	-	-	5.03 (2.44, 10.37)		-	-
PD-L1-negative/in-determinate patients, n (%)	136 (64.8)	134 (64.4)	Not reported	Not reported	64 (53.3)	23 (48.9)
Responders, n (%)(95% CI)	45 (33.1) (25.2, 41.7)	21 (15.7) (10.0, 23.0)			13 (20.3) (11.3, 32.2)	3 (13.0) (2.8, 33.6)
Unweighted ORR difference, % (95% CI)	-		-		7.3 (-13.4, 21.5)	
ORR %	-	-	41.3%	17.8%	-	-
Odds ratio (59% CI)	-		3.25 (2.05, 5.13)		-	

CI = confidence interval; DTIC = dacarbazine; ICC = investigators choice chemotherapy; IRCC = independent radiological review committee; ORR = objective response rate; PD-L1 = programmed death-ligand-1.

In all of the trials, objective response rates were higher in nivolumab-treated patients with positive PD-L1 status than in nivolumab-treated patients with PD-L1 negative status. Both groups experienced higher response rates than patients treated with alternative drugs. However, the ERG notes that the lower bound of the 95% CI around the unweighted ORR difference between treatments in the PD-L1-negative subgroup fell below zero, indicating a potential better response for ICC treated patients in this subgroup. The trial journal publication[9] notes that these analyses, although pre-defined, were 'exploratory' and 'descriptive in nature' (p. 381) and that the patient sample sizes in some of the subgroups

Table 4 - Objective response rate by BRAF mutation status (CheckMate 037)

	Nivolumab (n=120)	**ICC (n=47)**
BRAF mutation-positive n (%)	26 (21.7)[a]	11 (23.4)[a]
Responders n (%)	6 (23.1)	1 (9.1)
ORR % (95% Exact CI)	23.1 (9.0, 43.06)	9.1 (0.2 41.3)
Unweighted ORR difference % (95% CI)	14.0 (-17.1, 34.4)	
BRAF mutation-negative n (%)	94 (78.3)[a]	36 (76.6)[a]
Responders n (%)	32 (34.0)[a]	4 (11.1)[a]
ORR % (95% Exact CI)	34.0 (24.6, 44.5)	11.1 (3.1, 26.1)
Unweighted ORR difference % (95% CI)	22.9 (6.2, 35.0)	

CI = confidence interval; ICC = investigator choice of chemotherapy; ORR = objective response rate.
[a] % calculated by ERG.

Nivolumab-treated patients experienced higher response rates than those treated with ICC, irrespective of BRAF mutation status. However, response rates were highest in patients with BRAF mutation-negative status. Furthermore, the lower bound of the 95% CI around the unweighted ORR difference between treatments in the BRAF mutation-positive subgroup fell below zero, indicating a potential better response for ICC treated patients in this subgroup. As described above, these subgroup analyses should be interpreted with caution due to the small sample size within each stratum.

3.3.5 Summary of adverse events

Adverse events (AE) are reported in CS section 4.12 (p. 134-145), and summaries of overall rates of AE and discontinuations due to AE are presented in CS Table 46 (CS p. 136) for CheckMate 066,[4] Table 48 (CS p. 140) for CheckMate 067[5], and Table 50 (CS p. 143) for CheckMate 037.[9] These data from the CS are replicated here in **Error! Reference source not found.**.

Cost effectiveness analysis results

Results from the economic model are presented (CS Section 5.7.1, p. 206-7) as incremental cost per QALY gained for nivolumab compared with its comparators for BRAF-mutation-negative for and BRAF mutation-positive patients. Total and incremental costs, life years gained (LYG) and QALYs were also reported, along with a breakdown of total costs. Results are presented with drug prices based on list prices and then for drug prices assuming PAS prices for the comparator treatments. Total costs are reported as commercial in confidence by the company for all treatments, in order to avoid calculation of the confidential PAS prices for ipilimumab and vemurafenib.

For BRAF-mutation-negative patients an incremental cost per QALY gained of £23,583 was reported for nivolumab versus DTIC (see Table 17). For BRAF-mutation-positive patients an incremental cost per QALY gained of £7,346 was reported for nivolumab versus ipilimumab (see Table 6).

Table 5 - Base case cost effectiveness results for BRAF mutation-negative patients (drug prices based on list price, CS Table 80)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
DTIC	[redacted]	1.23			
Ipilimumab	[redacted]	2.64	£48,429	1.41	Excluded due to extended dominance
Nivolumab	[redacted]	4.31	£72,578	3.08	£23,583

Table 6 - Base case cost effectiveness results for BRAF mutation-positive patients (drug prices based on list price, CS Table 81)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Ipilimumab	[redacted]	2.44			
Nivolumab	[redacted]	4.27	£13,374	1.82	£7,346
Dabrafenib	[redacted]	1.69	£6,228	-2.57	Excluded due to dominance
Vemurafenib	[redacted]	1.70	£24,659	-2.56	Excluded due to dominance

In the deterministic sensitivity analyses of nivolumab, the results were presented in terms of net benefit with a willingness to pay threshold of £50,000 per QALY. The analyses showed that the

mutation-positive patients, the impact was similar with ICERs (nivolumab vs ipilimumab) ranging from £8,836 to £9,144, deviating from the base case ICER of £7,346.

Table 7 - Using the Weibull, log-normal, log-logistic and generalised distributions for the nivolumab arm to model time to progression at list price (BRAF mutation-negative patients)

Treatment	Distribution	Incremental Costs (vs DTIC)	Incremental QALYs (vs DTIC)	ICER (vs DTIC)	ICER (vs ipilimumab)
Nivolumab	Base case[1]	£72,578	3.08	£23,583	£14,513
Nivolumab	Weibull	£72,237	2.73	£26,483	£18,117
Nivolumab	Lognomal	£72,085	2.67	£27,027	£18,874
Nivolumab	log-logistic	£72,137	2.69	£26,829	£18,594
Nivolumab	generalised gamma	£72,098	2.67	£26,980	£18,806

1: Gompertz

Table 8 - Using Weibull, log-normal, log-logistic and generalised gamma distributions for the nivolumab arm to model time to progression at list price (BRAF mutation-positive patients)

Treatment	Distribution	Incremental Costs (vs ipilimumab)	Incremental QALYs (vs ipilimumab)	ICER (vs ipilimumab)
Nivolumab	Base case[1]	£13,374	1.83	£7,346
Nivolumab	Weibull	£13,060	1.48	£8,836
Nivolumab	Lognomal	£12,890	1.41	£9,144
Nivolumab	log-logistic	£12,947	1.43	£9,025
Nivolumab	generalised gamma	£12,903	1.41	£9,120
Nivolumab dominates dabrafenib and vemurafenib for all analyses				

1: Gompertz

4.3.2 Modelling progression-free survival using a range of distributions for BRAF inhibitors

For PFS, it was observed that the type of survival curve chosen for the BRAF inhibitors influenced the costs associated with the treatment arms in BRAF mutation-positive patients. The ERG explored this further by assigning a range of distributions (exponential, Gompertz, log-logistic, log-normal and Weibull) to the PFS in the BRAF inhibitors. Assigning different distributions influenced the total costs for both dabrafenib and vemurafenib but total QALYs in both the treatment arms remained similar to the base case values as shown in Table 29. As in the base case, the ICERs for both the BRAF inhibitors (vs nivolumab) remained dominated for the scenarios with different survival distributions.

CheckMate 067, has not been included in the company's analysis due to lack of available OS data.

5 End of life

The CS discusses the end of life criteria in Table 52 and states that advanced melanoma is associated with a short life expectancy, with median survival estimates of 6-10 months. Survival analyses of CheckMate 066 trial data indicate that nivolumab offers an extension to life of at least three months compared to palliative chemotherapy (DTIC). However, the survival benefit compared to ipilimumab is not yet fully established, pending follow-up OS data from CheckMate 067.[5] The CS reported that the expected number of new cases and relapsed cases of advanced melanoma in England in 2016 is 1,577. The CS therefore concluded that nivolumab is suitable for consideration as a life-extending treatment at the end of life.

The ERG also notes that in TA319[16] for ipilimumab for advanced melanoma, the Appraisal Committee was satisfied that ipilimumab met the criteria for being a life-extending, end of life treatment.

6 Innovation

The CS states that nivolumab should be considered innovative, representing a step-change in the management of advanced melanoma. The arguments in support of this include the stated significant clinical improvement associated with the drug, demonstrated through 45-50% of patients estimated to still be in remission two years after treatment initiation, based on extrapolation from the on-going Phase III RCTs. Furthermore, the CS reports that the Medicines and Healthcare products Regulatory Agency awarded nivolumab a Promising Innovative Medicine (PIM) designation for the treatment of advanced melanoma. Nivolumab was approved to treat advanced melanoma and locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) through the Early Access to Medicines Scheme. The criteria for drugs to be supported under this scheme include evidence that the product is likely to offer significant advantage over methods currently used in the UK.

7 DISCUSSION